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GUIDELINES

Italian adaptation of EuroGuiDerm guideline on the systemic treatment of chronic plaque psoriasis

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ABSTRACT

SIDeMaST (*Società Italiana di Dermatologia Medica, Chirurgica, Estetica e delle Malattie Sessualmente Trasmesse*) contributed to the development of the present guideline on the systemic treatment of chronic plaque psoriasis. With the permission of EuroGuiDerm, SIDeMaST adapted the guideline to the Italian healthcare context to supply a reliable and affordable tool to Italian physicians who take care of patients affected by moderate to severe plaque psoriasis. The content of the guideline includes general information on the scope and purpose, health questions covered, target users and strength/limitations of the guideline, suggestions for disease severity grading and treatment goals. It presents the general treatment recommendations as well as detailed management and monitoring recommendations for the individual drugs including acitretin, cyclosporine, fumarates, methotrexate, adalimumab, apremilast, brodalumab, certolizumab pegol, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tildrakizumab and ustekinumab. Moreover, the guideline provides guidance for specific clinical situations such as patient with concomitant psoriatic arthritis, inflammatory bowel disease, a history of malignancies, a history of depression, diabetes, viral hepatitis, disease affecting the heart or the kidneys as well as concomitant neurological disease. Advice on how to screen for tuberculosis and recommendations on how to manage patients with a positive tuberculosis test result are given. It further covers treatment for pregnant women or those with childbearing potential. Information on vaccination, immunogenicity and systemic treatment during the COVID-19 pandemic is also provided.

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KEY WORDS: Psoriasis; Guideline; Therapeutics; Biological products.

Scope and purpose of this guideline

The overall aim of this guideline is to provide guidance for optimal treatment selection and management in the treatment of adults with moderate to severe plaque type psoriasis. Optimal treatment selection and management are meant to reduce morbidity caused by psoriasis and to improve the health-related quality of life of affected individuals.

The objectives of the guideline are to:

- include new treatments and the evidence that has become available;
- update the recommendations regarding biologic systemic treatment options;
- develop a treatment algorithm including biologic and nonbiologic systemic treatment options;
- provide clear recommendations on how to best monitor and manage patients considering the available treatment options;
- develop several short guidance documents with visual tools for ease of implementation;
- provide guidance on the treatment of special populations and difficult clinical situations (mostly expert consensus).

The Italian adaptation of the EuroGuiDerm guideline is delivered in order to clarify the regulations, provisions, requirements and organizational structures of the National Health System that adapt to the Italian context.

For the list of abbreviations, see the Supplementary Digital Material 1: Supplementary Table I.

Population and health questions covered by the guideline

The target population are patients with plaque type psoriasis of moderate to severe severity, and patients with psoriatic arthritis, who have also been diagnosed with moderate to severe plaque psoriasis.

In Italy, the wording “plaque psoriasis” is generally preferred to “psoriasis vulgaris” by dermatologists. Therefore, this wording will be used from here on.

Leading health questions — all concerning to adult individuals (regardless of sex or gender) with moderate or severe plaque type psoriasis — are:

- which treatment option should be chosen about patients’ needs, taking efficacy, safety/tolerability of the different treatment options and comorbidities into consideration?;
- how should the selected treatment option best be managed and monitored?;
- how should frequent comorbid situations (*e.g*. concomitant arthritis) best be managed?

Necessary inclusion criteria for treatments were a European approval for the treatment of chronic plaque psoriasis. Whenever possible and feasible, the recommendations are evidence-based, taking the results of systematic evidence synthesis based on rigorous methods[1] as well as on the practical experience obtained by the expert group, into account.

This guideline covers the use of ‘conventional’ treatments (acitretin, cyclosporine, fumarates, methotrexate), biologicals targeting TNF-α (adalimumab, etanercept, cer-

tolizumab pegol, infliximab), IL-12/23p40 (ustekinumab), IL-17A (ixekizumab, secukinumab), IL-17RA (brodalumab) and IL-23p19 (guselkumab, risankizumab, tildrakizumab) and the 'small molecule' (apremilast). Relevant comparison is head-to-head studies of the above-mentioned. interventions or versus placebo. The outcomes chosen are as follows: 90% improvement in the Psoriasis Area Severity Index (PASI 90), 75% PASI improvement (PASI 75) and severe adverse events (SAEs) and adverse events (AEs).

Label indication

The conventional treatments, biologicals, and the small molecule apremilast are licensed in Italy for the treatment of moderate to severe plaque psoriasis following the approval of the competent regulatory bodies, first by the European Medical Agency (EMA) and then by the Agenzia Italiana del Farmaco (AIFA). The label therapeutic indication of each drug is reported in the summary of product characteristics (SmPC) and is consistent across Europe.

Reimbursement and prescription criteria

The reimbursement and prescription criteria in Italy are different from those of other European countries and they are established by AIFA. Biologicals and apremilast are fully reimbursed by the National Health System (NHS) based on criteria published in the Gazzetta Ufficiale della Repubblica Italiana (1). In particular, the treatment with biologicals should be limited to patients with moderate to severe plaque psoriasis (*i.e*. PASI >10 or BSA >10 or PASI <10 and BSA <10 but involvement of sensitive areas such as face, palmo-plantar, nails, genitalia) in case of non-response or intolerance (therapeutic failure) to a conventional synthetic disease modifying anti rheumatic drug (DMARD). Biologicals are not approved for non-plaque psoriasis forms such as localised (including Hallopeau's continuous acrodermatitis) or generalized pustular and guttate psoriasis when they are not associated with plaque psoriasis. Before prescribing brodalumab it is necessary to carefully evaluate from a clinical and anamnestic perspective, including, if necessary, a psychiatric visit, any condition of depression and/or suicidal ideation or behavior. For paediatric indications of biologicals, the dermatologist should refer to the respective SmPC. The treatment with apremilast should be limited to patients with moderate to severe plaque psoriasis in case of non-response or intolerance to a conventional DMARD (including cyclosporine, methotrexate or PUVA) and in those who have contraindication to or have been intolerant to biologicals (2). Biologicals can be prescribed only by dermatologists working in authorised centres including public hospitals, university-hospitals or other private structures affiliated with theNHS. Biologicals are classified as Class H (*i.e*. drugs delivered by the hospital pharmacy) and are distributed free of charge to patients. Each Region autonomously identifies which centres are authorized to prescribe biologicals and small molecules. There may also be significant differences in drug prescription criteria among the Italian Regions. Conventional treatments are classified as Class A (*i.e*. drugs delivered by the non-hospital pharmacy) and their cost is partially reimbursed to patients with plaque psoriasis and it is fully reimbursed if patients are affected by psoriatic arthritis and/ or generalized pustular psoriasis (Von Zumbush type). They can be prescribed by certified physicians (specialists and/or general practitioners) who are affiliated with the National Health Service.

1) Gazzetta Ufficiale n. 91 del 06/04/2020.
2) Gazzetta Ufficiale n. 80 del 06/04/2018.

Additionally, the below-listed comorbidities and special situations are addressed by the guideline (Table I and Decision Grid 1 and 2).[2-8]

Table I.—*Overview of topics and key question in relation to comorbidities and special patient populations/issues.*

Topic	Question
Psoriatic arthritis	How should psoriasis patients with concomitant psoriatic arthritis be managed?
Inflammatory bowel disease	How should psoriasis patients with inflammatory bowel disease be managed?
Cancer	How should psoriasis patients with a history of malignancies be managed?
Depression	How should psoriasis patients with a history of depression and/or suicidal ideation be managed?
Diabetes mellitus	How should psoriasis patients with diabetes mellitus be managed?
Heart disease	How should psoriasis patients with ischemic heart disease and/or congestive heart failure be managed?
Kidney disease	How should psoriasis patients with kidney failure / renal impairment be managed?
Neurology	Which treatments are appropriate for psoriasis patients with neurological diseases?
Hepatitis	When and how should psoriasis patients be screened for viral hepatitis and how should patients who test positive be managed?
Tuberculosis screening	How to screen for tuberculosis before and during biologic treatment?
Tuberculosis and treatment	How to manage psoriasis in patients with positive tuberculosis test results?
Pregnancy	How should psoriasis patients with a wish for pregnancy in the near future or who are pregnant be managed?
Vaccinations	How should vaccinations in psoriasis patients on systemic treatment be managed?
Immunogenicity	What is the role of anti-drug antibodies in biologic treatments?
COVID-19	Guidance for systemic therapy of psoriasis during COVID-19 pandemic

DECISION GRID I.—Overview of "conventional" treatment options and the expert assessment of their suitability in specific treatment circumstances.

Therapy / Specific circumstances	Conventional systemic agents			
	Acitretin	Ciclosporin	Fumarates	Methotrexate
Concomitant psoriatic arthritis				↑↑ peripheral active joint involvement
Chronic inflammatory bowel disease: Crohn's disease	↑ especially cases with mild paradoxical psoriasis			↑ 2nd choice oral treatment
Chronic inflammatory bowel disease: ulcerative colitis	↑ especially cases with mild paradoxical psoriasis	↑ 2nd choice oral treatment		
Diabetes mellitus/ metabolic syndrome		↓		↓
Dyslipidemia	↓			
Advanced heart failure	↑	↓		↑
Heart disease: ischemic heart disease	↓			↑
Concomitant latent/ treated TB	↑		↑	
Pregnancy	↓↓	↑ preferred conventional	↓	↓↓
Previous history of malignancies		↓↓		↑

Symbols	Implication (adapted from GRADE)
↑↑	We believe that all or almost all informed people would make that choice
↑	We believe that most informed people would make that choice, but a substantial number would not
	See background text and specific recommendations
↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not
↓↓	We believe that all or almost all informed people would make a choice against that choice

DECISION GRID II.—Overview of "biologics" treatment options and the expert assessment of their suitability in specific treatment circumstances

Therapy / Specific circumstances	Small molecules	TNF inhibitors				Anti-IL-12/23	Anti-IL-17			Anti-IL-23		
	Apremilast	Etanercept	Infliximab	Adalimumab	Certolizumab	Ustekinumab	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Tildrakizumab	Risankizumab
Concomitant psoriatic arthritis		↑↑ if non-responder to MTX										
Chronic inflammatory bowel disease: Crohn's disease			↑↑ 1st choice				↓			↑ 2nd choice if anti-TNF alpha not suitable		
Chronic inflammatory bowel disease: ulcerative colitis	↑ 2nd choice oral treatment		↑↑ 1st choice			↑↑ 1st choice	↓			↑ 2nd choice if anti-TNF alpha not suitable		
Diabetes mellitus/ metabolic syndrome												
Dyslipidemia												
Advanced heart failure	↑	↓↓				↑						
Heart disease: ischemic heart disease		↑										
Concomitant latent/ treated TB	↑	↓↓					↑			↑		
Pregnancy	↓				↑ preferred choice biologic							
Previous history of malignancies												

Symbols	Implication (adapted from GRADE)
↑↑	We believe that all or almost all informed people would make that choice
↑	We believe that most informed people would make that choice, but a substantial number would not
	See background text and specific recommendations
↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not
↓↓	We believe that all or almost all informed people would make a choice against that choice

Targeted users of this guideline

The targeted users of this guideline are mainly dermatologists, payers, and health care authorities.

Disease severity and treatment goals

Measuring disease severity

Although it has its drawbacks, the most established parameter to measure the severity of skin symptoms in psoriasis is the Psoriasis Area and Severity Index (PASI), which was first introduced in 1978 as an outcome measure in a retinoid trial.[9]

Health related quality of life (HRQoL) is an important aspect of psoriasis, not only in defining disease severity but also as an outcome measure in clinical trials. The Dermatology Life Quality Index (DLQI) is the most used score for assessing the impact of psoriasis on HRQoL. It consists of a questionnaire with ten questions related to symptoms, mental health, impact on daily life, leisure, work and school, personal relationships and burden psoriasis treatment.[10]

Defining disease severity

The first European consensus effort to define treatment goals for moderate-to-severe psoriasis was conducted in 2011.[11] According to the consensus, the definition of moderate-to-severe disease was '(PASI >10 or body surface area [BSA] >10) AND DLQI >10', and for mild psoriasis 'PASI ≤10 AND BSA ≤10 AND DLQI ≤10'. Criteria to further "upgrade" mild disease to moderate-to-severe were defined as major involvement of visible areas, major involvement of the scalp, involvement of genitals, onycholysis or onychodystrophy of at least two fingernails, presence of itch leading to scratching and the presence of recalcitrant plaques.

The DLQI describes the overall impact of skin disease on a person's HRQoL as follows: 0-1 = "no effect;" 2-5 = "small effect:" 6-10 = "moderate effect;" 11-20 = "very large effect;" 21-30 = "extremely large effect." A change of five points in the DLQI has been shown to correlate with the minimum clinically meaningful change in a person's HRQoL.[12] Although there is no correlation or only weak correlation between absolute PASI and absolute DLQI scores,[13] there seems to be a correlation between an improvement in PASI and an improvement in the DLQI.[14]

Since the European consensus, the discussion about defining disease severity has evolved further.

The International Psoriasis Council (IPC) ran a modified Delphi consensus process among its counsellors to categorize psoriasis severity and to redefine access criteria to systemic therapy. The most preferred statement from the IPC survey "rejects the mild, moderate, and severe categories in favour of a dichotomous definition: psoriasis patients should be classified as either candidates for topical therapy or candidates for systemic therapy; the latter are patients who meet at least one of the following criteria: 1) body surface area >10%; 2) disease involving special areas; and 3) failure of topical therapy."[15]

The severity definition that reached the second highest approval rate did provide a dichotomous distinction: "1) mild or mild to moderate: that which can be adequately controlled with topical therapy alone; 2) moderate to severe or severe: that which requires phototherapy or systemic therapy (including biologics)."[15]

A definition using precise numbers got only moderate support from the IPC counsellors, defining mild as BSA 0-5% with special areas not affected and with DLQI <5, defining moderate as BSA 5-10% or special areas affected; or BSA 1-5% and DLQI 5-10, and defining severe as >10% BSA or special areas affected; or BSA 5-10% and DLQI >10.[15]

A physician global assessment (PGA) score to evaluate disease severity can be beneficial for the everyday clinician in order to rapidly assess the severity of psoriasis. It is important to note that different PGAs exist and may differ in the way they are defined. A PGA score of 3 or more is commonly used in clinical trials in order to define a moderate-to-severe form of psoriasis and an indication for systemic treatment. PGA 0/1 is also used both in clinical trials as well as in the everyday clinical practice as a definition of treatment success.[16-18]

In Italy, the most common measures of disease severity in real life include PASI, BSA and DLQI. The psoriasis involvement of sensitive areas such as face, nails, genitalia and palmo-plantar is considered a criterion for defining moderate to severe psoriasis.

Treatment goals

The 2011 European Consensus on Treatment Goals

The European Consensus Program defined treatment goals for the first time for psoriasis.[11] In accordance with concepts of uncontrolled disease and the com-

monly used definition of treatment failure, an algorithm had been generated that can be used in daily practice to secure effective treatment. Treatment success was defined as an improvement of 75% or more in PASI. Treatment failure was defined as not achieving a PASI of 50. Reaching an improvement of more than 50% but less than 75% but achieving a DLQI score of equal to or lower than 5 was considered treatment success whereas a DLQI score above 5 was considered treatment failure. A first point in time to assess treatment success for fast acting drugs (*e.g*., CsA, infliximab) should start at the end of induction therapy up until 16 weeks after the initiation of treatment. For drugs with a slower onset of activity (*e.g*., MTX, fumarates [FUM], etanercept), treatment assessment should begin at the end of induction therapy up until 24 weeks after starting therapy. During maintenance treatment, an assessment of treatment success should be made in intervals in accordance with the safety monitoring recommendations (typically every 8 to 12 weeks).

An important consideration when utilizing treatment goals is the demand for action in case the goal is not met. In psoriasis there are several measures that can be applied to increase efficacy such as increasing the dose, reducing the time between applications, or adding another drug (combination therapy); however, with certain drugs this may represent off-label therapy as such variations are not backed-up by the summary of product characteristics (SmPC). When dose adjustments are either ineffective or not appropriate, changing the drug is an important step. As there is little evidence on how to shift from one drug to another, a global consensus program provided guidance based on a combination of evidence from the literature and on expert opinion.[19]

Advancements after the European Consensus on Treatment Goals

Since the European consensus group process, more treatment options for psoriasis have become available and considerable progress has been made. Because of these advancements, higher treatment goals (*e.g*. PASI 90 or PASI 100) are aimed for.[20] In addition, the focus has shifted away from percentage reduction and towards a targeted final outcome (*e.g*. PASI ≤2, DLQI <2 or PGA clear or almost clear).[18, 21]

Time till onset of action

Psoriasis can have a severe impact on an individual's health related quality of life. The time until the onset of action of different treatments for psoriasis has been found to vary between the different treatment options.[22] Although psoriasis is a chronic skin disease, rapid clearance has been identified as a crucial outcome for patients.[22] Taking the time necessary for 25% or 50% of patients to achieve a given PASI or ACR (modified American Rheumatology criteria) response, available systematic reviews summarize the evidence on the speed of onset of action of the different drugs.[23-25] Estimates of what is acceptable for a patient as 'waiting time' until a treatment becomes effective, vary largely from patient to patient. Looking at the proportion of patients dropping out of clinical trials due to a lack of efficacy as a proxy, a strong increase in the rate of dropouts was seen after 10-12 weeks.[26] Sequential combination of slow acting drugs with low response rates carries a risk of long patient 'waiting times,' until a noticeable, clinically meaningful improvement in their health related quality of life.[27]

Methods section

For the detailed description of the EuroGuidDerm guideline development process, please see the report that is available alongside the guideline document on the EDF website: https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html.

In short, the guideline development group is comprised of 23 dermatology experts from 14 countries, two patients' representatives nominated by the International Federation of Psoriasis Associations (IFPA) and the EuroGuiDerm methodologists. Twenty-eight percent declared personal-financial conflicts of interests (no vote/count). The guideline draft texts and recommendations were developed by the experts in working groups, reviewed, discussed, and amended where appropriate by the entire group. All texts and recommendations were voted on with a minimal agreement of >50%. A structured consensus technique was used during all three online consensus conferences.

Wording as suggested by the GRADE Working Group to standardize the wording of all recommendations was used.[28-33]

The recommendations are presented throughout this guideline as displayed below: first the content, then the arrows and colors indicating the direction and the strength of the recommendations, respectively, and lastly the rate of expert agreement (consensus strength). Evidence-based recommendations are indicated as such.

We **recommend** doing tuberculosis screening according to local regulations.	↑↑	STRONG CONSENSUS 100% Agreement EXPERT CONSENSUS

The tables "instruction for use" and "lab controls" have also been voted on – these are consensus-based. The rate of expert agreement is displayed too.

An internal and external review was conducted. Dissemination, implementation, and monitoring plans were developed as well as a joint Q&A section for patients. For more details, see Methods and Evidence report.

Recommendations

Initiation and selection of a systemic treatment

The Italian adaptation of EuroGuiDerm guideline for the systemic treatment of chronic plaque psoriasis (Figure 1, Table II) suggests the following treatment recommendations:[29-33]

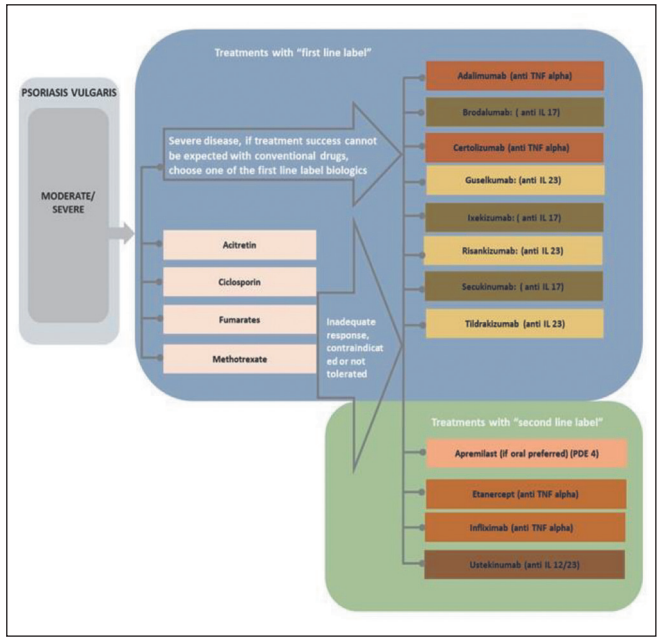

Figure 1.—Overview of treatment options for plaque type psoriasis as approved by European Medical Agency.

TABLE II.—*Wording of recommendations.*[29-33]

Strength	Wording	Symbols	Implications
Strong recommendation **for** the use of an intervention	"We recommend …"	↑↑	We believe that all or almost all informed people would make that choice. Clinicians will have to spend less time on the process of decision-making, and may devote that time to overcome barriers to implementation and adherence. In most clinical situations, the recommendation may be adopted as a policy
Weak recommendation **for** the use of an intervention	"We suggest …"	↑	We believe that most informed people would make that choice, but a substantial number would not. Clinicians and health care providers will need to devote more time on the process of shared decision-making. Policy makers will have to involve many stakeholders and policy making requires substantial debate
No recommendation with respect to an intervention	"We cannot make a recommendation with respect to …"	0	At the moment, a recommendation in favor or against an intervention cannot be made due to certain reasons (*e.g.* no reliable evidence data available, conflicting outcomes, etc.)
Weak recommendation **against** the use of an intervention	"We suggest against …"	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not
Strong recommendation **against** the use of an intervention	"We recommend against …"	↓↓	We believe that all or almost all informed people would make a choice against that intervention. This recommendation can be adopted as a policy in most clinical situations

We **recommend** taking efficacy and safety (see Cochrane Review[34] and drug chapters), time until onset of treatment response, comorbidities (see decision grids, section Guidance for specific clinical and comorbid situations), and individual patient factors into account when choosing a systemic treatment for moderate or severe psoriasis	↑↑	STRONG CONSENSUS# 100% Agreement EVIDENCE AND CONSENSUS BASED SEE EVIDENCE TO DECISION FRAMEWORK (APPENDIX 1 OF GL REPORT)
We **recommend** the initiation of systemic treatment in patients with moderate to severe (see also section "Defining disease severity") psoriasis*	↑↑	
For most patients who require systemic treatment, we **recommend** the initiation of 'conventional' systemic agents as first line treatment	↑↑	
In case of severe disease, where a sufficient treatment success cannot be expected with the use of a conventional treatment, the initiation of a biologic with a first line label* is **suggested** as a first line treatment	↑	
We **recommend** the initiation of a biologic if conventional systemic agents were inadequate in response, are contraindicated or not tolerated	↑↑	
We **suggest using** apremilast if an oral treatment is desired and "conventional" systemic agents were inadequate in response or if they are contraindicated or not tolerated	↑	

Due to personal-financial conflict of interest 3 abstentions; *UV therapy is not part of this guideline but it is recommended as an alternative induction therapy if suitable; ^ "First line label" refers to the therapeutic indication as approved by the European Medical Agency.

The EuroGuiDerm guideline for the systemic treatment of chronic plaque psoriasis development group considers the time a treatment has been available a relevant factor when considering different treatment options. Information on rare side effects and long-term safety data generally become more robust over time. Table III provides a general overview and summarizes how long the respective treatments have been in clinical use for psoriasis in Europe. The time for medications licensed before the joint EMA approval process may differ between the different countries. It is important to keep in mind that not only the date of availability is important for this but also the number of patients treated with the drug over time ('patient years').

TABLE III.—*Overview on how long each treatment option has been in clinical use for psoriasis in Europe.*

Treatment	In clinical use for psoriasis since
Conventional systemic agent	
Acitretin	>25 years
Ciclosporin	>25 years
Fumaric acid esters	>25 years (in Germany)
Dimethylfumarate	2017 in Europe
Methotrexate	>25 years
TNF-α inhibitors	
Etanercept	2004
Infliximab	2005
Adalimumab	2007 Plaque Psoriasis
Certolizumab-pegol	Since 2018 (use in other indications notably earlier: 2009)
Anti-IL-12/23p40	
Ustekinumab	2009
Anti-IL-17	
Secukinumab	2015
Ixekizumab	2016
Brodalumab	2018
Anti-IL-23p19	
Guselkumab	2017
Tildrakizumab	2018
Risankizumab	2019
Small molecules	
Apremilast	2015

Guideline text and recommendations: conventional systemic therapy

Acitretin

The Instructions for use of acitretin are reported in Table IV and the recommendations for laboratory controls[18, 35, 36] in Table V.

Adverse drug reactions

Please see SmPC for complete listing. The guideline subcommittee decided to comment on the following aspects.

In children treated with acitretin, it is advisable to monitor growth at regular intervals.

Hypertriglyceridemia, as defined by a fasting triglyceride level of ≥1.7 mmol/L, is a common adverse effect of acitretin use. Dietary and lifestyle interventions including alcohol limitation and a low-fat and low-carbohydrate diet, are effective first-line management in reducing triglyceride levels.

Dryness of skin and mucosa can be improved by moisturizing the skin and using lubricating eye drops.

TABLE IV.—*Instructions for use (acitretin).*[18, 35]

Pre-treatment 100% Agreement #
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/Skindex-29 or -17) • History and clinical examination should focus on musculoskeletal problems. If patient reports complaints, further imaging investigation may be performed • Exclude pregnancy/breastfeeding: patient must be informed explicitly and extensively about the teratogenic risk of the medication, the necessity of effective long-term contraception (three years after cessation of treatment), and the possible consequences of becoming pregnant while taking retinoids; written documentation of this informational interview should be obtained • Note that during and up to three years after treatment, blood donation is not permitted • Laboratory parameters
During treatment
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/Skindex-29 or -17) • Take capsules with a meal containing some fat or with whole milk to improve absorption • In order to prevent elevation of serum lipids and liver enzymes, alcohol abstinence and a low-fat and low-carbohydrate diet are advised. • Preventing pregnancy is mandatory. After satisfactory contraception for at least one month prior to treatment, start treatment on second or third day of the menstrual cycle. Double contraception is recommended (*e.g.*, condom + pill; IUD/Nuvaring + pill; cave: no low-dosed progesterone preparations/mini-pills) during and up to three years after end of therapy; effectiveness of oral contraceptives is reduced by acitretin • Ask patient about spine and joint complaints at follow-up visits. If patient reports complaints, further imaging investigation may be performed • Laboratory parameters
Post-treatment
• Reliable contraception in women of child-bearing age for up to three years after therapy, double contraception, as described above, is recommended • Patients may not donate blood for up to three years after the discontinuation of therapy
Due to personal-financial conflict of interest 4 abstentions.

TABLE V.—*Recommended laboratory controls (acitretin).*

		Period in weeks		
Parameter	Pre-treatment	4	8	Every 12 weeks thereafter
Blood count*	x		x	x
Liver enzymes**	x	x	x	
Serum creatinine	x			
Pregnancy test (urine or blood)	x	Monthly, during treatment and up to 3 years after discontinuation		
Fasting blood glucose	x			
Fasting triglycerides, cholesterol, HDL	x	x		x

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure. The recommendations are based on clinical experience. No evidence is available.
*Hb, Hct, leucocytes, platelets; **transaminases (AST, ALT), alkaline phosphatase (AP), γGT.

It is important that patients be informed about the possibility of hair loss, as well as the reversibility of any retinoid-induced hair loss.[37, 38]

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Surgery

There is no need to discontinue or pause acitretin use in case of elective surgery.[39]

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

The absolute contraindications include:

• severe renal or hepatic dysfunction or hypertriglyceridemia;

• as there are many other treatment options available, women of child-bearing age should generally not be treated with acitretin. Breastfeeding is also an absolute contraindication;

• alcoholism;

- blood donation;
- diabetes mellitus;
- history of pancreatitis.[40]

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

The concomitant administration of methotrexate and antifungal imidazoles could induce liver toxicity; tetracycline could induce idiopathic intracranial hypertension; lipid-lowering drugs could Increase risk of myotoxicity; low-dose progesterone pills could have insufficient contraceptive effect.[41]

In Italy, women of childbearing age must comply with the prescriptions and regulations of the Pregnancy Prevention Program of the Italian Medicine Agency (AIFA) that is available on the web site for each medical preparation containing acitretin (https://www.codifa.it/farmaci)
They must sign an informed consent (Materiale_per_il_medico_03.09.2018.pdf that is available at the web pagehttps://www.aifa.gov.it/ricerca?q=acitretina) that describes the teratogenic risk of the drug and the need of an efficient contraception. In addition, both male and female patients should sign that they will take care that the drug is not used by third parties. Each prescription should not cover more than 30 days of therapy.
Finally, we strongly suggest taking into account the recommendations Pharmacovigilance Risk Assessment Committee (PRAC) (https://www.aifa.gov.it/documents/20142/516919/IT_Retinoids_09.02.2018.pdf)

Cyclosporine

The instructions for use of cyclosporin are reported in Table VI[18, 35] and the recommendations for laboratory controls[18, 35, 36] in Table VII.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

The rate of adverse effects generally demonstrated a clear dose and duration dependency. In case of short-term

TABLE VI.—*Instructions for use (cyclosporine).*

Pre-treatment 100% Agreement #
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/ Skindex-29 or -17) • History and clinical examination should focus on previous and concomitant diseases (*e.g.*, arterial hypertension; severe infections; malignancies, including cutaneous malignancies; renal and liver diseases) and concomitant medication (see drug interactions) • Measurement of the blood pressure on two separate occasions • Laboratory parameters (see Table VII) • Reliable contraception (caution: reduced efficacy of progesterone-containing contraceptives) • Regular gynecologic screening according to national guidelines, particularly for HPV genital infection • Consultation on vaccination; susceptibility to infections (take infections seriously, seek medical attention promptly); drug interactions (inform other treating physicians about therapy); avoidance of excessive sun exposure and use of sunscreens
During treatment
• During therapy with low dose ciclosporin (CsA; 2.5 to 3 mg/kg daily), follow-up intervals may be extended to two months or more. Shorter intervals may be needed in patients with risk factors, after dose increases, or those who must take concomitant medications that are likely to contribute to adverse drug reactions. Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/Skindex-29 or -17) • Clinical examination should focus on status of skin and mucous membranes (hypertrichosis, gingival changes), signs of infections, gastrointestinal or neurological symptoms (tremor, dysesthesia), musculoskeletal/joint pain • Repeat recommendation for avoidance of excessive sun exposure and use of sunscreens • Check of concomitant medications • Measurement of blood pressure • Laboratory parameters (see Table VII) • Reliable contraception • Regular gynecologic screening according to national guidelines, particularly for HPV genital infection • If creatinine is significantly elevated and/or patient on therapy for >1 year, perform creatinine clearance (or creatinine-EDTA clearance where available). • Determination of the CsA level is recommended in selected cases
Post-treatment
• After discontinuation of CsA, patients should be followed up for skin cancer, especially in case of extensive prior therapeutic or natural UV exposure.

Due to personal-financial conflict of interest 3 abstentions.

Table VII.—*Recommended laboratory controls (cyclosporine).*

	Period in weeks				
Diagnostics	Pre-treatment	4	8	12	16, thereafter every 4-8 weeks
Full blood count [a]	x	x	x	x	x
Liver enzymes [b]	x	x	x	x	x
Sodium, potassium	x	x	x	x	x
Serum creatinine	x	x	x	x	x
Urine status	x	x			x
Uric acid	x	x	x	x	x
Pregnancy test (urine or blood) [c]	x				
Cholesterol, triglycerides	x [d]		x		x
Magnesium [e]	x		x		x
HBV	x				
HIV	x				

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs. The recommendations are based on clinical experience. No evidence is available.
[a] Erythrocytes, leucocytes, platelets; [b] transaminases (AST, ALT), AP, γGT, bilirubin; [c] pregnancy test is recommended as it is important to know if a patient is pregnant when starting a systemic treatment; [d] recommended two weeks before and on the day of treatment initiation (fasting); [e] only with indication (muscle cramps).

treatment, the adverse effects are generally reversible after drug withdrawal. In case of long-term treatment (*i.e.* over two years), kidney abnormalities may be irreversible.[38]

Kidney abnormalities

The most frequent and clinically relevant reported adverse effects include increment of serum creatinine, urea nitrogen and uric acid due to a reduced glomerular filtration rate and consequently creatinine clearance. Arterial hypertension could be also reported because of vasoconstriction of renal arteries. In case of long term CsA treatment the most clinically relevant adverse effect is the impairment of renal function. In particular, kidney abnormalities follow a pattern of increasing severity from elevation of serum creatinine, reduction of the glomerular filtration rate to structural damage such as interstitial fibrosis, tubular atrophy and glomerular sclerosis.

Malignancies

As with other immunosuppressive therapies, CsA carries an increased risk of developing lymphoproliferative disorders and other malignant tumors, especially of the skin. The incidence of malignancies appears to be dependent primarily on the degree and duration of immunosuppression and on other preceding or concomitant therapies, such as photochemotherapy or MTX. Patients must be monitored carefully following long-term therapy with CsA. An increased risk of skin cancer, especially squamous cell carcinomas, has been observed in patients with psoriasis who have received long-term photochemotherapy (high cumulative doses of PUVA, >1000 J/cm^2). Moreover, nodal or cutaneous B- and T-cell lymphomas and HPV-associated carcinoma have been reported in psoriasis patients treated with CsA.

Infections

As with other immunosuppressive therapies, CsA may increase the risk of various bacterial, parasitic, viral and fungal infections, as well as the risk of infections with opportunistic pathogens. Although CsA has some inhibitory effects on HCV replication, it should be considered with caution in patients with HCV, HBV as well as HPV infection. Infections deserve special attention as possible trigger factors for psoriasis relapse. Patients in whom an infection-triggered exacerbation of psoriasis is probable should first be treated with appropriate therapy for the infection, followed by a re-examination of the indication for CsA.

Others

Gingival hyperplasia and hypertrichosis are described in less than 15% of patients. Paresthesias, more commonly as burning sensations in the hands and/or feet, tremors and muscle cramps likely related to decreased serum Mg. CsA should be used with more caution in obese elderly persons because the risk of developing renal failure increases with age and obesity.

Special consideration during treatment

Surgery

Consider discontinuing CsA for one week prior to elective surgery.[39]

Measuring CsA blood levels

When treating patients with psoriasis, it is generally not necessary to measure CsA blood levels. An assay may be performed to obtain information about drug intake (in case of a discrepancy between [higher] doses and clinical response or discrepancy between [lower] doses and occurrence of ADR) or with the simultaneous intake of drugs that might influence CsA levels. In case drug levels are measured, C2 (post two hours) monitoring is the best predictor of exposure to CsA.

Measuring glomerular filtration rate

A periodic measurement of GFR is the most accurate method to assess renal tolerance under long-term or repeated treatments.

Duration of treatment

Most physicians consider CsA suitable as a short-term induction therapy only. Due to its possible adverse drug reactions during long term use and in light of many other treatment options, long term treatment for psoriasis of more than two years is usually avoided.

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

The absolute contraindications include the following:

- impaired renal function;
- insufficiently controlled arterial hypertension;
- severe infectious disease;
- history of malignancy (possible exceptions: treated basal cell carcinoma, history of squamous carcinoma *in situ*);
- current malignancy;
- simultaneous PUVA therapy or extensive previous UV exposure with high risk of cutaneous malignancy;
- severe hepatic diseases (*e.g.* liver failure);
- breastfeeding.[42]

Drug interactions

Please see SmPC and other sources for complete listing. There is the potential for multiple drug reactions, compared to other anti-psoriatic systemic agents. The guideline subcommittee decided to comment on the following aspects.

The availability of CsA depends primarily on the activity of two molecules – the hepatic enzyme cytochrome P450-3A4 (CYP3A4), which is involved in its metabolism, and the intestinal P-glycoprotein, an ATP-dependent transporter protein that transports various drugs, among them CsA, from the enterocytes back into the intestinal lumen. The activities of these molecules may both vary for genetic reasons and be influenced by drugs and herbal substances. Above all, modulators and substrates of CYP3A4 are relevant for therapeutic practice.[40]

CsA levels are increased by (CYP3A inhibition)

Calcium antagonists, amiodarone, macrolide antibiotics, aminoglycoside antibiotics, tetracyclines, quinolones, imidazoles antimycotics, oral contraceptives, androgenic steroids, danazol, allopurinol, bromocriptine, methylprednisolone (high doses), ranitidine, cimetidine, metoclopramide, propafenone, protease inhibitors (*e.g.*, saquinavir), acetazolamide, amikacin, statins (above all atorvastin and simvastatin because of increased risk of myopathies), cholic acids and derivatives (ursodeoxycholic acids), grapefruit juice.

CsA levels are decreased by (CYP3A induction)

Carbamazepine, phenytoin, barbiturates, metamizole, rifampicin, octreotide, ticlopidine, nafcillin, probucol, troglitazone, intravenously administered sulfadimidine and trimethoprim, St John's wort.

Other interactions

- Aminoglycosides, amphotericin B, trimethoprim and sulfamethoxazole, vancomycin, ciprofloxacin, acyclovir, melphalan, NSAIDs possibly reinforce nephrotoxic effects;
- increased risk of a gingival hyperplasia with the simultaneous intake of nifedipine;
- increased immunosuppression risk with simultaneous treatment with other immunosuppressive agents;
- CsA may reduce the effect of progesterone-containing contraceptives;
- during CsA therapy, an increased plasma level of some drugs including digoxin, colchicine, corticosteroids, statins and NSAIDs could occur as a result of reduced clearance.

Overdose/measures in case of overdose

Determine CsA blood level, interrupt CsA, determine vital parameters, liver, renal values, electrolytes and if needed, introduce additional measures (including consultation with other specialists).

Fumarates

The instructions for use of fumareates are reported in Table VIII. Dimethyl fumarate (DMF) is a pro-drug for oral administration; the active in vivo moiety is monomethylfumarate.[43] For the treatment of psoriasis, a drug containing DMF is registered in Europe (Skilarence®) and a mixture of DMF and three salts of ethylhydrogenfumarates (Fumaderm®) is registered in Germany only. Further reference is for the DMF drug with European label. Recommended laboratory controls (dimethyl fumarate) are reported in Table IX.

In Italy, Fumaderm® is not approved for prescription.
In Italy, Skilarence® is the only registered drug containing DMF.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Gastrointestinal complaints, mainly diarrhea and increased stool frequency (which occur in up to 60% of patients) and flush symptoms are the most frequent ADR during treatment with DMF.

Leukocytopenia, lymphocytopenia, and eosinophilia can be observed during therapy with DMF. An increase in eosinophils is temporary and is usually observed between weeks four and ten of treatment. Occasionally, proteinuria occurs during DMF therapy, but disappears after dose reduction or cessation of treatment (Table X).

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

TABLE VIII.—*Instructions for use (dimethyl fumarate).*

Pre-treatment 100% Agreement #
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/Skindex-29 or -17) • History and clinical examination • Reliable contraception • Laboratory parameters (see Table IX)
During treatment
• Objective assessment of the disease (such as PASI/BSA/PGA) • HRQoL (such as DLQI/Skindex-29 or -17) • Clinical examination • Reliable contraception • Laboratory parameters (see Table IX)
Post-treatment
• None

Due to personal-financial conflict of interest 2 abstentions.

TABLE IX.—*Recommended laboratory controls (dimethyl fumarate).*

	Period in months	
Parameter	Pre-treatment	Every 3 months
Blood count*	x	x
Liver enzymes	x	x
Serum creatinine	x	x
Urine status	x	x
Pregnancy test (urine or blood)	x	

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure. The recommendations are based on clinical experience. No evidence is available.
*If leukocytes are <3000/μL DMF therapy must be stopped. If lymphocytes are <1000/μL and >700/μL monthly monitoring is required. If lymphocytes remain below 700/μL at two consecutive visits DMF treatment must be stopped. Analysis should include platelets and eosinophils.

TABLE X.—*Overview of important side effects of fumarates.*

Very frequent	Diarrhea, flush, mild leukopenia, and lymphopenia (approx. 50% of patients)
Frequent	Abdominal cramps, flatulence, severe lymphocytopenia (approx. 3% of patients), transient eosinophilia
Occasional	Nausea, dizziness, headache, fatigue, proteinuria, increase in serum creatinine, increase in liver enzymes
Rare	Allergic skin reaction
Very rare	None

Gastrointestinal tolerance may be improved by taking the tablets after a meal. The administration of acetylsalicylic acid can help to decrease flush symptoms.

The dose of DMF can be adjusted to the individual effective dose ranging from the minimum available dose 30 mg/day to the maximum dose as per label 720 mg/day. In general, it is recommended to follow the dose titration schedule until clinical response and subsequently adjust the dose individually.

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

ABSOLUTE CONTRAINDICATIONS

• Severe disease of the gastrointestinal tract including liver and/or the kidneys;
• pregnancy or breastfeeding (lack of clinical experience).

Relative contraindications

Hematological disease.

Drug interactions

There are no known drug interactions with DMF. Because fumarates may impair renal function, drugs with known nephrotoxic potential should not be used concomitantly.

Overdose/measures in case of overdose

None.

Methotrexate (MTX)

Instructions for use of MTX are reported in Table XI. MTX should be preferentially given subcutaneously once weekly for increased safety (oral intake has higher risk for overdosing as patients are more likely to take tablets daily instead of once weekly) and improved bioavailability (MTX is a prodrug that is polyglutamylated into its active *in-vivo* moiety). The recommended initial and maintenance dose is usually 15 mg MTX once weekly. In case of insufficient response, the dose can be increased up to 20 mg MTX once weekly. A further increase up to 25 mg MTX is only beneficial for a small subgroup of patients. Subcutaneous dosing is recommended in patients with suboptimal response to oral treatment and may be considered as the starting route of administration in high need patients. Recommended laboratory controls for MTX are reported in Table XII.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Table XI.—*Instructions for use (MTX).*

Pre-treatment 100% Agreement #
• History and clinical examination • Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/Skindex-29 or -17) • Laboratory parameters (see Table X) • Chest X-ray • Reliable contraception in women of child-bearing age (starting after menstruation), and also in men • If abnormalities in liver screening are found, refer patient to specialist for further evaluation
During treatment
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/Skindex-29 or -17) • Check concomitant medications • Clinical examination • Laboratory controls (see Table X) • Reliable contraception in women of child-bearing age, and also in men • 5 mg folic acid once weekly 24 hours after MTX • Advise alcohol abstinence
Post-treatment
• Women should be advised not to become pregnant for at least six month and men must not conceive for at least three months thereafter*

*EMA recommends 6 months as a means of precaution, the practice of the guideline group differs from this; # due to personal-financial conflict of interest 2 abstentions.

The two most important ADR associated with MTX therapy are myelosuppression and hepatotoxicity. Alcohol consumption, obesity, hepatitis, and diabetes mellitus increase the risk of hepatotoxicity.

In fact, most causes of death due to MTX are the result of bone marrow suppression. Informing patients about the early symptoms of pancytopenia (dry cough, nausea,

Table XII.—*Recommended laboratory controls (MTX).*

	Period in weeks/months			
Parameter [a]	Pre-treatment	Within two weeks	During first two months, 1x every 4 weeks	Thereafter, every 3 months
Blood count	x	x	x	x
Liver enzymes [b]	x		x	x
Serum creatinine	x		x	x
Urine status	x			
Pregnancy test (urine or blood)	x			
HBV/HCV	x			
HIV	x			
Serum albumin [c]	x		x	x
PIIINP where available	x		Every 3 months [d]	

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure. The recommendations are based on clinical experience. No evidence is available.
[a] If blood leucocytes <3.0, neutrophils <1.0, thrombocytes <100, decrease the dose or discontinue the medication; [b] liver enzymes > 2-3x baseline values, initiate further diagnostics (including repeated testing/involve hepatologist) and consider decreasing the dose or discontinuing the medication; [c] in selected cases (e. g., in cases with suspected hypoalbuminemia or in patients using other drugs with high binding affinity for serum albumin); [d] in case of abnormal PIIINP during MTX treatment a hepatologist should be consulted.

fever, dyspnea, cyanosis, stomatitis/oral symptoms, and bleeding) may aid early detection.

Hypoalbuminemia and reduced renal function increase the risk of ADR. Special care should be taken when treating geriatric patients, in whom doses should usually be lower and kidney function monitored regularly. Nausea, malaise, hair loss are frequent side effects, whereas interstitial pneumonia, alveolitis are very rare.

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

In case of gastrointestinal complaints during MTX therapy drinking coffee and/or dark chocolate may be helpful in up to 30% of patients.[44]

Elderly patients

Special care should be taken when treating geriatric patients, in whom doses should usually be lower and kidney function monitored regularly.

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Absolute contraindications

- severe infections;
- severe liver disease;
- renal failure;
- pregnancy/breastfeeding;
- alcohol abuse;
- bone marrow dysfunction/hematologic changes;
- immunodeficiency;
- acute peptic ulcer;
- significantly reduced lung function.

Relative contraindications

- Kidney or liver disorders;
- old age;
- ulcerative colitis;
- history of hepatitis;
- lack of compliance;
- active desire to become pregnant (see pregnancy chapter);
- gastritis;
- obesity (BMI>30 kg/m^2);
- diabetes mellitus;
- previous malignancies (see also malignancy chapter).

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

A number of drugs, including salicylates, sulphonamides, diphenylhydantoin, and some antibiotics (*i.e.* penicillin, tetracyclines, chloramphenicol, trimethoprime), may decrease binding of MTX to serum albumin, thus raising the risk of MTX toxicity. Tubular secretion is inhibited by probenecid. Special care should be paid to patients who use azathioprine or retinoids simultaneously. Some NSAID may increase MTX levels and, consequently, MTX toxicity, especially when MTX is administered at high doses. As a result, it is recommended that NSAID be administered at different times of day than MTX. The question of whether folic acid reduces the efficacy of MTX remains controversial. There is some evidence that the combination of MTX and folic acid may reduce adverse reactions without affecting efficacy.[45-47] List of most important drugs with potential interactions with MTX are reported in Table XIII.

Overdose/measures in case of overdose

In MTX overdose, clinical manifestations of acute toxicity include myelosuppression, mucosal ulceration (particularly of the oral mucosa), and, rarely, cutaneous necrolysis. Relative overdose is usually precipitated by factors that interfere with MTX renal excretion or by drug interactions. Folinic acid is a fully reduced folate coenzyme that, after intracellular metabolism, can function in nucleic acid synthesis, thus bypassing the action of MTX. As the interval between MTX administration and the initiation of folinic acid increases, the efficacy of folinic acid as an antidote to hematological toxicity decreases.

Administer folinic acid (calcium leucovorin) immedi-

Table XIII.—*List of most important drugs with potential interactions (MTX).*

Drug	Type of interaction
Colchicines, CsA, NSAID, penicillin, probenecid, salicylates, sulfonamides	Decreased renal elimination of MTX
Chloramphenicol, co-trimoxazole, cytostatic agents, ethanol, NSAID, pyrimethamine, sulfonamides	Increased risk of bone marrow and gastrointestinal toxicity
Barbiturates, co-trimoxazole, phenytoin, probenecid, NSAID, sulfonamides	Interaction with plasma protein binding
Ethanol, leflunomide, retinoids, tetracyclines	Increased hepatotoxicity

ately at 20 mg (or 10 mg/m^2) intravenously or intramuscularly. Subsequent doses should be given at six-hour intervals either parenterally or orally.

Guideline text and recommendations: biologicals and small molecules

Adalimumab

The Instructions for use of adalimumab are reported in Table XIV[48] and the recommended laboratory controls in Table XV.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

In placebo-controlled trials, injection-site reactions (erythema, itching, pain, swelling, hemorrhage) were the most frequently reported ADR, occurring in 14% of patients treated with adalimumab compared to 8% of patients receiving placebo. The use of adalimumab can be associated with infectious adverse effects. These consisted primarily of upper respiratory tract infections, bronchitis, and urinary tract

TABLE XIV.—*Instructions for use (adalimumab).*[48]

Pre-treatment 100% Agreement #

• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI/Skindex-29 or -17)
• History and clinical examination should focus on prior exposure to treatments, malignancies, infections, congestive heart failure (CHF) and neurological disease or symptoms
• Recommended measures include:
  • Check for skin cancer
  • Check for lymphadenopathy
  • Laboratory parameters (see Table XIII)
  • Exclusion of tuberculosis (see tuberculosis chapter)
  • Check for evidence of active infection
  • Check need for vaccinations
• Reliable contraception

During treatment

• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI/Skindex-29 or -17)
• Clinical examination should focus on malignancies, risk factors for serious infections, congestive heart failure, and neurological symptoms
• Recommended measures include:
  • Check for skin cancer
  • Check for lymphadenopathy
  • Laboratory parameters (see Table XIII)
• Reliable contraception

Post-treatment
• After discontinuation of adalimumab, patients should be followed up with medical history and physical examination • For information on continued necessity of contraception or management in case of desire to become pregnant immediately after treatment cessation, please see chapter "wish for child / pregnancy"

Due to personal-financial conflict of interest 3 abstentions.

TABLE XV.—*Recommended laboratory controls (adalimumab).*

		Period in weeks		
Parameter	Pre-treatment	4	12	Thereafter, every 3-6 months
Full blood count	x	x	x	x
Liver enzymes	x	x	x	x
Serum creatinine	x			
Urine status	x			
Pregnancy test (urine or blood)	x			
CRP	x			
HBV/HCV	x			
HIV	x			
Interferon gamma release assay (TB exclusion)	x			

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure.
The recommendations are based on clinical experience. No evidence is available.

infections. More serious infections observed included infective endocarditis,[49] pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis. Adverse reactions of the hematologic system, including thrombocytopenia and leukopenia, have been infrequently reported with adalimumab. Other rare side effects of adalimumab are severe allergic reactions (rash, hives, itching, difficulty in breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue). Long-term data from global clinical trials are available and reported no new safety signals and a safety profile consistent with known information about the anti-TNF class.[50]

Treatment with adalimumab may result in the formation of autoantibodies and rarely in the development of lupus-like syndrome.[51-53]

Malignancies, especially lymphoma, associated with the use of adalimumab occur very rarely (see special considerations during treatment).[54-57] Side effects may be especially likely to occur in elderly patients, who are usually more sensitive than younger adults to the effects of adalimumab.

TNF-α-induced paradoxical psoriasis

TNF-α antagonists are effectively used in the field of inflammatory musculoskeletal, skin and bowel diseases. However, anti-TNF-α-induced cutaneous side effects are possible. Paradoxical reactions include the development of psoriasis, pustular psoriasis and psoriasiform lesions, reflecting an immunological paradox, as anti-TNF-α agents are used in the treatment of psoriasis. Psoriasis can be triggered in 1.5-5% under the use of anti-TNF-α agents. In 52% of the cases the appearance is a palmoplantar pustulosis, in 49% a plaque type and in 15% a guttata-type. A potential mechanism could be the increase of the interferon α production. These psoriasiform lesions can be managed by topical or systemic antipsoriatic-therapies and/or switching to another biological, preferably from a different class (Table XVI).[58-60] The overview of the most important side effects is reported in Table XVI.

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Surgery

There is little evidence on the effects of adalimumab in patients with psoriasis undergoing surgery. Studies in patients with rheumatoid arthritis suggest small increase in postoperative wound infections to even a reduction in case of continued treatment.[61, 62] For elective surgery it is conceivable to interrupt treatment prior to the procedure three to five half-lives, especially in patients with diabetes or other increased risk of infections.

Table XVI.—*Overview of important side effects50 (adalimumab).*

Very frequent	Injection-site reaction
Frequent	Infections
Occasional	Tuberculosis, reactivation of latent tuberculosis, heart failure
Rare	Allergic reactions, adverse reactions of the hematologic system, demyelinating diseases
Very rare	Autoantibodies, drug-induced lupus, malignancies

Infections

Monitoring measures during treatment should take into account that symptoms such as fever can be suppressed during anti-TNF therapy.

Combination of anti-TNF-α and MTX

Treatment with TNF-α antagonists and methotrexate can be combined. This may reduce the risk of antidrug antibodies formation.[63] This combination is particularly common for infliximab as the risk for the formation of antidrug antibodies formation is highest. The combination may lead to an increased risk of infection, especially when compared to MTX monotherapy, but data are still scarce[64] (see chapter: "Immunogenicity").

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Absolute contraindications

- Active tuberculosis or other severe infections such as sepsis, and/or opportunistic infections;
- congestive heart failure (NYHA class III/IV).

Relative contraindications

- Pregnancy/breastfeeding;
- latent tuberculosis;
- history of recurrent or severe infections, localized infections, conditions predisposing to infections;
- patients living in geographical areas where tuberculosis and histoplasmosis are widespread;

• psoriasis patients with concomitant systemic lupus erythematosus or multiple sclerosis (MS);
• PUVA>200 treatments (especially if followed by CsA use) (see chapter: "Cancer");
• malignancies and lymphoproliferative disorders (see chapter: "Malignancies").

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

There are no known interactions of adalimumab with the metabolism of other drugs. The combination of adalimumab with immunosuppressive drugs may enhance the risk of infection.

There is insufficient information regarding the concomitant use of adalimumab with other biological therapeutics used to treat the same conditions as adalimumab. The concomitant use of adalimumab with these biologics is not recommended because of the possibility of an increased risk of infection.

Overdose/measures in case of overdose

In case of overdose, the patient should be monitored, and appropriate symptomatic treatment should be instituted immediately.

In Italy, adalimumab is available as the originator drug Humira® (AbbVie, Lake Bluff, IL, USA) and some biosimilars.[48]
Healthcare offices of all Italian regions strongly support the use of biosimilars in all new patients. Italian dermatologists should always check relevant regulations at the regional level.

Apremilast

The instructions for use are reported in Table XVII and the recommendations for lab controls in Table XVIII.

Table XVII.—*Instructions for use (apremilast).*

Pre-treatment  #

• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI/Skindex-29 or -17)
• Medical history and physical examination including:
  • Check for skin cancer
  • Check for evidence of active and chronic infection
  • Check for contraception and breastfeeding
  • Check for need for vaccines (see "vaccination")
  • Check for hypersensitivity, metabolic, gastrointestinal and renal disorders/dysfunction and underweight
  • Check for depression, anxiety
  • Check for co-medication: CYP3A4 enzyme inducers
  • Laboratory parameters including pregnancy test (see Table XVI)

During treatment
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/ Skindex-29 or -17) • Medical history and physical examination focusing on malignancies, infections, contraception, depression and anxiety • Laboratory parameters only when indicated on medical history or physical examination • Reliable contraception
Post-treatment
• For information regarding the ongoing need for contraception immediately following treatment cessation, please see chapter "wish for child / pregnancy"

Due to personal-financial conflict of interest 4 abstentions.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Diarrhea and nausea

The most reported adverse reactions in Phase III clinical studies have been gastrointestinal (GI) disorders including diarrhea (15.7%) and nausea (13.9%). These GI adverse reactions were mostly mild to moderate in severity, with 0.3% of diarrhea and 0.3% of nausea reported as being severe. These adverse reactions generally occurred within the first 2 weeks of treatment and usually resolved within 4 weeks.[65]

Table XVIII.—*Recommended laboratory controls (apremilast).*

Parameter	Pretreatment	Only when indicated on medical history or physical examination
Blood count	x	(x)
ALT, AST	x	(x)
Serum creatinine/eGFR	x	(x)
Pregnancy test (urine or blood)	x	(x)
Hepatitis B and C	Optional	(x)
HIV	Optional	(x)

Not all tests may be necessary for all patients. Medical history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risks and exposure. The recommendations are based on clinical experience. No evidence is available.

Body weight loss

Patient weight was measured routinely in clinical studies. The mean observed weight loss in patients treated for up to 52 weeks with apremilast was 1.99 kg. A total of 14.3% of patients receiving apremilast had observed weight loss between 5-10% while 5.7% of the patients receiving apremilast had observed weight loss greater than 10%. None of these patients had overt clinical consequences resulting from weight loss. A total of 0.1% of patients treated with apremilast discontinued due to adverse reaction of weight decreased.[65] The weight of underweight patients should be monitored from start of treatment. In case of inexplicable and significant weight loss discontinuation of treatment should be considered.

Risk of infection

Phase II/III studies reported more upper respiratory infections with apremilast compared to placebo.[66-68] There are no reactivations of tuberculosis or opportunistic infections reported.[66-69] Screening for latent tuberculosis was not required before enrolment in the randomized clinical trials; however, a history of incompletely treated tuberculosis was an exclusion criterion.[66-69]

Depression and suicidal behaviour

Some patients may experience psychiatric symptoms with apremilast, including depression and suicidal thoughts. Stop treatment if patients have new psychiatric symptoms or if existing symptoms worsen (see chapter: "Depression").

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Surgery

There is no evidence to date that continuous treatment with apremilast will lead to perioperative complications. Patients who need minor surgical treatments including dental treatments and skin surgery, may continue apremilast treatment. In the case of major surgery, the decision of apremilast withdrawal should be taken case-by-case considering patient characteristics, the risk of infection, the risk of psoriasis worsening after counselling with the surgeon.

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Absolute contraindications

- Pregnancy or breast-feeding;
- severe acute infections.

Relative contraindications

- Galactose intolerance, lactase deficiency or glucose-galactose malabsorption;
- malignancies or lymphoproliferative disorders.
- severe impairment of renal function (eGFR less than <30 mL/min);
- major depression and suicidal ideation;
- anorexia.

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Co-administration of strong cytochrome P450 3A4 (CYP3A4) enzyme inducer including rifampicin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of apremilast.[70] Therefore, the use of strong CYP3A4 enzyme inducers including rifampicin, phenobarbital, carbamazepine, phenytoin with apremilast is not recommended. There was no clinically meaningful drug-drug interaction with ketoconazole, methotrexate and oral contraceptives.[70]

Overdose/measures in case of overdose

In case of an overdose, it is recommended that the patient is monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment is instituted.[65]

Brodalumab

The instructions for brodalumab use are reported in Table XIX and the recommendations for lab controls in Table XX.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Current evidence suggests a similar safety profile for brodalumab compared to other IL-17 antagonists ixeki-

Table XIX.—*Instructions for use (brodalumab).*

Pretreatment 100% Agreement #

• Objective assessment of disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI/Skindex-29 or -17)
• Medical history and physical examination including prior exposure to treatments, malignancies, infections, inflammatory bowel disease, depression and/or suicidal ideation or behaviour
• Recommended measures include:
  • check for skin cancer
  • check for lymphadenopathy
  • laboratory parameters (Table XVIII)
  • exclusion of tuberculosis (see chapter: "tuberculosis")
  • check for evidence of active infection
  • check need for vaccines
• Reliable contraception

During treatment
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI, Skindex-29 or 17) • Laboratory controls (Table XVIII) • Medical history and physical examination focusing on infections (in particular upper respiratory tract infections, candida, tuberculosis), contraception, symptoms of depression and/or suicidal behaviour and signs or symptoms of inflammatory bowel disease
Post-treatment
• After discontinuation of brodalumab, patients should be followed up with medical history and physical examination • For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter: "Wish for child/pregnancy"

#Due to personal-financial conflict of interest 4 abstentions.

Table XX.—*Recommended laboratory controls (brodalumab).*

Parameter	Pretreatment	After 3-6 months
Full blood count	x	x
Liver enzymes	x	x
Serum creatinine	x	
Urine status	x	
Pregnancy test (urine or blood)	x	
CRP	x	
HBV/HCV	x	
HIV	x	
Interferon gamma release assay (TB exclusion)	x	

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure. The recommendations are based on clinical experience. No evidence is available.

zumab and secukinumab. Serious infections, candidiasis, and neutropenia are considered adverse events of interest.

Common adverse events (occurring in ≥1/100 to <1/10 of patients) include influenza, tinea infections (including tinea pedis, tinea versicolor, tinea cruris), neutropenia, headache, orophageal pain, diarrhea, nausea, arthralgia, myalgia, fatigue and injection site reactions. A 120-week follow-up of a phase III trial (AMAGINE 2) with 1790 patients receiving brodalumab or ustekinumab or placebo with subsequently brodalumab, showed a comparable safety profile as the first year of the study. Among the most frequent treatment emergent adverse events in all brodalumab treatment groups throughout the duration of the study were arthralgia, headache, diarrhea, oropharyngeal pain, and *Candida* species infections. In this study 168 patients received brodalumab 210 Q2W during the entire 120-week period and in whom showed 319.7 AEs per 100 PY, and 8.8 SAEs per 100 PY.[71] Five-year safety data are available from an open label extension of a Phase II trial with 181 patients and showed one or more SAEs in 29 (16%) patients. The only SAE reported by more than one patient was myocardial infarction (3 patients; 1.7%).[72]

Neutropenia

The exposure adjusted event rates of neutropenia per 100 patient-years of exposure to brodalumab 210 mg Q2W through week 52 were 0.3 in the AMAGINE-2 Study and 0.3 in the AMAGINE-3 Study. The cases of neutropenia were not associated with serious infections, and most cases were mild (absolute neutrophil count, >1000 per cubic

millimeter), transient and reversible. No cases of thrombocytopenia were reported.[71, 73]

Suicidal ideation and behaviour

During the clinical development program for psoriasis, four events of suicide (one of which was later adjudicated as indeterminate) and ten attempts of suicide/suicidal behaviour were reported in phase II and III trials amongst 4464 patients with a total treatment duration of 9161.8 patient years of brodalumab exposure.[74] The follow-up time-adjusted incidence rates of SIB events were comparable between the brodalumab and ustekinumab groups throughout the 52-week controlled phases (0.20 *vs.* 0.60 per 100 patient-years).[73]

The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour and a causal association between treatment with brodalumab and increased risk of suicidal ideation and behaviour has not been established.[74-76]

On the other hand, of patients treated 12 weeks with brodalumab 210 mg 67% showed improvement of symptoms of depression and anxiety while approximately 20% showed a worsening of these symptoms.[74] The risk and benefit of treatment with brodalumab should be carefully weighed for patients with a history of depression and/or suicidal ideation or behaviour, or for patients who develop such symptoms. During treatment patients should be monitored for the emergence or worsening of depression, suicidal ideation, anxiety, or other mood changes. If a patient suffers from new or worsening symptoms of depression and/or suicidal ideation or behaviour is identified, it is recommended to discontinue treatment with brodalumab.

Candidiasis

Related to the mechanism of action of brodalumab higher rates of fungal infections, primarily non-serious skin and mucosal *Candida* infections are observed. Early treatment of *Candida* infections, either with topical or systemic treatment (Table XXI)[77-79] is recommended. Cases are usually described as mild-to-moderate, respond to standard treatment and do not require brodalumab treatment discontinuation. Note that clinically significant, severe infections are always a contraindication for all biologics. The fluconazole treatment recommendations are reported in Table XXI.[77-79]

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Surgery

There is no data on the management of surgery in patients treated with brodalumab. The decision to discontinue brodalumab prior to surgery must be based on individual factors, such as type and risk of surgical procedure, patient characteristics, severity of psoriasis in case of treatment discontinuation etc. Counselling with the surgeon is advised.

Inflammatory bowel disease

There is limited data in patients with IBD. Patients with a known history of Crohn's disease were excluded from phase III clinical trials. One case of Crohn's disease was reported in a patient who received various doses of brodalumab throughout the study. Caution is advised in prescribing brodalumab in patients with a history of IBD.[48, 73]

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Absolute contraindications

- Clinically important active infections.

Table XXI.—*Fluconazole treatment recommendations.*[77-79]

Candidiasis	Fluconazole dose (mg)	Duration
Oropharyngeal	100–200 daily	7–14 days
Esophageal		
Acute	200–400 daily	14–21 days
Recurrent	100–200	Three times weekly
Balanoposthitis	200	14 days
Vulvovaginal		
Acute	150	Single dose
Severe acute	150	Every 72 hours for a total of 2–3 doses
Recurring	150	Induction therapy by a topical agent or oral fluconazole, thereafter weekly for 6 months

Relative contraindications

- Depression and history of suicidal behaviour;
- pregnancy or breastfeeding;
- inflammatory bowel disease.

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

No drug interactions expected. Combination therapy with other immunosuppressant agents has not been studied.

Overdose/measures in case of overdose

No cases of overdose have been reported. Doses of up to 700 mg have been administered in clinical studies. In case of overdose, the patient should be monitored, and appropriate symptomatic treatment should be instituted immediately.

Certolizumab–pegol

The Instructions for Certolizumab–pegol use are reported in Table XXII and the recommendations for laboratory controls in Table XXIII.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Most evidence for adverse drug reactions to certolizumab–pegol are derived from studies on rheumatoid arthritis. Specific studies on psoriasis[80, 81] show a safety profile comparable to etanercept (12 weeks) and a safety profile that was consistent with the therapeutic class of TNF-α inhibitors for psoriasis up to 48 weeks. These data are de-

Table XXII.—*Instructions for use (certolizumab–pegol).*

Pretreatment  #

• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI/Skindex-29 or -17)
• History and clinical examination should focus on prior exposure to treatments, malignancies, infection, congestive heart failure, and neurological symptoms
• Recommended measures include:
  • check for malignancy, mainly skin cancer, and premalignant lesions
  • check for lymphadenopathy
  • laboratory parameters (Table XXI)
  • exclusion of tuberculosis (see chapter: "Tuberculosis")
  • check for evidence of active infections
  • check need for vaccinations
• Discuss contraception (see pregnancy: "Wish for child/pregnancy")

During treatment
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL such as (DLQI/Skindex-29 or -17) • Clinical examination should focus on lymphadenopathy, malignancies, especially skin cancer, premalignant lesions, risk factors for serious infections, congestive heart failure, and neurological symptoms • Recommended measures include: • laboratory parameters (Table XXI) • Discuss contraception (see chapter: "Wish for child/ pregnancy")
Post-treatment
• After discontinuation of certolizumab–pegol, patients should be followed up with medical history and physical examination • For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter: "Wish for child/pregnancy"

#Due to personal-financial conflict of interest 3 abstentions.

Table XXIII.—*Recommended laboratory controls (certolizumab–pegol).*

Parameters	Period in weeks			
	Pretreatment	4	12	Thereafter, every 3-6 months
Full blood count	x	x	x	x
Liver enzymes	x	x	x	x
Serum creatinine	x			
Urine status	x			
Pregnancy test (urine or blood)	x*			
CRP	x			
HBV/HCV	x			
HIV	x			
Interferon gamma release assay (TB exclusion)	x			

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure. The recommendations are based on clinical experience. No evidence is available.
*Pregnancy test is recommended as it is important to know if a patient is pregnant when starting a systemic treatment. Certolizumab is the suggested biologic treatment option, for women who are planning conception or are pregnant and require a systemic therapy.

rived from 234 (CIMPASI-1),[80] 227 (CIMPASI-2)[80] and 559 patients (CIMPACT).[81] Most common adverse drug reactions consisted of nasopharyngitis, upper respiratory tract infections, and headache. No opportunistic infections were reported. Serious infections were rare.

In line with the other TNF-α-inhibitors and the SmPC the following adverse events can be expected. Viral and bacterial infections are common. Serious bacterial infections (sepsis), tuberculosis or fungal infections are uncommon.

Special attention is needed for non-melanoma skin cancer (NMSC) as psoriasis patients are more at risk for NMSC,[82] particularly in case of prior phototherapy. For more detailed information see chapter: "Malignancies." Other malignancies, especially lymphoma, associated with the use of certolizumab–pegol are uncommon. Other rare side effects of certolizumab–pegol are severe allergic reactions and lupus-like syndrome.

Other

As a class, TNF inhibitors may be associated with the development or worsening of demyelinating diseases and multiple sclerosis (see respective chapters).

TNF blockers are contraindicated in patients with severe heart failure (NYHA class III or IV), and patients with less severe disease should be monitored carefully and undergo regular monitoring by a cardiologist (see respective chapters).

TNF-α-induced paradoxical psoriasis

TNF-α antagonists are effectively used in the field of inflammatory musculoskeletal, skin and bowel diseases. However, anti-TNF-α-induced cutaneous side effects are possible. Paradoxical reactions include the development of psoriasis, pustular psoriasis and psoriasiform lesions, reflecting an immunological paradox, as anti-TNF-α agents are used in the treatment of psoriasis. Psoriasis can be triggered in 1.5-5% under the use of anti-TNF-α agents. In 52% of the cases the appearance is a palmoplantar pustulosis, in 49% a plaque type and in 15% a guttata-type. A potential mechanism could be the increase of the interferon alpha production. These psoriasiform lesions can be managed by topical or systemic antipsoriatic-therapies and/or switch to another biological, preferably from a different class.[55-57] The overview of important side effects are reported in Table XXIV.

Table XXIV.—*Overview of important side effects (certolizumab).*

Very frequent	Injection-site reaction
Frequent	Infections
Occasional	Tuberculosis, reactivation of latent tuberculosis, heart failure
Rare	Allergic reactions, adverse reactions of the hematologic system, demyelinating diseases
Very rare	Autoantibodies, drug-induced lupus, malignancies

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Surgery

There is little evidence on the effects of certolizumab in patients with psoriasis undergoing surgery. For the group of TNF-α antagonist in general, studies in rheumatoid arthritis patients suggest a small increase in postoperative wound infections to even a reduction in case of continued treatment.[58, 59] For elective surgery it is conceivable to interrupt treatment prior to the procedure three to five half-lives, especially in patients with diabetes or other increased risk of infections.

Infections

Corresponding monitoring measures during treatment should take into account that symptoms such as fever can be suppressed during anti-TNF therapy.

Combination of TNF and MTX

A treatment with TNF-α antagonists and methotrexate can be combined. This may reduce the risk of formation of antidrug antibodies.[63] This combination is particularly common for infliximab as the risk for the formation of antidrug antibodies formation is highest. The combination may lead to an increased risk of infection, especially when compared to MTX monotherapy, but data is still scarce.[64]

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Absolute contraindications

- Active tuberculosis or other severe infections such as sepsis, and opportunistic infections;
- congestive heart failure (NYHA class III/IV).

Relative contraindications

- Latent tuberculosis;

• history of recurrent or severe infections, localized infections, conditions predisposing to infections;
• patients living in geographical areas where tuberculosis and histoplasmosis are widespread;
• psoriasis patients with concomitant systemic lupus erythematosus or multiple sclerosis;
• PUVA>200 treatments (especially if followed by CsA use) (see chapter: "Cancer");
• malignancies and lymphoproliferative disorders (see chapter: "Malignancies").

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

The combination of cetolizumab–pegol with immunosuppressive drugs may enhance the risk of infection. There is insufficient information regarding the concomitant use of certolizumab–pegol with other biological therapeutics used to treat the same conditions. The concomitant use of certolizumab–pegol with these biologics is not recommended because of the possibility of an increased risk of infection.

Overdose/measures in case of overdose

No dose-limited toxicity was observed in clinical trials. Repeated subcutaneous study injections of 800 mg have been given.

Etanercept

The instructions for etanercept use are reported in Table XXV and the recommendations for laboratory controls in Table XXVI.

Table XXV.—*Instructions for use (etanercept).*

Pretreatment 100% Agreement #

• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI/Skindex-29 or -17)
• History and clinical examination should focus on prior exposure to treatments, malignancies, infection, congestive heart failure, and neurological symptoms
• Recommended measures include:
  • check for malignancy, mainly skin cancer, and premalignant lesions
  • check for lymphadenopathy
  • laboratory parameters (Table XXIV)
  • exclusion of tuberculosis (see chapter: "Tuberculosis")
  • check for evidence of active infection
  • check need for vaccinations
• Reliable contraception

During treatment
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL such as (DLQI/Skindex-29 or -17) • Clinical examination should focus on lymphadenopathy, malignancies, especially skin cancer, premalignant lesions, risk factors for serious infections, congestive heart failure, and neurological symptoms • Recommended measures include: • laboratory parameters (Table XXIV) • Reliable contraception
Post-treatment
• After discontinuation of etanercept, patients should be followed up with medical history and physical examination • For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter: "Wish for child/pregnancy"

#Due to personal-financial conflict of interest 4 abstentions.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Analysis of results from two major North-American

Table XXVI.—*Recommended laboratory controls (etanercept).*

Parameters	Period in weeks			
	Pretreatment	4	12	Thereafter, every 3-6 months
Full blood count	x	x	x	x
Liver enzymes	x	x	x	x
Serum creatinine	x			
Urine status	x			
Pregnancy test (urine or blood)	x			
CRP	x			
HBV/HCV	x			
HIV	x			
Interferon gamma release assay (TB exclusion)	x			

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure. The recommendations are based on clinical experience. No evidence is available.

studies that followed up 506 patients up to four years showed no increase in the incidence of malignancies or infections among psoriasis patients treated with etanercept compared to patients receiving placebo and/or to the general population,[83] and a low risk of serious infection of 0.9 per 100 patient-years.[84] Of note, no case of lymphoma or of tuberculosis was reported, and major cardiovascular events were very rare.

As a class, TNF blockers may be associated with the development or worsening of demyelinating diseases and multiple sclerosis. Infliximab and etanercept have been associated with worsening of pre-existing heart failure, and accordingly TNF blockers are contraindicated in patients with severe heart failure (NYHA class III or IV), and patients with less severe disease should be monitored carefully and undergo regular monitoring by a cardiologist.

Although antinuclear antibodies (ANA) and, to a lesser extent, antidouble strand (ds) DNA antibodies may develop during the use of TNF antagonists (between 10 and 70% for etanercept in patients with RA and 18% in psoriasis patients),[83, 85] they are often of IgM isotype and disappear after discontinuation of therapy, while clinical autoimmune manifestations, notably drug-induced lupus, remain very rare.

TNF-α-induced paradoxical psoriasis

TNF-α antagonists are effectively used in the field of inflammatory musculoskeletal, skin and bowel diseases. However, anti-TNF-α-induced cutaneous side effects are possible. Paradoxical reactions include the development of psoriasis, pustular psoriasis and psoriasiform lesions, reflecting an immunological paradox, as anti-TNF-α agents are used in the treatment of psoriasis. Psoriasis can be triggered in 1.5-5% under the use of anti-TNF-α agents. In 52% of the cases the appearance is a palmoplantar pustulosis, in 49% a plaque type and in 15% a guttata-type. A potential mechanism could be the increase of the interferon alpha production. These psoriasiform lesions can be managed by topical or systemic antipsoriatic-therapies and/or switch to another biological, preferably from a different class (Table XXVII).[55-57] An overview of the important side effects are reported in Table XXVII.

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Table XXVII.—*Overview of important side effects.*

Very frequent	Injection-site reaction
Frequent	Infections
Occasional	Tuberculosis, reactivation of latent tuberculosis, heart failure
Rare	Allergic reactions, adverse reactions of the haematologic system, demyelinating diseases
Very rare	Autoantibodies, drug-induced lupus, malignancies

Surgery

There is little evidence on the effects of etanercept in patients with psoriasis undergoing surgery. Studies in patients with rheumatoid arthritis suggest a small increase in postoperative wound infections to even a reduction in case of continued treatment. For elective surgery it is conceivable to interrupt treatment prior to the procedure three to five half-lives, especially in patients with diabetes or other increased risk of infections.

Infections

Corresponding monitoring measures during treatment should take into account that symptoms such as fever can be suppressed during anti-TNF therapy.

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Absolute contraindications

- Active tuberculosis or other severe infections such as sepsis, and opportunistic infections;
- congestive heart failure (NYHA class III/IV).

Relative contraindications

- Pregnancy/breastfeeding;
- latent tuberculosis;
- history of recurrent or severe infections, localized infections, conditions predisposing to infections;
- PUVA>200 treatments (especially if followed by CsA use) – see also chapter: "Cancer;"
- demyelinating disease;
- malignancies or lymphoproliferative disorders (see chapter: "Malignancies").

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

There are no known interactions of etanercept with the metabolism of other drugs. The combination of etanercept with immunosuppressive drugs may enhance the risk of infection. The combination of etanercept and anakinra has been associated with an increased risk of serious infections and neutropenia and has not demonstrated increased clinical benefit. The concurrent administration of etanercept and abatacept did not demonstrate an increased clinical benefit. On the contrary, there was an increased incidence of SAE. The concomitant use of etanercept with these biologics is not recommended because of the possibility of an increased risk of infection.

Overdose/measures in case of overdose

No dose-limited toxicity was observed in clinical trials with patients suffering from RA. Intravenous administration of 32 mg/m² was the highest examined dose, followed by subcutaneous injections of 16 mg/m² twice weekly (BIW). There is no known antidote for etanercept.[86]

In Italy, Etanercept is available as the originator drug Enbrel® (Pfizer Inc., Brooklyn, NY, USA) and some biosimilars.
Healthcare offices of all Italian Regions strongly support the use of biosimilars in all new patients.
Italian dermatologists should always check relevant regulations at the regional level.

Guselkumab

The instructions for guselkumab use are reported in Table XXVIII and the recommendations for laboratory controls in Table XXIX.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Overall, guselkumab was well tolerated in clinical trials in psoriasis. The most reported adverse drug reactions were upper respiratory tract infections, and, less frequently, gastroenteritis, herpes, headache, diarrhea, urticaria and arthralgias. Less than 1% of injections led to usually mild or moderate injection site reaction such as erythema.

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Table XXVIII.—*Instructions for use (guselkumab).*

Pretreatment  #

• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI, Skindex-29 or 17)
• Medical history and physical examination including prior exposure to treatments, malignancies, infections
• Recommended measures include:
  • check for skin cancer
  • check for lymphadenopathy
  • laboratory parameters (Table XXVII)
  • exclusion of tuberculosis (see chapter: "Tuberculosis")
  • check for evidence of active infection
  • check need for vaccines
• Reliable contraception

During treatment
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI, Skindex-29 or 17) • Laboratory controls (Table XXVII) • Medical history and physical examination including infections, including monitoring signs and symptoms of tuberculosis • Reliable contraception
Post-treatment
• After discontinuation of guselkumab, patients should be followed up with medical history and physical examination • For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter: "Wish for child/pregnancy"

#Due to personal-financial conflict of interest 4 abstentions.

Table XXIX.—*Recommended laboratory controls (guselkumab).*

Parameters	Period in weeks/months	
	Pretreatment	Thereafter, every 3-6 months
Full blood count	x	x
Liver enzymes	x	x
Serum creatinine	x	
Urine status	x	
Pregnancy test (urine or blood)	x	
CRP	x	
HBV/HCV	x	
HIV	x	
Interferon gamma release assay (TB exclusion)	x	

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics must be considered. Further specific testing may be required according to clinical signs, risk, and exposure. The recommendations are based on clinical experience. No evidence is available.

Surgery

The overall risk of infections in patients treated with anti-IL-23 antibodies (for example the rate of serious infections observed per 100 patient-years of exposure in clinical trials in psoriasis) appears to be comparable to that of other classes of targeted therapies in psoriasis; however, specific infections related to the mechanism of action, such as an increased tuberculosis risk with TNF inhibitors and an increased risk of mucocutaneous *Candida* infections with IL-17 inhibitors have not been reported for anti-IL-23 antibodies. There is only limited data available on the management of surgery in patients receiving anti-IL-23 treatment. The decision to interrupt guselkumab treatment prior to surgery must be based on individual factors, such as type and risk of surgical procedure, patient characteristics, individual infection risk etc. In case of continuing treatment, the procedure is best placed between two doses.

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Absolute contraindications

- Clinically relevant active infections such as active tuberculosis.

Relative contraindications

- Acute, recurrent or chronic infections;
- pregnant or breastfeeding woman (due to lack of experience in humans).

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Combination therapy with immunosuppressants, including biologics, or phototherapy have not been evaluated.

Overdose/measures in case of overdose

In clinical trials single guselkumab doses of up to 10 mg/kg bodyweight have been administered intravenously and up to 300 mg subcutaneously with no observation of toxic effects. In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

Infliximab

The instructions for infliximab use are reported in Table XXX[87, 88] and the recommendations for laboratory controls in Table XXXI.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Key safety considerations for infliximab include common side effects (mainly infections and infusion reactions), as well as rare but important side effects, such as opportunistic infections, particularly tuberculosis. The relationship between infliximab and some other significant events that have been observed infrequently during treatment, including cases of severe liver toxicity, lymphoma or other malignancy, or congestive heart failure is less clear and therefore increased caution is recommended.

Table XXX.—*Instructions for use (infliximab).*[87, 88]

Pretreatment — 100% Agreement [#]

• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI/Skindex-29 or -17)
• History focusing on prior exposure to treatments. History and clinical examination should focus on malignancies, infection, congestive heart failure, and neurological symptoms
• Recommended measures include:
  • check for skin cancer
  • check for lymphadenopathy
  • laboratory parameters (Table XXIX)
  • exclusion of tuberculosis (see chapter: "Tuberculosis")
  • check for evidence of active infection
  • check need for vaccinations
• Reliable contraception

During treatment

• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI/ Skindex-29 or -17)
• Clinical examination should focus on malignancies, risk factors for serious infections, congestive heart failure, and neurological symptoms
• Recommended measures include:
  • check for skin cancer
  • check for lymphadenopathy
  • laboratory parameters (Table XXIX)
• Reliable contraception

Post-treatment
• After discontinuation of infliximab, patients should be followed up with medical history and physical examination • For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter: "Wish for child/pregnancy"
[#]Due to personal-financial conflict of interest 3 abstentions.

TABLE XXXI.—*Recommended laboratory controls (infliximab).*

Parameters	Period in weeks			
	Pretreatment	2	6	Thereafter, prior to each infusion
Full blood count	x	x	x	x
Liver enzymes	x	x	x	x
Serum creatinine	x			
Urine status	x			
Pregnancy test (urine or blood)	x			
CRP	x	x	x	x
HBV/HCV	x			
HIV	x			
Interferon gamma release assay (TB exclusion)	x			

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure. The recommendations are based on clinical experience. No evidence is available.

Infusion reactions

In clinical trials, infusion reactions (defined as any adverse event occurring during or within one hour after completion of the infusion) were the most common reasons for discontinuation of therapy. Infusion reactions were seen in approximately 18% of infliximab-treated patients in phase III clinical trials *vs.* approximately 5% of patients receiving placebo. Most infusion reactions were mild to moderate, and included symptoms such as flushing, pruritus, fever or chills, headache, and urticaria. Severe infusion reactions, such as anaphylactic reactions, convulsions, erythematous rash and serum-sickness-like delayed-type hypersensitivity reactions (myalgia, arthralgia and/or exanthema occurring between one and 14 days after infusion) occurred in ~1% of patients. One percent of infusions were accompanied by cardiopulmonary reactions, primarily chest pain, hypotension, hypertension or dyspnea. Approximately 3% of patients discontinued infliximab because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion.

If mild to moderate infusion reactions occur, treatment can usually be continued after decreasing the infusion rate or temporarily stopping the infusion. In these cases, pretreatment with oral antihistamines, paracetamol/acetaminophen, and/or corticosteroids should be considered for future infusions.

Infections

Infections are the most common serious adverse event described in spontaneous post-launch reports. Tuberculosis, bacterial infections (including sepsis and pneumonia), invasive fungal, viral, and other opportunistic infections have been observed in patients receiving infliximab. Some infections have been fatal; the most frequently reported opportunistic infections with a mortality rate of >5% include pneumocystis, candidiasis, listeriosis and aspergillosis. In all completed clinical trials with infliximab, 36.4% of patients in the placebo groups (N.=1600; average weeks of follow-up: 29.0) and 52.0% of patients in the infliximab groups (N.=5706; average weeks of follow-up: 45.5) experienced more than one infection (Centocor, Inc., Horsham, PA, USA; data on file, module 2.7.4 summary of clinical safety) (Psoriasis BLA, 2006; Pages 207, 209, 219). Serious infections were seen in 2% of placebo-treated and in 4% of infliximab-treated patients, the difference being due mainly to a higher rate of pneumonia and abscesses among patients receiving infliximab.

Antinuclear antibodies and skin symptoms reminiscent of cutaneous lupus erythematosus

Approximately half of patients treated with infliximab may develop ANA that are frequently of transient nature. Anti-dsDNA antibodies were newly detected in approximately one-fifth of infliximab-treated patients compared with 0% of placebo-treated patients. These autoantibodies are usually of low titer and mostly not associated with clinical symptoms. Treatment can be continued in patients with newly developed ANA without associated symptoms. The formation of autoantibodies has been associated in less than 1% of cases with the onset of symptoms reminiscent of lupus erythematosus, which are almost always confined to the skin. In such patients it is recommended to discontinue infliximab treatment.

TNF-α-induced paradoxical psoriasis

TNF-α antagonists are effectively used in the field of inflammatory musculoskeletal, skin and bowel diseases.

Table XXXII.—*Overview of important side effects (infliximab).*

Very frequent	Infusion reaction
Frequent	Infections
Occasional	Tuberculosis, reactivation of latent tuberculosis, heart failure
Rare	Allergic reactions, adverse reactions of the hematologic system, demyelinating diseases
Very rare	Autoantibodies, drug-induced lupus, malignancies

However, anti-TNF-α-induced cutaneous side effects are possible. Paradoxical reactions include the development of psoriasis, pustular psoriasis and psoriasiform lesions, reflecting an immunological paradox, as anti-TNF-α agents are used in the treatment of psoriasis. Psoriasis can be triggered in 1.5-5% under the use of anti-TNF-α agents. In 52% of the cases the appearance is a palmoplantar pustulosis, in 49% a plaque type and in 15% a guttata-type. A potential mechanism could be the increase of the Interferon alpha production. These psoriasiform lesions can be managed by topical or systemic antipsoriatic-therapies and/or switch to another biological, preferably from a different class (Table XXXII).[55-57] The overview of important side effects is reported in Table XXXII.

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Surgery

In the absence of controlled studies, the decision on how to manage anti-TNF therapy during surgery will be primarily based on individual factors such as activity of underlying disease, individual infection risk, reason for, type and risk of surgical procedure etc. While in many patients, minor surgical procedures may be carried out without interrupting anti-TNF therapy but with intensified prophylaxis and monitoring for pre- and peri-operative infections, treatment may be halted for some weeks in others. Elective surgery may best be placed between two infliximab infusions given at eight weeks intervals. In addition, an increased risk for infusion reaction may have to be considered when infusions are paused and restarted.

Infections

Monitoring measures during treatment should take into account that symptoms such as fever can be suppressed during anti-TNF therapy.

Combination of TNF and MTX

A treatment with TNF-α antagonists and methotrexate can be combined. This may reduce the risk of formation of antidrug antibodies.[63] This combination is particularly common for infliximab as the risk for the formation of antidrug antibodies formation is highest. The combination may lead to an increased risk of infection, especially when compared to MTX monotherapy, but data is still scarce[64] (see chapter: "Immunogenicity").

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Absolute contraindications

- Active tuberculosis or other severe infections such as sepsis, and opportunistic infections;
- active chronic hepatitis B;
- congestive heart failure (NYHA class III/IV);
- hypersensitivity to infliximab, murine proteins or any component of the formulation.

Relative contraindications

- Pregnancy or breastfeeding;
- demyelinating diseases;
- latent tuberculosis;
- history of recurrent or severe infections, localized infections, conditions predisposing to infections;
- patients living in geographical areas where tuberculosis and histoplasmosis are widespread;
- psoriasis patients with concomitant systemic lupus erythematosus or multiple sclerosis;
- PUVA>200 treatments (especially if followed by CsA use) (see chapter: "Cancer");
- malignancies or lymphoproliferative disorders (see chapter: "Malignancies");
- hepatobiliary disorders.

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

There are no known interactions of infliximab with the metabolism of other drugs. The combination of infliximab with immunosuppressive drugs may enhance the risk of infection.[64] The combination with PUVA

therapy might enhance the risk for skin cancer development.

There is insufficient information regarding the concomitant use of infliximab with other biological therapeutics used to treat the same conditions as infliximab. The concomitant use of infliximab with these biologics is not recommended because of the possibility of an increased risk of infection.

In Italy, infliximab is available as the originator drug Remicade® (Schering-Plough, Kenilworth, NJ, USA) and a some biosimilars.
Healthcare offices of all Italian Regions strongly support the use of biosimilars in all new patients.
Italian dermatologists should always check relevant regulations at the regional level.

Ixekizumab

The instructions for ixekizumab use are reported in Table XXXIII and the recommendations for lab controls in Table XXXIV.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Common adverse events (occurring in ≥10% of patients) include injection site reactions, upper airway infections. Adverse events (occurring in 1-10% of patients) include oropharyngeal pain, nausea, tinea infections, mucocutaneous herpes simplex.

Injection site reactions

The most frequent injection site reactions observed were erythema and pain. These reactions were predominantly mild to moderate in severity and did not lead to discontinuation of ixekizumab.[89]

Table XXXIII.—*Instructions for use (ixekizumab).*

Pretreatment  #

• Objective assessment of disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI/Skindex-29 or -17)
• Medical history and physical examination including prior exposure to treatments, malignancies, infection, inflammatory bowel disease
• Recommended measures include:
  • check for skin cancer
  • check for lymphadenopathy
  • laboratory parameters (Table XXXII)
  • exclusion of tuberculosis (see chapter tuberculosis)
  • check for evidence of active infection
  • check need for vaccines
• Reliable contraception

During treatment
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI, Skindex-29 or 17) • Laboratory parameters (Table XXXII) • Medical history and physical examination focusing on infections (in particular upper respiratory tract infections, candida, tuberculosis), contraception, signs or symptoms of inflammatory bowel disease
Post-treatment
• After discontinuation of ixekizumab, patients should be followed up with medical history and physical examination • For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter: "Wish for child/pregnancy"

#Due to personal-financial conflict of interest 3 abstentions.

Infections

In the placebo-controlled period of the phase III clinical studies in plaque psoriasis, infections were reported in 27.2% of patients treated with ixekizumab for up to 12 weeks compared with 22.9% of patients treated with placebo.

The majority of infections were non-serious and mild

Table XXXIV.—*Recommended laboratory controls (ixzekizumab).*

	Period in weeks/months	
Parameter	Pretreatment	After 3-6 months
Full blood count	X	X
Liver enzymes	X	X
Serum creatinine	X	
Urine status	X	
Pregnancy test (urine or blood)	X	
CRP	X	
HBV/HCV	X	
HIV	X	
Interferon gamma release assay (TB exclusion)	X	

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure. The recommendations are based on clinical experience. No evidence is available.

to moderate in severity, most of which did not necessitate treatment discontinuation. Serious infections occurred in 13 (0.6%) of patients treated with ixekizumab and in three (0.4%) of patients treated with placebo. Over the entire treatment period, infections were reported in 52.8% of patients treated with ixekizumab (46.9 per 100 patient years). Serious infections were reported in 1.6% of patients treated with ixekizumab (1.5 per 100 patient years).

Laboratory assessment of neutropenia and thrombocytopenia

In plaque psoriasis studies, 9% of patients receiving ixekizumab developed neutropenia. In most cases, the blood neutrophil count was ≥1000 cells/mm^3. Such levels of neutropenia may persist, fluctuate or be transient. 0.1% of patients receiving ixekizumab developed a neutrophil count <1000 cells/mm^3. In general, neutropenia did not require discontinuation of ixekizumab. 3% of patients exposed to ixekizumab had a shift from a normal baseline platelet value to <150,000 platelet cells/mm^3 to ≥75,000 cells/mm^3. Thrombocytopenia may persist, fluctuate or be transient.

Inflammatory bowel disease

Cases of new or exacerbations of Crohn's disease and ulcerative colitis have been reported. Caution should be exercised when prescribing ixekizumab to patients with inflammatory bowel disease, including Crohn's disease and ulcerative colitis, and patients should be monitored closely.

Candidiasis

Related to the mechanism of action of ixekizumab higher rates of fungal infections, primarily non-serious skin and mucosal *Candida* infections are observed. Early treatment of *Candida* infections, either with topical or systemic treatment (Table XXI) is recommended. Treatment with IL-17 inhibitors is associated with increased risk of infection, particularly by mucocutaneous and cutaneous candidiasis. Cases are usually described as mild-to-moderate, respond to standard treatment (Table XXI) and do not require treatment discontinuation. Note that clinically significant, severe infections are always a contraindication for all biologics.

Special consideration during treatment

Please see SmPC and other sources for complete listing.[90] The guideline subcommittee decided to comment on the following aspects based on references.[90-94]

Surgery

There is no data on the management of surgery in patients treated with ixekizumab. The decision to discontinue ixekizumab prior to surgery must be based on individual factors, such as type and risk of surgical procedure, patient characteristics, severity of psoriasis in case of treatment discontinuation etc. Counselling with the surgeon is advised.

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Absolute contraindications

- Clinically important active infections.

Relative contraindications

- Pregnancy or breastfeeding;
- inflammatory bowel disease.

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

In plaque psoriasis studies, the safety of ixekizumab in combination with other immunomodulatory agents or phototherapy has not been evaluated.

No interaction was seen when ixekizumab was administered concomitantly with methotrexate (MTX) and/or corticosteroids in patients with psoriatic arthritis.

Overdose/measures in case of overdose

Doses up to 180 mg have been administered subcutaneously in clinical trials without dose-limiting toxicity. Overdoses up to 240 mg, subcutaneously, as a single administration in clinical trials, have been reported without any serious adverse events. In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

Risankizumab

The instructions for risankizumab use are reported in Table XXXV and the recommendations for laboratory controls in Table XXXVI.[95]

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Most reported adverse drug reactions were upper respiratory tract infections, including nasopharyngitis, rhinitis, pharyngitis, sinusitis, and tonsillitis.

Injection-site reactions include erythema, pain, pruritus, reaction, swelling, hematoma, and hemorrhage.

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

SURGERY

There is only limited data available on the management of surgery in patients receiving anti-IL-23 treatment. The decision of interrupting risankizumab treatment prior to surgery must be based on individual factors, such as type and risk of surgical procedure, patient characteristics, individual infection risk etc. In case of continuing treatment, the procedure is best placed between two doses.

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.[95]

ABSOLUTE CONTRAINDICATIONS

- Clinically important active infections.

TABLE XXXV.—*Instructions for use (risankizumab).*

Pretreatment 100% Agreement #

• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI, Skindex-29 or 17)
• Medical history and physical examination including prior exposure to treatments, malignancies, infections
• Recommended measures include:
  • Check for skin cancer
  • Check for lymphadenopathy
  • Laboratory parameters (see Table XXXIV)
  • Exclusion of tuberculosis (see chapter: "tuberculosis")
  • Check for evidence of active infection
  • Check need for vaccines
• Reliable contraception

During treatment
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI, Skindex-29 or 17) • Laboratory parameters (see Table XXXIV) • Medical history and physical examination including infections, including monitoring signs and symptoms of tuberculosis • Reliable contraception
Post-treatment
• After discontinuation of risankizumab, patients should be followed up with medical history and physical examination • For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter "wish for child/pregnancy"

#Due to personal-financial conflict of interest 4 abstentions.

RELATIVE CONTRAINDICATIONS

- Acute, recurrent or chronic infections;
- pregnancy or breastfeeding.

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

TABLE XXXVI.—*Recommended laboratory controls (risankizumab).*[95]

	Period in weeks/months	
Parameter	Pretreatment	Thereafter, every 3-6 months
Full Blood count	x	x
Liver enzymes	x	x
Serum creatinine	x	
Urine status	x	
Pregnancy test (urine or blood)	x	
CRP	x	
HBV/HCV	x	
HIV	x	
Interferon gamma release assay (TB exclusion)	x	

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics must be considered. Further specific testing may be required according to clinical signs, risk, and exposure. The recommendations are based on clinical experience. No additional evidence available.

Combination therapy with immunosuppressants, including biologics, or phototherapy have not been evaluated.[95, 96]

Overdose/measures in case of overdose

In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.[95]

Secukinumab

The instructions for secukinumab use are reported in Table XXXVII and the recommendations for laboratory controls in Table XXXVIII.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Infections

In the placebo-controlled period of clinical studies in plaque psoriasis infections were reported in 28.7% of patients treated with secukinumab and 18.9% of patients with placebo. Most cases of infection were mild or moderate upper respiratory tract infections which did not require treatment discontinuation. Mucosal or cutaneous candidiasis were more frequent with secukinumab. Cases responded to standard treatment and did not require treatment discontinuation.[97]

Neutropenia

Neutropenia is a rare adverse effect. The exposure-adjusted incidence rate per 100 patient-years for neutropenia with secukinumab treatment was 0.3% in a total of 5181 patients from plaque psoriasis clinical trials representing secukinumab exposures of 10,416.9 patient-years. Grade 3 neutropenia (defined as an absolute neutrophil count between 1.0 and 0.5×109/L) was reported in 0.6% patients and grade 4 neutropenia (defined as an absolute neutrophil count of less than 0.5×109/L) was reported in 0.04% patients with no dose dependency or temporal relationship to infection in most cases. Most cases of neutropenia were mild, transient and reversible. In contrast to ixekizumab, thrombocytopenia has not been reported.[98]

Table XXXVII.—*Instructions for use (secukinumab).*

Pretreatment  #

• Objective assessment of disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI/Skindex-29 or -17)
• Medical history and physical examination including prior exposure to treatments, malignancies, infections, inflammatory bowel disease
• Recommended measures include:
  • Check for skin cancer
  • Check for lymphadenopathy
  • Laboratory parameters (Table XXXVI)
  • Exclusion of tuberculosis (see chapter: "tuberculosis")
  • Check for evidence of active infection
  • Check need for vaccines
• Reliable contraception

During treatment
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI, Skindex-29 or 17) • Laboratory parameters (see Table XXXVI) • Medical history and physical examination focusing on infections (in particular upper respiratory tract infections, candida, tuberculosis), contraception, signs or symptoms of inflammatory bowel disease
Post-treatment
• After discontinuation of secukinumab, patients should be followed up with medical history and physical examination • For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter "wish for child / pregnancy"

#Due to personal-financial conflict of interest 4 abstentions.

Table XXXVIII.—*Recommended laboratory controls (secukinumab).*

	Period in weeks/months	
Parameter	Pretreatment	After 3-6 months
Full blood count	X	X
Liver enzymes	X	X
Serum creatinine	X	
Urine status	X	
Pregnancy test (urine or blood)	X	
CRP	X	
HBV/HCV	X	
HIV	X	
Tuberculosis	X	

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure. The recommendations are based on clinical experience. No evidence is available.

Crohn's disease

The effect of secukinumab on Crohn's disease was studied in a randomized placebo-controlled proof-of-concept trial.[99, 100] Secukinumab 2×10 mg/kg was administered i.v. on day one and day 22. The study was prematurely discontinued due to lack of effect. Four of 39 patients reported exacerbations of Crohn's disease. In the phase III psoriasis clinical trial program, three cases of Crohn's disease were reported as serious adverse events out of which two were exacerbations of pre-existing disease.[101] In patients with psoriasis and Crohn's disease caution, should be exercised and alternative biologicals may be considered before using secukinumab.

Candidiasis

Related to the mechanism of action of secukinumab, higher rates of fungal infections, primarily non-serious skin and mucosal *Candida* infections are observed. Early treatment of *Candida* infections, either with topical or systemic treatment (Table XXI) is recommended. Cases are usually described as mild-to-moderate, respond to standard antifungal therapy and do not require treatment discontinuation. Note that clinically significant, severe infections are always a contraindication for all biologics.

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Surgery

Real life data on perioperative management of secukinumab has not yet become available. However, there is no evidence to date that continuous treatment with secukinumab will lead to perioperative complications. Patients who need minor surgical treatments including dental treatments and skin surgery, may continue secukinumab treatment. In the case of major surgery, the decision of secukinumab withdrawal should be taken case-by-case considering patient characteristics, the risk of infection, the risk of psoriasis worsening and after counselling with the surgeon.

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Absolute contraindications

- Clinically important active infections

Relative contraindications

- Pregnancy or breastfeeding;
- inflammatory bowel disease.

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Combinations of secukinumab with other immunosuppressive agents (except for methotrexate)[97] or phototherapy have not been studied.

IL-17 has no direct effect on CYP450 expression. The anti-inflammatory effect of secukinumab may influence CYP450 levels and therefore might interact with the doses of CYP450 dependent medication, especially those with a narrow therapeutic range such as warfarin.[97] Therapeutic monitoring of such drugs should be considered while starting secukinumab.

Overdose/measures in case of overdose

No cases of overdose have been reported. Doses of up to 30 mg/kg have been administered in clinical studies. In case of overdose, the patient should be monitored, and appropriate symptomatic treatment be instituted immediately.

Tildrakizumab

The instructions for tildrakizumab use are reported in Table XXXIX and the recommendations for laboratory controls in Table XL.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

During the placebo-controlled phase of clinical studies, all types of infections were low and equal to placebo[102] as well as exposure-adjusted incidence rates of severe infections, malignancies, confirmed extended MACEs, and hypersensitivity reactions over 148 weeks.[103]

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Surgery

Due to the specific mechanism of action of tildrakizumab, IL23p19 inhibition, the probability of wound healing disorders occurring is low. Patients undergoing surgery should be closely screened for infections and it is recommended to schedule operations so that they do not fall within the period of the next tildrakizumab dose.

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Absolute contraindications

- Clinically important active infections.

Relative contraindications

- Acute, recurrent or chronic infections;
- pregnancy/breastfeeding.

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Tildrakizumab is cleared by general protein catabolism processes with no contribution of cytochrome P450 enzymes, and it is not eliminated by renal or hepatic pathways. Therefore, tildrakizumab does not affect the pharmacokinetics of concomitant medications metabolised by CYP enzyme.[104]

Overdose

Doses up to 10 mg/kg intravenously have been safely administered in clinical trials.[104]

Table XXXIX.—*Instructions for use (tildrakizumab).*

Pretreatment 100% Agreement #

• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI, Skindex-29 or 17)
• Medical history and physical examination including prior exposure to treatments, malignancies, infections
• Recommended measures include:
  • Check for skin cancer
  • Check for lymphadenopathy
  • Laboratory parameters (Table XXXVIII)
  • Exclusion of tuberculosis (see chapter: "tuberculosis")
  • Check for evidence of active infection
  • Check need for vaccines
• Reliable contraception

During treatment
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI, Skindex-29 or 17) • Laboratory parameters (see Table XXXVIII) • Medical history and physical examination including infections, including monitoring signs and symptoms of tuberculosis • Reliable contraception
Post-treatment
• After discontinuation of tildrakizumab, patients should be followed up with medical history and physical examination • For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter: "Wish for child/pregnancy"
#Due to personal-financial conflict of interest 4 abstentions.

Ustekinumab

The instructions for ustekinumab use are reported in Table XLI[105] and the recommendations for laboratory controls in Table XLII.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Table XL.—*Recommended laboratory controls (tildrakizumab).*

	Period in weeks/months	
Parameter	Pretreatment	Thereafter, every 3-6 months
Full blood count	x	x
Liver enzymes	x	x
Serum creatinine	x	
Urine status	x	
Pregnancy test (urine or blood)	x	
CRP	x	
HBV/HCV	x	
HIV	x	
Interferon gamma release assay (TB exclusion)	x	

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics must be considered. Further specific testing may be required according to clinical signs, risk, and exposure. The recommendations are based on clinical experience. No evidence is available.

TABLE XLI.—*Instructions for use (Ustekinumab).*[105]

Pretreatment 100% Agreement #

• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI, Skindex-29 or 17)
• Medical history and physical examination including prior exposure to treatments, malignancies, infections
• Recommended measures include:
  • Check for skin cancer
  • Check for lymphadenopathy
  • Laboratory parameters (see Table XL)
  • Exclusion of tuberculosis (see chapter: "tuberculosis")
  • Check for evidence of active infection
  • Check need for vaccines
• Reliable contraception

During treatment
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI, Skindex-29 or 17) • Laboratory parameters (see Table XL) • Medical history and physical examination including infections, including monitoring signs and symptoms of tuberculosis • Reliable contraception
Post-treatment
• After discontinuation of ustekinumab, patients should be followed up with medical history and physical examination • For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter "wish for child/pregnancy"
#Due to personal-financial conflict of interest 3 abstentions.

Infections

Placebo-controlled studies of patients with psoriasis or psoriatic arthritis demonstrate a similar incidence of infections including serious infections between ustekinumab-treated and placebo-treated patients with no relationship between incidence of infections and dose of ustekinumab received. No patient with latent tuberculosis who received antibiotic prophylaxis prior to ustekinumab treatment developed tuberculosis.

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Surgery

No recommendation exists in the SmPC regarding surgery in patients treated with ustekinumab. In case of major surgery with high risk of infectious complications, it seems prudent to withhold ustekinumab treatment 15 weeks before surgical intervention. Re-start treatment following surgery if wound healing is satisfactory and there is no evidence of infection.

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

Absolute contraindications

- Clinically important active infections.

Relative contraindications

- Acute, recurrent or chronic infections;
- pregnancy or breastfeeding;
- previous history of malignancies.

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

As IL-12 and IL-23 do not alter CYP 450 enzymes *in vitro*, no relevant interactions with drugs are expected with ustekinumab.

TABLE XLII.—*Recommended laboratory controls (ustekinumab).*

	Period in weeks/months	
Parameter	Pretreatment	Thereafter, every 3-6 months
Full blood count	x	x
Liver enzymes	x	x
Serum creatinine	x	
Urine status	x	
Pregnancy test (urine or blood)	x	
CRP	x	
HBV/HCV	x	
HIV	x	
Interferon gamma release assay (TB exclusion)	x	

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics must be considered. Further specific testing may be required according to clinical signs, risk, and exposure. The recommendations are based on clinical experience. No evidence is available.

Overdose/measures in case of overdose

Single doses of up to 6 mg/kg have been administered in clinical studies with no apparent toxicity.

Guideline text and recommendations: biosimilars

Biosimilars are defined as "a biological medicine that is similar to another biological medicine that has already been authorized for use. Biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies."[106] Biosimilars are developed to be similar to an existing biologic (the 'reference medicine'). They are not 100% identical but "essentially the same biological substance, though there may be minor differences due to their complex nature and production methods."[106] For etanercept and its biosimilar GP2015, multiple switches have been shown to not impact efficacy, safety and immunogenicity in patients with chronic plaque-type psoriasis.[107] At the time of preparing this guideline, biosimilars were available in Europe for adalimumab, etanercept and infliximab. The recommendations of this guideline apply equally to the originator and its biosimilar.

Guidance for specific clinical and comorbid situations

Psoriatic arthritis: how should psoriasis patients with concomitant psoriatic arthritis be managed?

We **recommend** interdisciplinary cooperation with a rheumatologist for the confirmation of the diagnosis of psoriatic arthritis and the selection of a suitable treatment whenever needed.	↑↑	STRONG CONSENSUS# 100% Agreement EXPERT CONSENSUS

#No abstentions due to personal-financial conflict of interest.

Treatments are usually categorized as NSAIDs (*e.g.*, diclofenac), conventional synthetic disease modifying anti rheumatic drugs (csDMARDs) *e.g.*, MTX, targeted synthetic (ts)DMARDS (*e.g.*, apremilast) and biological (b) DMARDs (*e.g.*, TNF-antagonists).

Head-to-head trials allowing direct comparison between the different groups or between the individual drugs are extremely rare. Indirect comparisons, *e.g.,* network meta-analyses, are limited by the low number of trials for psoriatic arthritis. Table XLIII summarize an overview of RCT data on psoriatic arthritis[108-111] (Dressler *et al.*[112] updated, see methods report).

Non-steroidal anti-inflammatory drugs (NSAIDs)

The role of NSAIDs is usually in the relief of symptoms of psoriatic arthritis for patients with mild and non-erosive articular as well as para-articular involvement. Treatment of NSAIDs should be limited to the lowest required dosage for the shortest period as needed.[113-115]

Conventional synthetic DMARDs (e.g., MTX)

We **recommend** starting a conventional synthetic DMARD (MTX) early to prevent progression of disease and erosive destruction of joints for patients with moderate to severe psoriasis and peripheral active joint involvement (PsA) despite the usage of NSAIDs, or glucocorticoid site injections if applicable and/or potential poor prognosis due to polyarthritis, increased inflammatory markers and erosive changes, and extra-articular musculoskeletal manifestations	↑↑	STRONG CONSENSUS# 100% Agreement EVIDENCE AND EXPERT CONSENSUS Table XLI

MTX is recommended, taking the label, the efficacy on skin and peripheral joints, the safety profile and the available long-term experience in the treatment of rheumatic joint disorders into to account.[113-115]

We **do not recommend** synthetic monotherapy DMARDs (MTX) for the treatment of axial involvement or enthesitis, as they appear to be not effective in these patients	↓↓	STRONG CONSENSUS# 100% Agreement EVIDENCE AND EXPERT CONSENSUS

Biological DMARDs

For inadequately responding patients after at least one synthetic DMARD, we **recommend** the use of biological DMARDs as monotherapy or in combination with synthetic DMARDs	↑↑	STRONG CONSENSUS# 100% Agreement EVIDENCE AND EXPERT CONSENSUS Table XLI
For the selection of a biological DMARD for patients with moderate to severe psoriasis of the skin and active joint involvement (PsA), we **recommend** taking aspects of efficacy with regard to skin and the joints, comorbidity, practicability and safety into account	↑↑	STRONG CONSENSUS# 100% Agreement EXPERT CONSENSUS

TABLE XLIII.—*Summary of the results for drugs approved for psoriasis of the skin and psoriatic arthritis (Dressler et al.*112 updated, see methods report).

	Patients achieving ACR20			Patients with at least one adverse event		
	RR	95% CI	Quality of the evidence (GRADE)	RR	95% CI	Quality of the evidence (GRADE)
Head-to-head comparisons						
ETA 50 mg + MTX *vs*. MTX 20 mg QW	1.28	1.11 to 1.48	Low	1.01	0.92 to 1.11	Moderate
INF 5 mg/kg W 0, 2, 6, 14 + MTX *vs*. MTX 15mg QW	1.40	1.07 to 1.84	Very low	1.65	1.08 to 2.52	Very low
IXE 80 mg Q2W *vs*. ADA 40 mg Q2W	1.08	0.86 to 1.36	Low	1.02	0.83 to 1.25	Moderate
IXE 80 mg Q4W *vs*. ADA 40 mg Q2W	0.96	0.86 to 1.06	Low	1.14	1.01 to 1.28	Very low
Placebo comparisons						
ADA 40 mg EOW *vs*. PBO	3.35	2.24 to 4.99	Moderate	0.67	0.50 to 0.89	Very low
APR 30 mg BID *vs*. PBO	1.94	1.59 to 2.38	Moderate	1.24	1.12 to 1.36	Low
APR 20 mg BID *vs.* PBO	1.86	1.49 to 2.31	Moderate	1.27	1.15 to1.41	Low
CZP 400 mg Q4W *vs*. PBO	2.36	1.68 to 3.31	Moderate	1.05	0.90 to 1.23	Moderate
CZP 200 mg Q2W *vs*. PBO	2.71	1.95 to 3.76	Moderate	1.01	0.86 to 1.19	Moderate
ETA 25 mg BIW *vs*. PBO	4.05	2.56 to 6.40	Low	n.d.		
INF 5 mg/kg W 0, 2, 6, 14 *vs*. PBO	4.38	2.24 to 8.56	Moderate	1.13	0.87 to 1.47	Low
IXE 80 mg Q2W *vs*. PBO	2.21	1.71 to 2.86	Moderate	1.39	1.09 to 1.78	Low
IXE 80 mg Q4W *vs*. PBO	2.25	1.59 to 3.18	Moderate	1.41	1.10 to 1.79	Low
MTX 7.5 mg QW *vs*. PBO	1.82	0.97 to 3.40	Low	n.d.		
SEC 150mg Q4W *vs*. PBO	2.44	2.10 to 2.84	High	1.03	0.95 to 1.12	High
SEC 150 mg Q4W + LD *vs*. PBO	2.06	1.70 to 2.49	High	1.01	0.89 to 1.15	Moderate
SEC 300 mg Q4W + LD *vs*. PBO	2.28	1.87 to 2.80	Moderate	1.02	0.89 to 1.16	Moderate
UST 45 mg W 0, 4 and Q12W *vs.* PBO	1.95	1.52 to 2.50	High	n.d.		
UST 90 mg W 0, 4 and Q12W *vs* PBO	2.26	1.80 to 2.82	Moderate	0.96	0.75 to1.24	Very low

ACR20: 20% improvement in American College of Rheumatology response criteria; RR: risk ratio; 95% CI: 95% confidence interval; ETA: etanercept; MTX: methotrexate; mg: milligrams; QW: once week; INF: infliximab; kg: kilograms IXE: ixekizumab; ADA: adalimumab; Q2W: once every 2 weeks; EOW: every other week; PBO: placebo; APR: apremilast; BID: twice a day; CZP: certolizumab pegol; Q4W: once every 4 weeks; BIW: twice a week; W: week; Sec: secukinumab; LD: loading dose; UST: ustekinumab; Q12W: every 12 weeks.

The treatment with a biological DMARD can be performed in monotherapy or in combination with a conventional synthetic DMARD.[113-115]

Other treatment options

As apremilast is less efficacious than bDMARDs, it is suggested for patients with psoriatic arthritis and an inadequate response to at least one csDMARD, in whom biological treatments are not appropriate.

Local injection of glucocorticoids can be recommended in patients with active mono- or oligoarthritis, dactylitis and in entheseal areas (enthesitis).

Systemic usage of glucocorticoids should not be standard for treatment of psoriatic arthritis, but if needed, *e.g.* during flares, "systemic steroids at the lowest effective dose may be used with caution." Tapering of glucocorticoids should be done slowly and stepwise when feasible.

Inflammatory bowel disease: how should psoriasis patients be managed with concomitant inflammatory bowel disease?

The recommendations for patients with concomitant inflammatory bowel disease are reported in Table XLIV. Likely due to an overlap in the pathophysiology and genetic background of psoriasis and Crohn's disease, the risk of psoriasis patients developing Crohn's disease is approximately two- to threefold higher compared to the general population.[116, 117]

The IL-17A antibody secukinumab and the IL-17RA antibody brodalumab have failed in studies in Crohn's disease, with some patients experiencing worsening of their disease during treatment (Table XLIV).[100, 118] Cases of newly onset Crohn's disease and ulcerative colitis have been observed during treatment of psoriasis patients with IL-17 inhibitors. The observed signal is, however, low, and it is presently unclear if the rate exceeds the rate expected in a psoriasis population.[119] In a recent summary of the safety observed in clinical trials of secukinumab in psoriasis, for example, the event-rate per 100 patient-years of exposure was 0.05 (95% confidence interval 0.02-0.1) for Crohn's disease (approximately one case per 2000 patients treated for one year) and 0.1 (0.07-0.2) for ulcerative colitis (approximately one case per 1000 patients treated for one year).[98] Since anti-TNF antibodies and ustekinumab, and possibly anti-IL-23 antibodies, are effective in treating Crohn's disease,[120] the use of these biologics in psoriasis

TABLE XLIV.—*Recommendations for patients with concomitant inflammatory bowel disease.*

We recommend working in collaboration with the treating gastroenterologist when prescribing a systemic therapy in psoriasis patients with concomitant chronic inflammatory bowel disease	↑↑	STRONG CONSENSUS# 100% Agreement EXPERT CONSENSUS
In patients with psoriasis and active IBD or a history of IBD, we **recommend** to preferentially use approved targeted therapies with a documented efficacy in these conditions: *Crohn's disease:* anti-TNF (infliximab, adalimumab, certolizumab) and anti-IL-12/23p40 (ustekinumab) *Ulcerative colitis:* anti-TNF (infliximab, adalimumab) and anti-IL-12/23p40 (ustekinumab)	↑↑	
If these first-choice treatments cannot be used, **we suggest** the following treatments to be considered as second choice targeted treatment options in patients with psoriasis and IBD: *Crohn's disease:* anti-IL-23p19 (preferred risankizumab, guselkumab; also possible: tildrakizumab) *Ulcerative colitis:* anti-IL-23p19 (preferred risankizumab, guselkumab; also possible: tildrakizumab)	↑	
If these first-choice treatments cannot be used, we **suggest** the following treatments to be considered as second choice oral treatment options in patients with psoriasis and IBD *Crohn's disease:* Methotrexate *Active ulcerative colitis:* Cyclosporine (preferred), apremilast (also possible)	↑	
In combination with other treatments, we **suggest** acitretin as an adjunct therapy for patients with IBD and psoriasis, especially in cases with mild paradoxical psoriasis	↑	
We **suggest against** the use of anti-IL-17 antibodies in patients with inflammatory bowel disease	↓	

#No abstentions due to personal-financial conflict of interest.

may decrease the occurrence of new onset Crohn's disease cases in psoriasis patients.[121] The prescription information for secukinumab and ixekizumab include a warning regarding the use of these drugs in patients with inflammatory bowel disease, while active Crohn's disease is a contraindication for the use of brodalumab.

In contrast, ustekinumab, adalimumab, infliximab, and certolizumab are all targeted therapies approved not only for the treatment of psoriasis, but also for the treatment of Crohn's disease and, in the case of adalimumab, infliximab and ustekinumab, ulcerative colitis. Notably, the anti-TNF fusion protein etanercept failed in clinical trials in Crohn's disease (reviewed in Whitlock *et al.,* 2018).[122]

There is an ongoing phase II/III clinical development program for the IL-23p19 inhibitors guselkumab and risankizumab in Crohn's disease and ulcerative colitis. In the case of risankizumab, positive clinical effects have been published for the induction and long term treatment of patients with Crohn's disease[120, 123] and are supported by immunological findings in the intestinal mucosa of patients with Crohn's disease receiving the drug.[124] There are several published case reports on the successful use of guselkumab in patients with Crohn's disease.[125, 126]

Due to their intestinal side effect profile with a relatively frequent induction of abdominal pain, loose stools and diarrhoea, fumarates should not be used in patients with inflammatory bowel disease. Severe gastrointestinal diseases are listed as contraindication in the prescription information of Fumaderm® and Skilarence®.

Inhibition of PDE4 with apremilast has shown positive effects in a phase 2 trial with ulcerative colitis.[127]

Methotrexate has limited efficacy in Crohn's disease[128,129] and probably even less in ulcerative colitis,[130, 131] but there is a considerable body of experience and no signal for a worsening of these conditions.

Acitretin may be considered neutral in patients with psoriasis and inflammatory bowel disease and has been used in the treatment of patients with inflammatory bowel disease that developed psoriasiform lesions (including cases of so-called paradoxical psoriasis) during treatment with TNF antagonist.[60]

Cyclosporine is frequently used in the treatment of steroid-refractory ulcerative colitis and has demonstrated long term outcomes like those of infliximab.[132]

Cancer: how should psoriasis patients with a history of malignancies be managed?

Theoretically, immunomodulatory therapies used for psoriasis have the potential to affect the course of a malignant disease, and the safety of using them in this context is uncertain. The Recommendations for patients with a history of malignancies are reported in Table XLV.

In clinical practice, different scenarios are associated with different risks and the answer might not be the same

TABLE XLV.—*Recommendations for patients with a history of malignancies.*

We **recommend** taking the burden of psoriasis, and the risk of cancer worsening or recurrence (precancer *vs.* low risk *vs.* high risk) into account for shared therapeutic decision making	↑↑	STRONG CONSENSUS# 100% Agreement EXPERT CONSENSUS
For patients with recent malignancy we **recommend** topical therapies, phototherapy (narrow band UVB) * and/or acitretin *Except patients with a recent, and/or high risk of cutaneous malignancy	↑↑	
We **recommend** to discuss the decision to initiate immunosuppressive therapies in psoriasis patients with a current or recent diagnosis of cancer in the previous five years case-by-case with cancer specialists and to reach an informed decision, respecting the patient's preference	↑↑	
In case of inadequate response to topical therapies, phototherapy, (narrow band UVB) and/or acitretin we **suggest** using MTX in psoriasis patients with a previous history of cancer* *For patients with history of non-melanoma skin cancer, see background text	↑	
We **suggest** apremilast can be used in psoriasis patients with a previous history of cancer despite the lack of long-term experience based on pathophysiological considerations on a case-by-case basis including discussion with cancer specialist	↑	
We **suggested against** using ciclosporin in psoriasis patients with a previous history of cancer	↓	
We **suggest** anti-TNF, ustekinumab can be used based on existing safety data on a case-by-case basis including discussion with cancer specialist We **suggest** anti-IL17, anti IL23, can be used in psoriasis patients with a previous history of cancer despite the lack of long term experience based on pathophysiological considerations on a case-by-case basis including discussion with a cancer specialist	↑	

#Due to personal-financial conflict of interest 3 abstentions.

for each of them. Patients can present with precancer (such as cervical dysplasia, colonic polyps or Barrett's esophagus), low risk cancer (NMSC, cancer with a long period of non-recurrence, usually defined as more than 5 years), or high-risk cancer (active cancer, recent aggressive cancer).

Available evidence to guide clinicians in these situations is scarce. Patients with malignancies are excluded from randomized clinical trials, so RCTs will not provide valid answers. Information about patients with previous cancer can only come from observational studies, which are less valid, as they are commonly affected by confounding by indication. There are techniques that can help control for this type of confounding, but these kinds of analyses require large numbers of patients that are difficult to enroll. This power issue is the reason for results usually being given for different cancers merged and also for different drugs grouped.

Most of the data available is of marginal relevance to this question:

Overall risk of cancer in psoriasis

Psoriasis is associated with increased mortality due to many diseases, including an increased risk of cancer. It is not clear whether this is due to the disease itself, or is influenced by lifestyle factors (mainly alcohol and smoking) or therapy.[133]

A recent systematic review and meta-analysis of 112 observational cohort studies of patients with psoriasis and psoriatic arthritis revealed a slightly increased risk of several cancer types, particularly keratinocyte cancer and lymphoma.[134]

Association of therapy and incident cancer in psoriasis and other immune-mediated disease

Some studies have studied the possible association of the use of systemic therapies for psoriasis and incident of cancer (in patients without previous history of cancer).

A systematic review of RCTs and observational studies exploring the risk of cancer in psoriasis patients treated with biologics described an increased risk of non-melanoma skin cancer in those patients being treated with anti-TNFs. However, included studies lacked adjustment for highly relevant confounding factors such as prior phototherapy. Data on other cancers do not show a risk associated with exposure to drugs. However, the studies are likely to be underpowered to ascertain the risk of individual types of cancer.[135] Vaengebjerg *et al.* did not find increased risk of cancer in patients with psoriasis and psoriatic arthritis on biologics compared with other systemic therapies.[134]

There are also some studies describing the risk of cancer associated with systemic therapy for other immune-medi-

ated disorders, mainly rheumatoid arthritis, other rheumatic disorders and inflammatory bowel disease. Results in these disorders might not be appropriately extrapolated to psoriasis patients, as psoriatic patients receive less immunosuppressive therapy (especially corticosteroids) and the associated disorders are different.[136]

Most studies are reassuring and did not find a relationship between exposure to anti-TNFs and risk of incident cancer in rheumatoid arthritis and psoriatic arthritis.[137] Luo *et al.*, analyzing data from nine cohorts, described an increased risk of cancer in psoriatic arthritis patients treated with disease modifying antirheumatic drugs, which was not seen in patients receiving biologics. However, this increase was due to NMSC and included studies have not considered the likely effect of previous PUVA therapy.[138] SmPCs of TNF inhibitors contain information regarding the risk of lymphoma/leukemia. However, these are rare events and data supporting this association are conflicting. So far no such association have been shown for psoriasis patients.[135]

Risk of cancer recurrence in patients exposed to systemic therapy for psoriasis

Few studies provide information that is relevant for answering this question.

Regarding patients with precancerous conditions (data available only for cervical dysplasia), a study using routine data of women with rheumatoid arthritis, describe that initiation of therapy with a biological disease-modifying antirheumatic drug (bDMARD) was associated with an increased, but not statistically significant, risk of high-grade cervical dysplasia or cervical cancer compared to initiation of a nonbiological (nb)DMARD.[139] Conversely, a review analysing 238 women with RA and a history of cervical carcinoma in situ, no genital cancer was observed in the TNFi-treated group over a median of 5.2 years of follow-up compared with two incidents of genital cancer in the nbDMARD-treated group, during a median follow-up of 3.9 years.[140]

A systematic review of patients with a history of cancer and exposed to anti-TNF therapy assessing for the risk of the occurrence of new cancer or cancer re-occurrence compared to non-biologic disease modifying antirheumatic drugs (DMARD), included nine studies with 11679 patients. None of them were studies on psoriasis. The outcome measures were heterogeneous, with many studies focused on describing NMSC. Overall, the study did not find an increased risk of recurrence in patients treated with anti-TNFs compared to nbDMARD.[141]

A retrospective study, based on routine data, of patients with rheumatoid arthritis and inflammatory bowel disease, and a previous NMSC, described an increased risk of a second NMSC in patients treated with methotrexate that was higher with longer exposures. Anti-TNF use was also associated with an increased risk, mostly in a subgroup (patients with RA and concomitant use of methotrexate).[142]

Another systematic review analyzed the risk of cancer recurrence in patients with immune-mediated diseases exposed to immune-suppressive therapies. They included 16 observational studies with 11702 participants after a cancer diagnosis and with 1698 new or recurrent cases of cancer. Only one very small study, and not contributing to the final analysis, was focused on psoriasis patients. Overall, rates of cancer recurrence were similar among participants receiving anti-TNF therapy, immune-modulator therapy or no immunosuppression, but was higher among patients receiving combination immune suppression.[143]

French guidelines have reviewed the risk of cancer associated with systemic therapies. Cyclosporine has been clearly linked to an increased risk of cancer and a recommendation to avoid it has been issued. Evidence from larger patient cohort over long periods of time on the risk of the newer drugs such as the anti IL-17, anti IL-23 antibodies and apremilast is still very scarce.[40] From a theoretical point of view, acitretin has lower efficacy but might also have the lowest risk in these patients. Phototherapy is associated with skin cancer, but not with other cancers. Although evidence is not strong, there does not seem to be a difference in risk with methotrexate and anti-TNFs, except for a possible increase in risk of NMSC for methotrexate.[40]

Depression: how should psoriasis patients with a history of depression and/or suicidal ideation be managed?

Psoriasis is associated with a higher risk for psychiatric comorbidities including anxiety and depression while results on suicide ideation and suicide are more unclear.[115, 144-147] In general, interventions that are effective for psoriasis correspondingly also improve symptoms of depression. Clinical studies using adalimumab, etanercept, ustekinumab, ixekizumab, guselkumab or fumarates for the treatment of psoriasis have shown that all these anti-inflammatory drugs not only improve psoriatic manifestations, but also symptoms of depression.[146, 148-153] In a head-to-head study, guselkumab was associated with greater improvements in symptoms of depression compared with adalimumab.[150] In a prospective, longitudinal registry study, biologic therapy was found to have the greatest improvement on symptoms of depression followed by conventional systemic therapy

and phototherapy.[115, 154] Taken together, these data suggest that the more effective the intervention for psoriasis, the greater the benefit to the mood. However, whether the overall beneficial effect on depressive symptoms is direct, or indirect (through improvement in psoriasis and therefore mood) is not clear.

Systemic treatments for psoriasis with special attention to a possible increased risk of depression, suicide ideation and completed suicide are discussed below.

Acitretin

Acitretin has been reported to be associated with depression in some case reports.[155, 156] However, more recent reviews of the literature conclude that except for very few cases of depression and suicidal ideation there are no convincing evidence-based data to support an association between acitretin and depression/suicidality.[157, 158] A formal review of retinoids (including acitretin and isotretionin) carried out by EMA's Pharmacovigilance Risk Assessment Committee in 2018[159] concluded that it was not possible to identify a clear increase in the risk of neuropsychiatric disorders in people taking oral retinoids compared to those that did not. However, the EMA decided to include a warning about the possible risk in the product information for oral retinoids, since PRAC noticed that severe skin disorders themselves increase the risk of psychiatric disorders.[160] Based on the above, the guideline group did not consider there to be sufficient evidence to specifically counsel against use of acitretin in those patients with mood disorders but, in common with all systemic therapies, clinicians should monitor for mood changes given that people with psoriasis are at increased risk of anxiety and depression.

Brodalumab

In two out of three phase III studies of efficacy and safety of brodalumab in patients with plaque psoriasis (AMAGINE 1-3) cases of suicide were reported (two patients in each of studies 1 and 2).[161, 162] An expert opinion (2019) discussing these observed cases of suicide highlighted the following aspects:[163] further review of the suicides by the Columbia Classification Algorithm of Suicide Assessment Review Board confirmed only three of the cases as suicides. All of them had underlying psychiatric disorders or stressors and all three suicides occurred at one center. Both symptoms of depression and anxiety decreased during treatment with brodalumab.[162]

In the European SmPC, the reported Suicidal ideation and behavior, including completed suicide in patients treated with brodalumab was mentioned. However, it was also stated that a causal association between treatment with brodalumab and increased risk of suicidal ideation and behavior has not been established. In the SmPC, it is recommended that risk and benefit of treatment with brodalumab should be carefully weighed for patients with a history of depression and/or suicidal ideation. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal ideation, anxiety, or other mood changes, and they should contact their healthcare provider if such events occur. If a patient suffers from new or worsening symptoms of depression and/or suicidal ideation or behavior is identified, it was recommended to discontinue treatment with brodalumab.[164]

Apremilast

Results from two phase III studies including patients with moderate-to-severe psoriasis (ESTEEM 1 and ESTEEM 2) with open-label extension for up to four years, showed that patient reported depression occurred in 1.4% of patients treated with apremilast and in 0.5% of receiving placebo. The incidence of depression did not increase over time. There was one suicide attempt, and no completed suicides with apremilast.[165] Similar results were achieved in an open-label extension study (for up to additional four years) of three phase III studies of patients with psoriatic arthritis (PsA); 1.2% in patients treated with apremilast and 0.8% in patients receiving placebo. There were two suicide attempts, and no completed suicides with apremilast.[166] Post marketing experience, including five cases of completed suicides, was reported and a new safety information was published for apremilast provided by Celgene in agreement with the European Medicines Agency and the Health Products Regulatory Authority in 2016.[167] In here it was stated that evidence from clinical trials and post marketing experience suggested a causal association between suicidal ideation and behaviour with the use of apremilast. The SmPC and patient leaflet for apremilst was updated to add a warning about depression (common adverse reaction (≥1/100 to <1/10)) and suicidal behaviour and ideation (uncommon adverse reaction [≥1/1000 to <1/100]).[168]

It was recommended that risks and benefits of starting or continuing treatment with apremilast should be carefully assessed in patients with previous or existing psychiatric symptoms or if concomitant treatment with other medicinal products likely to cause psychiatric events are in use or intended. Additionally, it was recommended to

TABLE XLVI.—*Recommendations for patients with a history of depression and/or suicidal ideation.*

We **recommend** to be aware of signs and symptoms of anxiety and depression in patients with psoriasis and monitor for symptoms of depression and/or suicidal ideation or anxiety during systemic treatments for psoriasis especially in those with a history of any of the above	↑↑	STRONG CONSENSUS# 100% Agreement
We **suggest** using alternatives to brodalumab and apremilast in patients with a history of depression and/or suicidal ideation	↑	EXPERT CONSENSUS

#Due to personal-financial conflict of interest 3 abstentions.

discontinue treatment with apremilast in patients suffering from new or worsening psychiatric symptoms, or if suicidal ideation or suicidal attempt is identified. The recommendations for patients with a history of depression and/or suicidal ideation are reported in Table XLVI.

Diabetes: how should psoriasis patients with diabetes mellitus be managed?

Recommendations for patients with diabetes mellitus are reported in Table XLVII. Although, no treatment is fully contraindicated in case of diabetes, CsA is better avoided because it could favor insulin resistance, particularly on long term treatment course. Moderate-to-severe psoriasis is commonly accompanied by metabolic disorders including type 2 diabetes mellitus, obesity, dyslipidemia, non-alcoholic fatty liver disease and metabolic syndrome.[169] In particular, several meta-analyses confirmed the association between psoriasis and diabetes as well as the new AAD guidelines[115, 169-171] Amstrong *et al.*[169] found that psoriasis had an odds ratio (OR) of 1.59 (95% CI: 1.38-1.83) for diabetes. The pooled OR was 1.53 (95% CI: 1.16-2.04) for mild psoriasis and 1.97 (95% CI: 1.48-2.62) for severe psoriasis. A nationwide population-based cohort study involving 14,158 adults with psoriasis confirmed that the risk of diabetes in psoriatic patients correlated to the severity of psoriasis.[172] The association between psoriasis and diabetes could be explained considering a common genetic background, insulin resistance, and the unhealthy lifestyles such as over-eating and sedentary lifestyle, which are common in patients with psoriasis.[173]

In addition, there is a strong association between psoriasis and obesity which induces itself insulin resistance.[174] Obesity itself is a significant risk factor to develop type 2 diabetes.[115] Systemic treatments for psoriasis could also impair glucose homeostasis and/or other metabolic parameters, especially in case of continuous and prolonged use. Short-term treatment with methotrexate does not appear to have a negative effect on carbohydrate metabolism parameters in patients with psoriasis or psoriatic arthritis.[175-177] However, MTX should be administered with caution in the case of diabetes and obesity, due to the increased risk of hepatic fibrosis when the cumulative dose exceeds 1.5 g.[178, 179] CsA can increase insulin resistance, interfere with fatty acid metabolism favoring the development of dyslipidemia and the increase of serum uric acid.[180] In a prospective cohort study on the Psocare registry, it was found that CsA was associated with a significant risk of developing diabetes at week 52, which is not surprising because the calcineurin inhibitors either tacrolimus or CsA are associated with a higher risk of new-onset diabetes in transplant recipients.[181] The diabetogenic effect of CsA has been related to inhibition of insulin secretion from pancreas islet cells,[182] an effect that may be even more relevant in obese psoriatic patients. Acitretin effects on insulin resistance are not clearly established. There is no evidence that fumarates and apremilast could affect insulin resistance. Ad-

TABLE XLVII.—*Recommendations for patients with diabetes mellitus.*

We **suggest against** using CsA or MTX as a first line treatment in patients with diabetes and/or features of the metabolic syndrome	↓	CONSENSUS# 89% 89% Agreement EXPERT CONSENSUS
We **suggest against** using acitretin as a first line treatment in patients with dyslipidaemia	↓	STRONG CONSENSUS# 100% Agreement EXPERT CONSENSUS

#Due to personal-financial conflict of interest 2 abstentions.

ditionally, diabetes is not a contraindication for the use of apremilast or fumarates.

Clinically significant dyslipidemia has been rarely reported in patients receiving TNF-α antagonists, but this is not a common issue in clinical practice.[183] Body weight gain could occur in patients treated with TNF-α antagonists.[184, 185] In contrast, IL-23 and IL-17 inhibitors usually does not increase body weight in patients with chronic plaque psoriasis.[186, 187] Apremilast has been shown to cause weight loss in clinical trials.[187] Studies addressing the effects of TNF-α blockade on glucose homeostasis in patients with psoriasis and/or PsA were very limited and gave conflicting results. The Homeostasis Model Assessment (HOMA) and the Quantitative Insulin Sensitivity Check Index (QUICKI) are two widely used non-invasive surrogate markers of insulin resistance, used in the following studies. A study in 62 patients with chronic inflammatory rheumatic diseases, of whom 18 patients were affected by PsA, did not show any significant improvement in glucose homeostasis during the first six months of treatment with TNF-α inhibitors.[188] A recent prospective study in a cohort of 210 PsA patients treated with various anti-TNF-α inhibitors (adalimumab N.=70, etanercept N.=70) or MTX (N.=70) found that those receiving TNF-α inhibitors had significant improvements in glucose levels and other features of the metabolic syndrome compared with those treated with MTX.[189] Similarly, the effects of TNF-α inhibitors on insulin sensitivity/resistance in patients with psoriasis gave discordant results. A small randomized, double-blind study in twelve psoriatic patients at high risk of developing type 2 diabetes failed to observe a significant effect of a two-week treatment with etanercept on insulin secretion and sensitivity.[190] No significant changes in either insulin sensitivity or levels of fasting blood glucose were observed in a study in psoriatic patients after twelve weeks of treatment with adalimumab.[191] In contrast, in two different studies respectively on nine and 89 patients with plaque psoriasis etanercept improved insulin sensitivity.[192, 193] Other TNF- α inhibitors also appear to improve insulin sensitivity in diabetic and non-diabetic patients with psoriasis.[194, 195]

A pooled analysis of data from the phase III randomized controlled trials for secukinumab showed a neutral effect on fasting plasma glucose, lipid parameters and liver enzymes. In patients with fasting plasma glucose >125 mg/dL at baseline (diagnostic criterion for diabetes) secukinumab treatment presented a trend towards lowering fasting glucose concentration compared to placebo treatment during the first 12 weeks.[196] Finally, patients with moderate-to-severe psoriasis are candidate for interventions aimed to reduce their cardiovascular risk profile. Screening for cardiovascular risks including diabetes, hypertension and dyslipidemia should be recommended for all psoriasis patients.[115] Nonpharmacological interventions, such as weight loss, should be recommended to obese patients. Indeed, it has been reported that a low-calorie diet inducing a moderate weight loss (*i.e.*, 5 to 10 % of body weight) increases the responsiveness of obese patients with moderate-to-severe chronic plaque psoriasis to systemic treatments.[197-200] Moreover, body weight loss could also increase insulin sensitivity in obese patients with psoriasis.

Psoriasis patients who suffered also from diabetes showed a lower response rate to secukinumab (N.=867) as well as to ustekinumab (N.=318) analyzed in pooled phase III data from the FIXURE, ERASURE and CLEAR studies.[201] Pinter *et al.* suggested up-dosing to optimize the treatment outcome to 300 mg secukinumab every two weeks instead which is tested in patients >90 kg. The inflammatory history in cardiometabolic comorbidities including diabetes might rather influence the therapy response than the severity of psoriasis itself, which can be interpreted as an expression of a higher inflammatory burden.[201] However, further studies are needed to understand the mechanisms why cardiometabolic comorbidities are associated with lower response rates.

Etanercept does not have an impact on the glycemic control in diabetes patients, which was shown in the PRISTINE Trial.[202]

Finally, it should be considered that diabetic nephropathy eventually occurring in patients with psoriasis could reduce the clearance of any systemic treatments for psoriasis including MTX and CsA.[203, 204] CsA should be considered cautiously in patients with diabetes mellitus as significantly increased serum creatinine concentration could be observed.[205]

In addition to any medical treatment, appropriate supportive care should be offered, *e.g.*, weight loss programs for obese patients with metabolic syndrome or dyslipidemia.

Heart disease: how should psoriasis patients with ischemic heart disease and/or congestive heart failure be managed?

Ischemic heart disease/atherosclerosis

The summary/key points are:

- patients with psoriasis have an approximately two- to threefold increased relative risk for developing cardiovas-

cular events such as myocardial infarction or stroke compared to individuals without psoriasis. The cardiovascular risk seems to correlate with disease severity. The link between psoriasis and cardiovascular disease is likely to be driven by an increased prevalence of classical cardiovascular risk factors among patients with psoriasis such as the components of the metabolic syndrome. There is also evidence for an independent risk conferred by the systemic inflammatory nature of the disease.;

• a careful history should be obtained from all patients to determine whether they have established cardiovascular disease. Appropriate investigations and treatment should be initiated in accordance with current European Society of Cardiology guidance;[206]

• patients without a history of cardiovascular disease, should have their cardiovascular risk factors assessed and be given lifestyle advice including avoiding smoking, maintaining a healthy diet, increasing physical activity and maintaining a healthy blood pressure with other treatments in accordance with current European Society of Cardiology guidance;[207, 208]

• with the exception of methotrexate, there are no studies formally evaluating the effect of any antipsoriatic therapy as a treatment for coronary heart disease. In general, it seems that the reduction of psoriatic inflammation is beneficial in psoriatic patients with cardiovascular comorbidity (indirect effect), but direct effects of treatments for psoriasis on atherosclerotic inflammation may also play a role;

• multiple studies with different therapies have produced evidence on parameters of cardiovascular risk and/or assessed cardiovascular events during the treatment of patients with psoriasis,

• from these studies it appears that methotrexate, the anti-TNFs, in particular adalimumab, and ustekinumab improve parameters of cardiovascular risk in patients with psoriasis;

• while in some experimental models IL-17 has been associated with stabilizing properties of unstable atherosclerotic disease, treatment with IL-17 inhibitors has not been associated with an increased rate of cardiovascular events. Moreover, inhibition of IL-17, especially with secukinumab, has shown to improve surrogate markers of endothelial dysfunction;

• the data available on inhibitors of IL-23p19 indicate that they are safe in patients with cardiovascular comorbidity, but information on their potential effects on cardiovascular factors risk is limited;

• treatment with apremilast is associated with weight loss in some patients. Experimental studies indicate potentially beneficial effects of apremilast in models of atherosclerosis. Neither clinical trial data nor observational studies indicate that apremilast is associated with an increased risk of cardiovascular events in psoriasis patients with ischemic heart disease or cardiovascular risk factors;

• there is no evidence that fumarates are associated with increased cardiovascular events in patients with ischemic heart disease;

• CsA may induce or worsen arterial hypertension, a condition often found in patients with ischemic heart disease, and worsen dyslipidemia. The metabolism of CsA may interfere with drugs used in patients with ischemic heart disease such as beta-blockers or calcium antagonists;

• acitretin has very limited anti-inflammatory potential and may induce or worsen hyperlipidemia.

Recommendations for patients with ischemic heart disease are summarized in Table XLVIII. Moderate-to-severe psoriasis is associated with several well-established cardiovascular risk factors including obesity, hypertension, diabetes, dyslipidemia, and metabolic syndrome.[209] Psoriasis severity has been linked to a higher prevalence of these risk factors. However, there is conflicting evidence as to whether psoriasis is associated with increased cardiovascular events and whether psoriasis itself represents is an independent cardiovascular risk factor.[210] Indeed, a large cohort study in Rotterdam found no difference in the risk of ischemic heart disease hospitalizations in patients with psoriasis compared with matched control sub-

TABLE XLVIII.—*Recommendations for patients with ischemic heart disease.*

We **suggest against** cyclosporine or acitretin as preferred treatments in patients with psoriasis and ischemic heart disease.	↓	STRONG CONSENSUS# 100% Agreement
We **suggest** methotrexate as preferred first-line therapy in patients with psoriasis and ischemic heart disease* if other patient characteristics do not preclude its use.	↑	
We **suggest** anti-TNFs, ustekinumab, and IL-17 inhibitors as preferred targeted therapies in patients with psoriasis and ischemic heart disease*.	↑	EXPERT CONSENSUS

#No abstentions due to personal-financial conflict of interest; *in case of concomitant congestive heart failure, also note the recommendations from the respective section.

jects.[211] Stern and Huibregtse[212] found that patients with very severe psoriasis have increased all-cause mortality, but that severe psoriasis is not an independent risk factor for ischemic heart disease. The aforementioned studies are in contrast to a large and growing body of literature that suggests patients with more severe psoriasis carry a clinically relevant increased risk of mortality due to ischemic heart disease. Samarasekera *et al.*[213] critically evaluated 14 cohort studies and meta-analyzed the magnitude of cardiovascular risk for the primary outcomes of cardiovascular mortality, stroke, and myocardial infarction (MI). Increased risk was identified only in individuals with severe psoriasis (defined as requiring systemic therapy or hospital admission): the risk ratio relative to the general population was 1.37 (95% CI: 1.17-1.60) for cardiovascular mortality, 3.04 (95 % CI 0.65-14.35) for MI, and 1.59 (95% CI: 1.34-1.89) for stroke. The relative risks of cardiovascular disease were highest in the younger, severe psoriasis population (*e.g.*, 3.10 [95% CI: 1.98-4.86] for MI at 30 years), and absolute risks were greatest in older individuals with severe psoriasis (*e.g.*, 23.2 excess MIs per 10,000 person-years at 60 years).[213] Geata *et al.* showed an approximately 25% increased relative risk of cardiovascular disease in patients with psoriasis, independently of smoking, obesity and hyperlipidaemia.[214] The pooled relative risks for cardiovascular mortality in psoriasis compared with general population were 1.15 (95% CI: 1.09-1.21) in all patients with psoriasis, 1.05 (95% CI: 0.92-1.20) in those with mild psoriasis, and 1.38 (95% CI: 1.09-1.74) in severe disease.[133] A recent systematic review and meta-analysis indicates that subclinical coronary artery disease diagnosed with cardiac computed tomography angiography is more prevalent in patients with psoriasis, with an increased burden of disease and number of high-risk coronary plaques.[215]

It has been proposed that there may be overlapping immune pathways in both psoriasis and ischemic heart diseases that may underlie this association.[216,217] It is also a matter of great interest whether systemic antipsoriatic treatments affect cardiovascular risk by reducing the overall inflammatory burden. It is not known whether systemic treatments could modify cardiovascular outcomes including the rate of MI. However, studies investigating the effects of systemic treatments on cardiovascular risk factors including metabolic parameters (*e.g.*, serum lipids), blood pressure or biomarkers of inflammation and atherosclerosis (*e.g.*, C-reactive protein, endothelial dysfunction) have been completed. Multiple studies have failed to show any significant changes in metabolic parameters in patients receiving both PUVA and narrowband UVB therapy.[218, 219] In contrast, systemic retinoids (*i.e.*, acitretin) commonly increase serum triglycerides and cholesterol by shifting high-density lipoproteins to low-density lipoproteins.[219, 220] Similarly, CsA can increase serum lipids, plasma glucose and blood pressure in a dose-dependent fashion.[180, 221] Therapy with MTX is associated with a reduced risk of cardiovascular morbidity and mortality in patients with RA as well as in patients with psoriasis and psoriatic arthritis.[222-225] In a longitudinal cohort study of 6902 patients with psoriasis, Ahlehoff *et al.* found that treatment with MTX was associated with a reduced risk of cardiovascular events compared to patients treated with other antipsoriatic therapies such as CsA and retinoids.[226] MTX therapy decreases carotid intima-media thickness (a marker of arteriosclerosis) in patients with moderate-to-severe psoriasis.[227] Preclinical and pilot studies suggest possible cardioprotective effects of apremilast and fumarates but there is no clinical evidence that either affect cardiovascular risk.[152, 228]

The effect of biological therapies on the risk of ischemic heart disease is unclear.[229, 230] Treatment with TNFi and ustekinumab have been shown to reduce aortic vascular inflammation and decrease systemic inflammatory biomarkers.[231-235] Moreover, therapy with TNFi improves biomarkers of atherosclerosis by reducing either intima media thickness and arterial stiffness in patients with RA, spondyloarthropathies, PsA and psoriasis.[236-238] Secukinumab may have a beneficial effect on cardiovascular risk in patients with psoriasis by improving endothelial function measured by flow-mediated dilation.[239]

There is conflicting evidence on the effects of biologic therapy on the incidence of cardiovascular incidents in patients with psoriasis. A large cohort study of 25,554 patients with psoriasis followed for eight years using administrative and pharmacy claims data from a large U.S. insurer (*i.e.*, United Health Group) did not show a reduced risk of MI in those receiving systemic therapy compared to those exposed to phototherapy.[240] A recent comparison of patients with first time hospital-diagnosed psoriasis between 1995 and 2002 (early era cohort) and those diagnosed between 2006 and 2013 (late era cohort), did not show any change in MI risk despite increased cardiovascular disease prevention and the availability of biologic therapy.[241] A meta-analysis of 22 randomized, placebo-controlled, double-blind studies of IL-12/23 antibodies and anti-TNF-α agents comprising 10,183 adult patients evaluated the possible association between biologic therapies and major adverse cardiovascular events (MACE). Compared with placebo, there was no

significant difference in the rate of MACE observed in patients receiving anti-IL-12/IL-23 antibodies or anti-TNF-α treatments. However, the authors acknowledged that the study may have been underpowered to identify a significant difference.[242] However, other studies have shown different outcomes. In particular, Wu *et al.*[243] assessed whether patients with psoriasis treated with TNFi inhibitors had a decreased risk of MI compared with those treated with other systemic therapies, phototherapy or topical. This was a retrospective cohort study of 8845 patients, 1673 received a TNFi for at least two months, 2097 received conventional systemic treatments or phototherapy, and 5075 received only topical treatment. After adjusting for MI risk factors, the TNFi cohort had a significantly lower risk of MI compared with the topical cohort (adjusted hazard ratio, 0.50; 95% CI: 0.32-0.79). The difference in incidence of MI between TNFi and conventional systemic treatments or phototherapy was not significant.[243] In a Danish nationwide real-world study of 2400 patients with severe psoriasis enrolled in a registry, treatment with biological agents (N.=693) or MTX (N.=799) was associated with lower cardiovascular disease event rates than treatment with other antipsoriatic therapies.[244] This is consistent with Wu *et al.* who found that psoriasis patients receiving TNFis had a lower major cardiovascular event risk compared to those receiving methotrexate and cumulative exposure to TNFis was associated with an 11% cardiovascular event risk reduction.[245] Concern was expressed over initial analyses linking IL-12/23 inhibitors with MACE in the first week of therapy. However, additional meta-analysis of clinical trials and data from registries in psoriasis and psoriatic arthritis suggest that licensed biologic therapies, including TNFi (adalimumab, etanercept and infliximab), anti-IL-17A agents (secukinumab and ixekizumab) or ustekinumab are not associated with MACEs.[246-249] In a large prospective cohort study using the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) there was no significant differences in the risk of major cardiovascular events between etanercept, adalimumab, ustekinumab and methotrexate.[250] Similarly, in 60028 patients with psoriasis or psoriatic arthritis from multiple US databases, no significant difference was found in the risk of MACEs after initiation of therapy with TNFi or ustekinumab.[251]

Heart failure

The summary/key points are:

• heart failure (HF) is a clinical syndrome characterized by typical symptoms (*e.g.* breathlessness, ankle swelling and fatigue) that may be accompanied by signs (*e.g.* elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress;[207]

• common causes include coronary artery disease (previous myocardial infarction), arterial hypertension, atrial fibrillation, valvular heart disease and cardiomyopathies. The condition may, therefore, coexist with ischemic heart disease;

• patients with suspected or confirmed heart failure should be referred to a cardiologist for investigation and treatment in accordance with current European Society of Cardiology guidance;[252]

• the NYHA functional classification is commonly used to describe the severity of symptoms and exercise intolerance in patients with heart failure. (https://manual.jointcommission.org/releases/TJC2018A/DataElem0439.html):

  • Class I - No symptoms and no limitation in ordinary physical activity, *e.g.*, shortness of breath when walking, climbing stairs etc.;

  • Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity;

  • Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, *e.g.*, walking short distances (20-100 m). Comfortable only at rest;

  • Class IV - Severe limitations. Symptoms even while at rest. Mostly bedbound patients;

• there is evidence that anti-TNFs, especially adalimumab and infliximab, worsen advanced heart failure and both drugs are contraindicated in patients with congestive heart failure NYHAIII/IV and must be used with caution in patients with milder forms of congestive heart failure (NYHA I/II). Etanercept must be used with caution in patients with congestive heart failure;

• the use of other targeted therapies in patients with psoriasis and congestive heart failure seems to be neutral depending on the underlying cause (caution infection);

• the use of methotrexate, acitretin and apremilast in patients with psoriasis and heart failure seems to be neutral depending on the underlying cause;

• CsA may increase the blood pressure and reduce kidney function in patients with psoriasis and heart failure and interfere with many drugs used in the treatment of this condition;

Table XLIX.—*Recommendations for patients with congestive heart failure.*

We **suggest against** using cyclosporine in patients with psoriasis and advanced congestive heart failure	↓	STRONG CONSENSUS# 100% Agreement EXPERT CONSENSUS
We **suggest** that methotrexate, acitretin and apremilast are considered as treatment in patients with psoriasis and advanced congestive heart failure*	↑	
We **suggest** that ustekinumab, inhibitors of IL-17 and of IL-23 are considered as treatment in patients with psoriasis and advanced congestive heart failure*	↑	
We **recommend against** using anti-TNFs in patients with psoriasis and advanced congestive heart failure	↓↓	
We **recommend** discussing the choice of a systemic therapy in psoriasis patients with **advanced** congestive heart failure with a cardiologist	↑↑	

#Due to personal-financial conflict of interest 1 abstention; *in case of concomitant ischaemic heart failure, also note the recommendations from the respective section.

• fumarates may reduce kidney function in patients with psoriasis and heart failure.

Recommendations for patients with congestive heart failure are summarized in Table XLIX. TNF-α in heart failure (HF) stems from the observations that TNF-α exerts negative inotropic effects and is capable of promoting fibrosis, hypertrophy and cardiomyopathy in animal models.[253] Moreover, cardiac specific TNF-α levels are regulated by pressure and volume load in animals and in humans.[254] Therefore, a small series of clinical trials was conducted with TNFi to investigate their potential beneficial effects in patients with HF. Both RENAISSANCE and RECOVER[255, 256] were large, multicenter, randomized, double blind, placebo-controlled trials of etanercept in HF. Both studies failed to show improved mortality or decreased hospitalizations due to CHF. The key finding of the RENAISSANCE Trial was a trend towards higher mortality in etanercept-treated subjects, a concern heightened by the apparent dose-response relationship. The combined analysis of these studies showed a trend towards increased mortality and/or HF hospitalizations in the combined twice-weekly/thrice-weekly etanercept group compared with placebo.[255, 256] Infliximab was evaluated in a phase II randomized, double-blind, placebo-controlled pilot study.[257] This pilot study did not show any beneficial effect of infliximab over placebo in terms of efficacy. Higher-dose infliximab (10 mg/kg) was associated with an increase in both all-cause mortality and the number of hospitalizations due to HF at weeks 28 and 54. In summary, the results of randomized, placebo-controlled trials with both etanercept and infliximab suggest a deleterious effect of higher doses of TNF blockers in patients with NYHA class III or IV HF. There was a trend toward higher mortality and a greater number of hospitalizations for HF. However, a recent Cochrane systematic review including 163 randomized controls trials with 50,010 participants and 46 extension studies with 11,954 participants, found that the rate of new diagnosis of HF were not statistically significantly different between those patients treated with biologics and those with control treatments.[258] The cardiovascular safety data extracted from 74 articles and, corresponding to 77 randomized controlled trials of TNFi, anti-IL 12/23, anti-IL 23 and anti-IL 17 agents for the treatment of psoriatic arthritis or psoriasis showed no significant difference in CHF incidence in patients receiving biological agents in comparison to placebo.[249] In conclusion, only moderate-to-severe CHF is a concern for initiating TNFi therapy in patients with psoriasis.

Kidney disease: how should psoriasis patients with kidney failure / renal impairment be managed?

Recommendations for patients with kidney failure / renal impairment are summarized in Table L. A number of risk factors that predispose one to chronic kidney disease (CKD) are especially prevalent in people with multiple comorbidities including diabetes, hypertension, cardiovascular disease being treated with drugs that may impair kidney function. A UK population-based study suggests that the risk of CKD was increased in people with moderate-to-severe psoriasis, independent of these risk factors.[259] Thus, the optimal choice of systemic therapy in the context of CKD is likely to be a relatively common clinical scenario. This is supported by data from the Spanish long-term pharmacovigilance registry indicating that 13 % of the total cohort were categorized as having "chronic renal failure."[260]

In people with established CKD, the following factors

TABLE L.—*Recommendations for patients with kidney failure/renal impairment.*

We **recommend** ensuring an accurate assessment of renal function in any psoriasis patient with known or suspected chronic kidney disease prior to therapy	↑↑	STRONG CONSENSUS# 100% Agreement EXPERT CONSENSUS
We **recommend** working in collaboration with the nephrologist when prescribing systemic therapy in any psoriasis patient with chronic kidney disease of stage 3 (eGFR <60 mL/min/1.73 m²) or more	↑↑	
We **suggest** acitretin*, apremilast, fumarates*, methotrexate* **may be used** in psoriasis patients with **mild to moderate renal impairment** (eGFR ≥30 mL/min/1.73m²) *(carefull dosing/dose adjustment may be needed)	↑	
We **suggest** using biologics in psoriasis patients with chronic kidney disease and all stages of renal impairment	↑	
We **recommend against** using ciclosporin, fumarates, or methotrexate in psoriasis patients with **chronic kidney disease and severe renal** impairment (eGFR <30 mL/min/1.73m²)	↓↓	

#No abstentions due to personal-financial conflict of interest.

were considered when evaluating the treatment options for psoriasis:

- the likely effect of the psoriasis treatment on residual kidney function;
- the impact of CKD on pharmacokinetics/pharmacodynamics of the psoriasis treatment;
- potential drug interactions;
- associated CKD comorbidity.

Systemic therapies

Acitretin

National guidelines in the UK[261], USA[42] and Spain[41] all recommend avoiding acitretin in moderate-to-severe renal disease, although no evidence is cited underpinning these recommendations. There were no studies identified that specifically address the use of acitretin for psoriasis in the context of CKD. Acitretin is widely used in the renal transplant population for skin cancer prophylaxis where stage 3 CKD is common; a recent systematic review in this population showed no increased in AEs when compared to placebo.[262] Limited data from RCTs do not indicate that acitretin is a nephrotoxic drug. Acitretin is highly lipophilic, penetrates readily into body tissues and is highly protein (albumin) bound. Hypoalbuminemia in association with CKD may therefore potentially increase drug clearance. It is metabolized in the liver to 13-cis acitretin and etretinate, and then undergoes glucuronidation into inactive, water-soluble forms. In healthy patients, acitretin is excreted entirely in the form of these inactive metabolites, in approximately equal parts via the kidneys and the bile. In a single report,[263] the mean areas under the plasma concentration *versus* time curves of acitretin and 13-cis acitretin following a single oral dose of 50 mg of acitretin in six patients on hemodialysis were, in fact, about 50 % lower than healthy controls. No retinoids were detectable in the dialysate.

In summary, acitretin is not known to be nephrotoxic, and CKD (any stage) would not be predicted to markedly impact on drug disposition.

Apremilast

Apremilast has no known nephrotoxic potential. In the pivotal clinical trials, there was no evidence for treatment emergent adverse events related to renal function.[168, 264]

In patients with mild to moderate impairment of kidney function, no dose adjustment of apremilast is necessary. When patients have severe impairment of kidney function (eGFR below 30 ml/min/1,73 m2 or creatinine clearance <30 mL/min) the dose of apremilast should be reduced to 30 mg once daily. When starting treatment with apremilast in case of severe renal insufficiency only the morning dose should be given as total daily dose (recommendations according to SmPC).

Fumarates

Fumarates are known to be potentially nephrotoxic, and may rarely cause an irreversible, proximal renal tubular nephropathy with long-term use. Recent studies[265] of dimethyl fumarate (for MS) confirm proteinuria and reduction in eGFR to occur more commonly than placebo; German guidelines and the SmPC specify careful monitoring of serum creatinine, and treatment cessation in the event of significant change. In health, fumarates are extensively metabolized by ubiquitous esterase, and so CKD would not be predicted to significantly impact on drug clearance.[266, 267]

Cyclosporine

Cyclosporine has established nephrotoxic potential. Acute nephrotoxicity can occur within weeks of treatment initiation, is reversible, and arises due to dose-dependent vascular dysfunction, involving afferent arteriolar constriction that leads to increased vascular resistance and a decrease in glomerular filtration rate. Tubular dysfunction may also occur, characterized by decreased magnesium re-absorption, decreased uric acid excretion, decreased potassium and hydrogen ion secretion, and distal tubular acidosis. Chronic nephrotoxicity[268, 269] is largely irreversible and is characterized by progressive arteriolar hyalinosis, interstitial fibrosis, tubular atrophy, and glomerular sclerosis. Chronic nephrotoxicity is more likely to occur with higher daily doses, larger cumulative doses, and long-term therapy (more than 1-2 years). In one long-term psoriasis study, patients with a pretreatment creatinine of >100 µmol/L were more likely to discontinue therapy. In a study performed in patients with (stage 5) terminal renal failure, the systemic clearance was approximately two thirds of that in patients with normally functioning kidneys. Less than 1% of the administered dose is removed by dialysis.

Guidelines recommend using cyclosporine with caution in people with CKD; in those with significant reduction in renal function (CKD stage 3 or more),[270] cyclosporine nephrotoxicity may lead to further critical reduction in function.

Methotrexate

Methotrexate (MTX) is not generally considered nephrotoxic when used at low doses for inflammatory disease, although renal impairment is reported,[271] and may be an under-recognized event. MTX and 7-hydroxymethotrexate are mainly excreted through the kidneys, via glomerular filtration and active transport. MTX clearance is therefore reduced (and thus risk of toxicity increased) in the context of CKD, depending on the stage. In a cohort of 77 patients with RA and various stages of CKD, the elimination half-life of a single dose of intramuscular MTX (7.5-15 mg) was directly related to GFR, with a decrease in MTX of 44.7 % in the category of patients with the poorest renal function (*i.e.*, creatinine clearance <45 mL/min, roughly equivalent to stage 3b).[272] Pooling data from RCTs of MTX for RA also indicates that presence of renal impairment (creatinine clearance <79 mL/min) increases the OR for severe and pulmonary toxicity by four compared to those with a creatinine clearance > 99.8 mL/min (reference group).[273] There are no studies evaluating use of MTX for psoriasis with CKD. US guidelines[42] consider renal impairment a relative contra-indication to MTX, and all recent RCTs with a MTX arm exclude patients with significant renal impairment. There are several case reports of life-threatening toxicity following MTX use in people on dialysis.[274] Guidelines in the rheumatology literature, largely consequent on the two studies referenced above, recommend avoiding MTX in people with creatinine clearance of <20 mL/min, and halving the dose in those between 20 and 50 mL/min.[275]

Biological therapy

To date, nephrotoxicity has not been reported as an AE in relation to all groups of biologic agents (TNF-α antagonists, IL-17A/IL-17RA antagonists, IL-12/23p40 antagonists, and IL-23p19 antagonists. Clearance of biological therapies should not be affected in case of CKD (of any stage).

Neurological diseases: which treatments are appropriate for psoriasis patients with neurological diseases?

Standard systemic therapy

Cyclosporine

Neurotoxicity is a well-established complication of CsA although it receives surprisingly little attention in literature. A comprehensive review[276] referencing data from (primarily) the transplant population, estimated that 10 and 28 % of patients receiving calcineurin-inhibitors experience neurotoxic side effects ranging from mild paresthesia and peripheral neuropathy through to centrally mediated complications such as altered cognition, visual disturbances, and seizures. Of these tremor and paresthesia are the commonest, and in the early trials in psoriasis, affected 40 and 25 % of participants receiving 5 mg/kg respectively.[277] Calcineurin is major component of neural tissue, and plays a key role in the regulation of nerve cell function, and neurotransmission;[278, 279] toxicity is dose-dependent and largely reversible. CsA does not readily cross the blood-brain barrier, however, conditions that disrupt the integrity of this, such as neurodegenerative disease, systemic infections, or hypertension, may perhaps also make patients more prone to the neurotoxic effects of CsA.[278] Additional factors such as CsA-related hypomagnesaemia[280] may also contribute. No studies were identified specifically reporting on outcomes in people with pre-existing neurological disease treated with CsA for psoriasis. Existing guidelines and the SmPC do not stipulate neurological disease to be a contraindication to treatment.

Fumarates

Dimethyl fumarate (DMF) has more recently been licensed and developed for use in psoriasis and is also a licensed treatment for MS[281] at doses of 240 mg BID. Fumarates may be a preferred option for the treatment of psoriasis in people with established MS. There has been a total of nine reports of confirmed progressive multifocal leukoencephalopathy (PML) in patients with psoriasis treated with fumarates; six with Fumaderm® (Biogen Idec, Cambridge, MA, USA), two with Psorinovo® (a slow release DMF formulation; Infinity Pharmaceuticals, Cambridge, MA, USA) and one with compounded fumaric acid esters.[282-290] In all cases, a degree of lymphopenia and/or other contributary factors for PML are thought to have been of direct etiological relevance.

Methotrexate

CNS toxicity is a well-recognized AE of high dose MTX, especially with intra-thecal administration. Low dose oral and s/c MTX have rarely been reported to cause a reversible leukoencephalopathy.[291,292] The SmPC cites drowsiness, ataxia, blurred vision, transient subtle cognitive dysfunction, mood alteration, and unusual cranial sensations as occasionally reported with low-dose MTX. No studies were identified specifically reporting on outcomes in people with pre-existing neurological disease treated with MTX for psoriasis. Existing guidelines and the SmPC do not stipulate neurological disease to be a contraindication to treatment.

Biological therapy

TNF-α antagonists

In vitro, murine and human data suggest that TNF has an important role in the pathogenesis of inflammatory demyelinating disease.[293] However, an early report of increased lesion activity in two MS patients receiving infliximab[294] as well as the withdrawal of Lenercept (a soluble p55 receptor developed for the treatment of MS) due to increasing severity and duration of symptoms in clinical trial subjects led to heightened awareness of potential risk of TNF-α antagonist therapy in the context of MS. More recently,[295] the single nucleotide polymorphism (SNP) rs1800693 in the TNFRSF1A gene associated with MS but not psoriasis (or other autoimmune conditions) has been shown to direct expression of a novel, soluble form of TNFR1 that can block TNF, hence lending further biological plausibility to a causal relationship between TNF-antagonism and demyelination. All five TNF antagonists have been associated with aggravation of MS and/or new onset central demyelination, which have been reviewed by Mahil *et al.* and Bosch *et al.*[296, 297] Case reports in more recently licensed anti-TNF agents golimumab[298, 299] and certolizumab[300] have been described. Of 84 cases of central demyelination reported in patients with psoriasis, the majority occurred within the first year of therapy; 33% (25/76) achieved complete recovery after cessation of anti-TNF +/- adjunctive therapy, 72% (55/76) did not achieve complete clinical recovery after cessation of TNF antagonist therapy. There were fourteen cases of worsening neurological disease despite cessation of anti-TNF therapy and several reports of new, clinically silent lesions detected on follow-up imaging.[296, 299-310] A case control study in rheumatoid arthritis using Canadian administrative claims and an electronic medical records database showed a trend towards an increased rate of demyelination in 891 patients with no risk factors (for demyelination). The authors suggested that TNF antagonist therapy may increase the risk of truly incident demyelinating events by ~30 %, although this result failed to meet statistical significance (adjusted rate ratio 1.31 [95% CI 0.68 to 2.50]).[311] To date, trial and pharmacovigilance registry data have not shown any increased risk, although this may relate to a low overall incidence, as well as exclusion of people at particular risk. With respect to peripheral disease, all forms of demyelinating neuropathies, including Guillain-Barrée syndrome, Miller-Fisher syndrome, multifocal motor neuropathy with conduction blocks, Lewis-Sumner syndrome, and chronic polyradiculoneuritis have been reported in association with TNF-α antagonist therapy, although the number of case reports in the literature are fewer when compared to central demyelination.[297, 312, 313] One report of five patients providing longer term data (up 3-4 years) indicated that once triggered, chronic demyelinating neuropathy may persist or recur irrespective of whether the TNF antagonist is discontinued.[313] Isolated cases of axonal neuropathy and vasculitis neuropathy are also reported.[297] US, UK and German psoriasis guidelines all advise avoidance of or caution with TNF-α antagonists in people with demyelination and caution in those at risk.

IL-12/23 pathway inhibitors

The IL (interleukin) 12 p40 family of cytokines (IL-12 and IL-23) has been strongly implicated in the pathogenesis of both MS and experimental autoimmune encephalomyelitis (EAE), an animal model that mimics many clinical and histological characteristics of MS. This prompted a phase II study evaluating the role of ustekinumab in patients with relapsing and remitting MS. Patients were randomly assigned 1:1:1:1:1 to placebo or 27 mg, 90 mg, or 180 mg ustekinumab every four weeks or 90 mg ustekinumab every eight weeks up to week 23. A total of 200 patients received at least one dose

of ustekinumab and whilst there was no evidence of benefit, there was no evidence of worsening neurological disease or increase in AEs when compared to placebo. To date, there has been one case report of primary progressive MS in a patient taking ustekinumab for refractory Crohn's disease[314] with the first neurological symptoms occurring around one year into therapy. She had received TNF antagonist therapy (infliximab, adalimumab, and certolizumab) prior to ustekinumab. With respect to peripheral demyelinating disease, a single case of Guillain Barré has been reported in a 23-year-old male with refractory Crohn's disease one year after commencing treatment with ustekinumab, having previously been treated with adalimumab.[315] A further isolated case of peripheral neuropathy of unspecified aetiology after three doses of ustekinumab was reported in an observational, retrospective 5-year follow-up study of ustekinumab in psoriasis.[316] Furthermore, the first case of reversible posterior leukoencephalopathy syndrome (RPLS) in a 65-year-old woman who received ustekinumab for over 2.5 years for psoriasis has been reported. She presented with mild hypertension, confusion, headache, nausea, vomiting, multiple seizures. Computed tomographic scans and magnetic resonance images of her head revealed characteristic findings of RPLS. Complete clinical recovery and reversal of the radiologic findings occurred, which is also considered typical of RPLS.[317] No data on the newer p19 inhibitors were identified.

IL-17 inhibitors

The IL 17A/F pathway is implicated in both psoriasis and multiple sclerosis, with elevated levels of IL-17A and IL-17F levels detected in both diseases.[318] Phase II randomized controlled data has shown encouraging results with secukinumab associated with a reduction in both the number of active and new MRI brain lesions in patients relapsing-remitting MS which were reduced by 49% and 67% respectively;[319] but this is yet to be replicated in further studies. There are five cases in the literature of patients receiving secukinumab for immune-mediated inflammatory diseases with concomitant MS. 80% (4/5) of patients with MS remained stable with no progression of disease and achieved remission of psoriasis/psoriatic arthritis/ankylosing spondylitis. 20% (1/5) had a relapse of MS and required treatment with rituximab.[320-323] There are no reported de novo cases of central demyelination with secukinumab, however longer-term safety data is required. No data on other IL17 agents (ixekizumab, brodalumab) were identified.

Summary and synthesis of recommendations

Except for TNF-α antagonists, any of the standard or biologic treatments can be used in people with co-existing neurological disease (Table LI). Although neurotoxicity is reported with CsA, and (rarely) with MTX, there is no evidence that those with pre-existing neurological disease are more at risk. The causal association between TNF antagonists and demyelination remains yet to be proven, although accumulating anecdotal reports, biological plausibility and expert consensus indicate that this class of drugs should be avoided in patients with a clear history of central demyelination. Given evidence for a genetic basis to MS,[324] and that asymptomatic first- degree relatives may have morphological evidence of subclinical disease and/or CSF oligoclonal bands,[325] it would seem prudent to use TNF antagonists with caution in this group too. Dimethyl fumarate is licensed for use in MS, and so may be a preferred first line option, however, surveillance monitoring of peripheral leukocyte counts is strongly recommended to minimize the risk of PML. Ustekinumab p19 and anti - IL 17 represent alternative treatment options. Recommendations for patients with neurological diseases are summarized in Table LI.

Viral hepatitis: When and how should psoriasis patients be screened for viral hepatitis and how should patients who test positive be managed?

Screening

Recommendations for the screening for viral hepatitis are summarized in Table LII (Figure 2).

Table LI.—*Recommendations for patients with neurological diseases.*

We **suggest** using fumarates in psoriasis patients with multiple sclerosis	↑	STRONG CONSENSUS# 100% Agreement
We **recommend against** using TNF antagonist therapy in psoriasis patients with a diagnosis of multiple sclerosis or other demyelinating disease	↓↓	
In psoriasis patients with a first-degree relative with multiple sclerosis or other demyelinating disease, we **suggest against** the use of TNF antagonist therapy if other suitable treatment options are available	↓	EXPERT CONSENSUS

#No abstentions due to personal-financial conflict of interest.

TABLE LII.—*Recommendations for the screening for viral hepatitis.*

We **recommend against** screening for **hepatitis A** as a routine measure before starting a systemic treatment	↓↓	STRONG CONSENSUS# 100% Agreement EXPERT CONSENSUS
We **recommend** screening patients for **hepatitis B** (HBsAg, anti-HBsAg, anti-HBcAg) as a routine measure before starting a treatment with cyclosporine, methotrexate or biologics	↑↑	
We **recommend** following the algorithm presented in fig. 7 for the interpretation of the **hepatitis B** test results	↑↑	
We **recommend** screening patients for **hepatitis C** as a routine measure before starting a treatment with methotrexate or biologics	↑↑	
In case of positive findings for **hepatitis C**, we **recommend** referral to a hepatologist	↑↑	

#No abstentions due to personal-financial conflict of interest.

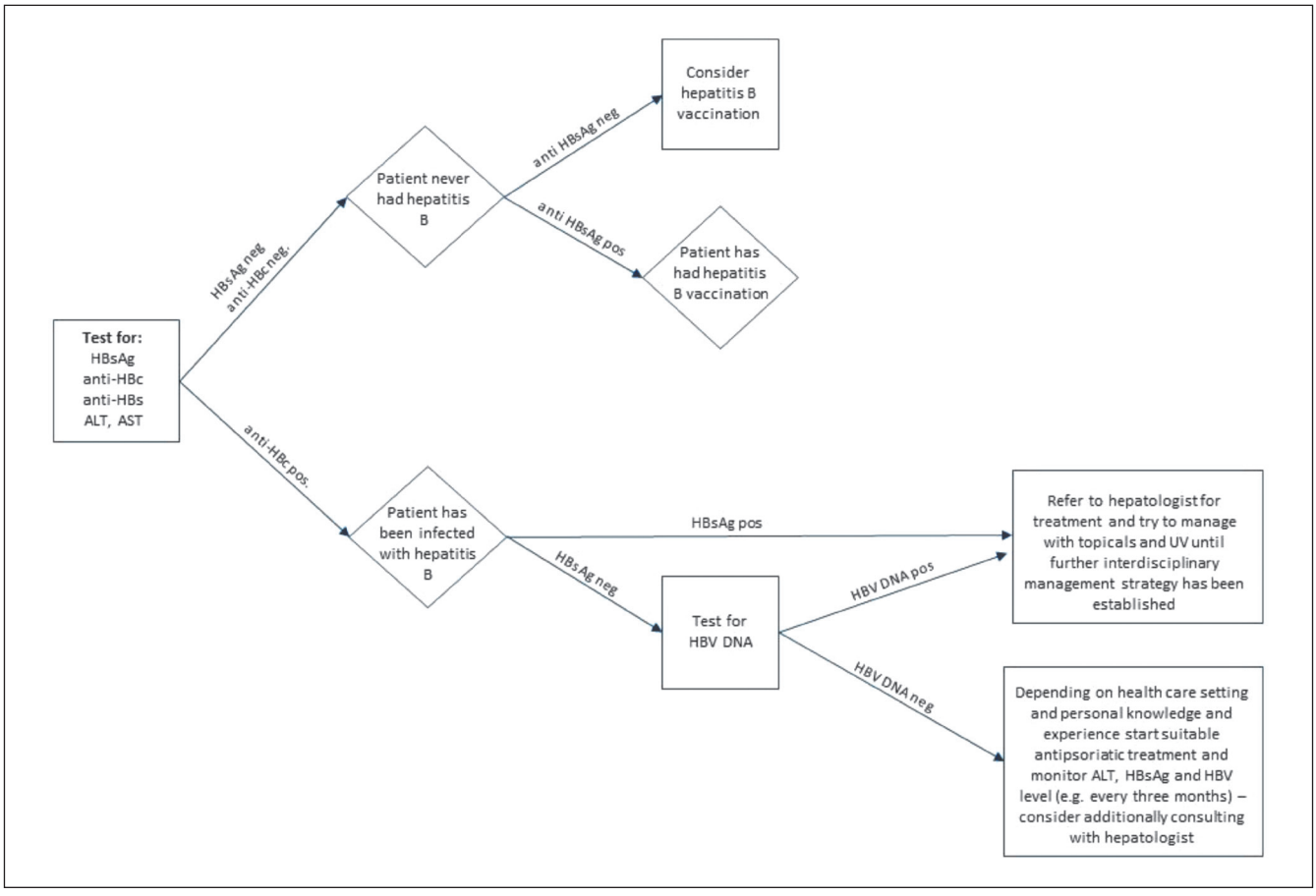

Figure 2.—Algorithm for the interpretation of the hepatitis B test results.

Choice of treatment

Recommendations for the choice of treatment for patients with viral hepatitis are summarized in Table LIII. The available data published is insufficient to give strong recommendations for or against using the available antipsoriatic drugs in patients with moderate-to-severe psoriasis and concomitant hepatitis B. Table LIV offers a summary

Table LIII.—*Recommendations for the choice of treatment.*

We **recommend** that treatment decision for patients with positive test result for HBsAg or positive HBV DNA should always be taken together with a hepatologist	↑↑	STRONG CONSENSUS#  EXPERT CONSENSUS
Depending on the individual health care setting and personal experience and training, we **suggest** consulting with a hepatologist to choose a systemic treatment for patients that have a positive anti-HBc with a neg. HBsAg/HBV-DNA test We **suggest**, based on the common practice within the guideline group, acitretin, apremilast, fumarates, MTX, ustekinumab and the anti-IL 17 and anti-IL 23 antibodies as preferred systemic treatment options for this patient group	↑	STRONG CONSENSUS#  EVIDENCE AND CONSENSUS BASED, SEE METHODS & EVIDENCE REPORT
We **recommend** regular testing for HBsAG/HBV-DNA (*e.g.,* every three months) during systemic treatment	↑↑	STRONG CONSENSUS# 
We **recommend** recording all treatment initiations and follow up visits of psoriasis patients with concomitant hepatitis B or C cases in drug registries	↑↑	EXPERT CONSENSUS

#No abstentions due to personal-financial conflict of interest.

Table LIV.—*Risk of hepatitis B reactivation during psoriasis treatment.*

Systemic treatments		Case of hepatitis B reactivation during psoriasis treatment identified in systematic search
Conventional systemic agents	Acitretin	No
	Ciclosporin	No
	Fumarates	No
	Methotrexate	No
Small molecules	Apremilast	No*
Anti-TNF alpha	Etanercept	Yes (see methods report for details)
	Infliximab	Yes (see methods report for details)
	Adalimumab	Yes (see methods report for details)
	Certolizumab	?
Anti-IL 12/23	Ustekinumab	Yes (see methods report for details)
Anti-IL 17	Secukinumab	Yes (see methods report for details)
	Ixekizumab	No*
	Brodalumab	No*
Anti-IL 23	Guselkumab	No*
	Tildrakizumab	No*
	Risankizumab	No*

*Reported cases need to be seen in correlation to approval date, especially with years and numbers of psoriasis patients with hepatitis exposed to the drug. For detailed information see methods report.

of reported cases of reactivation. Reported cases need to be seen in correlation to approval date, especially with years and numbers of psoriasis patients with hepatitis exposed to the drug. For detailed information, see methods report.

Italy is known to have a high prevalence rate of HCV infection, particularly in the regions of southern Italy. However, recently a much lower anti-HCV prevalence than those previously found was detected, along with a substantial change in HCV transmission modes. This epidemiological change is due to the implementation of a massive screening and therapy campaign after the advent of new generation antiviral drugs. A greater understanding of the HCV genome and proteins has enabled efforts to improve efficacy and tolerability of HCV treatment. Notably, this has led to the development of multiple direct-acting antivirals (DAAs), which are medications targeted at specific steps within the HCV life cycle. DAAs are molecules that target specific nonstructural proteins of the virus and results in disruption of viral replication and infection. The landscape of treatment has evolved substantially since the introduction of highly active dDAAs in 2011. The goals of treatment aim at viral complete eradication, delay fibrosis

progression, alleviate symptoms, prevent complications, minimize all-cause mortality, and ultimately maximize the quality-of-life. The application of the screening will make Italy a country on track for the World Health Organization HCV elimination goals within the year 2030. If a patient with psoriasis is screened positive for HCV, an infectious disease consultation is indicated for the eradicating treatment of hepatitis C. Once eradication therapy is completed, the patient may be a candidate for systemic treatment.

For some of the treatments, hepatitis is mentioned as a contraindication in the SmPC, although clinical practice, available case series or registry data may indicate a safety profile in line with treatments where this is not mentioned as a contraindication. This holds particularly true for methotrexate, where study data indicates at least no increase in liver fibrosis.[326]

Tuberculosis: how to screen for tuberculosis before and during biologic treatment?

Current guideline and recommendations for screening for tuberculosis (TB) vary between countries and specialties. There are variations in the recommended diagnostic tests, cut off values, follow up and preventive therapy regimens. A uniform approach for the diagnostic procedures and the interpretation of the test results for latent tuberculosis infection (LTBI) screening may reduce the cases of reactivation, but binding pan-European recommendations are partly hampered by different regional regulations. For recommendation for which treatment TB screening is recommended, please see respective drug chapters. Recommendations for the screening for tuberculosis and the screening algorithm are summarized in Table LV, LVI, respectively.

Tuberculin skin test (TST)

Diagnostic tests for the tuberculosis screening are summarized in Table LVII. False negative TST include those related to the protein purified derivative (PPD) (PPD expiration, experience, or loss of antigen [*e.g.,* subcutaneous administration]), and those related to the situation of the patient (HIV infection, recent infections and vaccinations, malignancy, metabolic diseases, immuno-suppressant therapy, or extreme ages [new-born, elderly]). False positive TST include those related to the administration and PPD lecture (inexperience, high amount of antigen), and cross-reactions (BCG vaccination, and most environmental nontuberculous mycobacteria). Although a BCG-

Table LVI.—*Algorithm for tuberculosis screening.*

Tuberculosis screening
Diagnostic for TB, regardless Bacillus Calmette-Guérin (BCG) vaccination, prior to and during follow up with biologic. One must be alert for TB infections during biologic treatment and up to six months after discontinuation. During treatment, rescreening for LTBI is recommended and frequency should be based on patient history, risk of exposure, as well as tuberculin skin test (TST) and interferon gamma release assay (IGRA) results
Patient's history
• Suspicious symptoms for TB
• History of TB, adequate treatment
• Exposure to TB
• Origin from or recently stayed for a long time in an endemic area
• High risk patient
• BCG vaccination
Physical examination, to consider
• Auscultation of the lungs if symptomatic (not specific for TB diagnosis)
• Scar (left) upper arm (may indicate a BCG vaccination)
• Enlarged lymph nodes, abscess scars
Chest X-ray (if the chest X-ray has been performed more than 3 months ago, a new chest X-ray is required)
• Suspicious for active, LTBI or history of TB?
• Consult pulmonologist if abnormalities
TST* and/or IGRA
• If IGRA and TST are performed, the IGRA can best be drawn right after the TST is assessed. If drawing is done more than three days after the TST, the TST can booster the IGRA and result in a false-positive response
• The recommendation to perform IGRA testing rather than TST testing is strong for those who have received the BCG vaccination

*It is necessary to follow the local recommendations, as the threshold for the TST is different among countries and even among regions within the same country. In most of the countries ≥5 mm is considered positive.

Table LV.—*Recommendations for the screening for tuberculosis.*

We **recommend** screening for tuberculosis according to local regulations	↑↑	STRONG CONSENSUS# 100% Agreement
For pre-screening, we **recommend** taking a thorough patient history including tuberculosis history; a chest X-ray; TST and/or IGRA	↑↑	
We **recommend** remaining alert to the possibility of tuberculosis infection during therapy. This includes taking medical history and might include tuberculosis testing	↑↑	EXPERT CONSENSUS

#No abstentions due to personal-financial conflict of interest.

Table LVII.—*Diagnostic tests for the tuberculosis screening*

TST*	IGRA	Diagnosis	Policy
<5 mm	negative	Depends on patient history	If no TB suspicious patient history or symptoms, no history of TB, no TB exposure, no living in or travel to endemic area, and no high-risk patient, a biologic can be given
			If yes: consult pulmonologist for any further diagnosis and treatment
			TB infection can still be present in HIV-infected patients with a low CD-4 count
≥5 mm <10 mm	negative	LTBI or active TB with false negative IGRA, or false positive TST	Consult pulmonologist for any further diagnosis and treatment
> 10 mm	negative	Strongly consider LTBI or active TB with false negative IGRA, or false positive TST	Consult pulmonologist for treatment
Every result	QFT-G 0.2-0.35 U/ml	Consider LTBI or active TB, or IGRA false positive	Consult pulmonologist for any further diagnosis and treatment
Every result	Positive (QFT-G > 0.35 U/ml)	Strongly consider LTBI or active TB	Consult pulmonologist for treatment

*Tuberculin skin test.

vaccination or an atypical mycobacterial infection may cross-react with the TST, causing a false positive result, the tuberculin reaction would usually be much higher if active TB is truly present. The BCG vaccination may fade over time and no cross-reaction would occur. Regardless the BCG vaccination, in general, an assessment of ≥5 mm induration will be considered as positive. A patient may then be referred directly to a pulmonologist. In patients with a history of BCG vaccination, IGRA testing is preferred over TST.

IGRA

IGRA is a specific blood test. After a *Mycobacterium Tuberculosis* infection, T cells will release interferon-gamma (IFN-γ) in response to contact with the TB antigens. Two measurements for interferon-gamma are known; the QuantiFERON®-TB Gold-test (QFT-G; QIAGEN, Hilden, Germany), based on the amount of IFN-γ that is released in response to the antigens, and the T-SPOT® TB test (T-SPOT; Medics Labor, Bern, Germany), counting the number of T cells that produce IFN-γ in a sample of blood. The IGRA is not affected by prior BCG vaccination, however the interpretation of results (borderline results) might be limited due to issues in the cut-off values, shifting conversions and reversion rates over time, and varying test reproducibility. Neither TST or IGRA allow to distinguish between active or latent TB.[327] A suppressed immune system reduces the sensitivity of tests based on T cell responses. Only positive results will be convincing in that case, while negative results cannot rule out a TB infection. A negative IGRA, following a positive TST, can still suggest a LTBI. Besides, the IGRA can be unreliable (false negative) if other immunosuppressive medications were applied in advance. An IGRA is also recommended if the TST was less than 5 mm in induration. Negative results of TST or IGRA of HIV-infected patients with a low CD-4 count cannot rule out a TB infection.

Screening during biologic treatment

Physicians must be aware that there is still a risk of active tuberculosis under biologic therapy, even if LTBI was correctly treated. Therefore, LTBI rescreening is preferable during biologic treatment. The frequency should take risk exposure into consideration. Besides medical history, both TST and IGRA are recommended, because of the influence that the biologic may have (false-negative) on these tests. A high index of suspicion should also be maintained for six months following discontinuation.

Tuberculosis: how to manage psoriasis in patients with positive tuberculosis test results?

Depending on the prevalence of TB and on the health care situation, dermatologists may be able to interpret positive findings, to make further management decisions themselves or to directly refer patients to infectious disease specialists where interdisciplinary cooperation is common.

Interpretation of positive findings in IGRA/TST

Patients with active and latent tuberculosis (TB) can be identified using either the interferon gamma release assay (IGRA) or tuberculin skin test (TST). However, neither test can distinguish between the latent and active states of the disease.[327] **IGRA** is a specific blood test. The interpre-

tation of IGRA test results (especially borderline results) can be limited due to issues in the cut-off values, shifting conversions and reversion rates over time, and varying test reproducibility. In case of borderline results, repeating the test may be advisable.[327] The sensitivity of **TST** for latent tuberculosis infection (LTBI) has been described as 74 % and the specificity of 89 % in a meta-analysis.[328, 329] The positive predictive value for TB infection by the TST depends on the prevalence of TB within a given region/population and the possibility of cross-reactions. False positive TST include those related to the administration of purified protein derivative (PPD) and its lecture (inexperience, high amount of antigen), and cross-reactions (BCG vaccination, and most environmental non-tuberculous mycobacteria). Although the TST would usually be, much higher if active TB is truly present. Means to distinguish between active and latent TB commonly used in the guidelines group experts' setting include medical history (exposure risk), signs and symptoms (*e.g.,* current cough, fever, weight loss, night sweats), chest X-ray[330] and urinalysis (pyuria).[331-333] For details of differential diagnosis of latent *versus* active TB, please see respective guidelines and reviews.[327, 330, 334] Recommendations for the management of psoriasis patients with positive tuberculosis test results are summarized in Table LVIII. Different treatment regimens are available for LTBI with duration depending on monotherapy or combinations. In clinical practice, the most widely accepted treatments are isoniazid (INH) for six months and INH + rifampicin (RIF) for three months (Table LIX).[335] Patients should have regular check-ups during chemoprophylaxis treatment to detect any drug-related adverse events (*e.g.*, hepatotoxicity) and to monitor for symptoms of TB during treatment with biologics, as reactivation has been reported even after screening and chemoprophylaxis for LTBI has been completed.[137] Therapeutic regimens for LTBI are summarized in Table LIX.[330]

Risk of TBC reactivation with different treatments

Conventional treatments/small molecules

Data on the reactivation risk with acitretin, CsA, fumarates, MTX and apremilast is scarce. Most published guidelines have not recommended TB screening for these drugs (except MTX and CsA).[336] Screening before treatment with MTX is recommended in the summary of products characteristics (SmPC). The sensitivity of IGRA and TST may be influenced by conventional immunosuppressive treatments, so doing IGRA initially may be beneficial if a later switch, especially from MTX to other drug categories appears likely.[337]

Biologics

A higher risk of latent TB reactivation under treatment with infliximab or adalimumb has been identified, with a lower risk of reactivation with etanercept. Cases of latent TB reactivation with ustekinumab have been reported in a long-term study of up to 5 years.[249] The risk of latent TB reactivation seems to be lowest during treatment with anti-IL 17 and anti-IL 23 targeted treatments.[137, 338] In a systematic review by Snast *et al.*, 78 patients who developed active TB during biologic treatment were analyzed. Eighty percent of all cases were treated with adalimumab or infliximab, 12% were treated with etanercept. No case

Table LVIII.—*Recommendations for the management of psoriasis patients with positive tuberculosis test results.*

We **recommend** discussing the decision to initiate immuno-suppressive therapies in patients with signs of latent tuberculosis with an infectious disease specialist (case-by-case basis)	↑↑	STRONG CONSENSUS# 100% Agreement
As a commonly used procedure in case of latent TB, a treatment with isoniazid can be **recommended** with treatment initiation one month before the start of the immunosuppressive therapy and should be continued for 6 months (for alternatives see Table 43)	↑↑	EXPERT CONSENSUS

#Due to personal-financial conflict of interest 4 abstentions.

Table LIX.—*Therapeutic regimens for LTBI. Modified from WHO.*[330]

Drug	Dose	Treatment duration
INH alone (daily)	5 mg/kg; max dose: 300 mg	6-9 months
RIF alone (daily)	10 mg/kg; max dose: 600 mg	3-4 months
INH+RIF (daily)	INH: 5 mg/kg; max dose: 300 mg RIF: 10mg/kg; max dose: 600 mg	3-4 months

Treatments with pyrazinamide should be avoided (high risk of hepatotoxicity).
INH: isoniazide; RIF: rifampicin.

of active TB was identified with the anti–interleukin-17 agents (ixekizumab, secukinumab, and brodalumab); however, the total patient exposure years for these at the time of analysis were much shorter than for the TNF antagonists. All patients in this review had initially been screened for TB. In most cases of reactivation, patients presented with extra-pulmonary disease within the first six months of biologic therapy.[339] Table LX[340-349] provides an overview of the screening practice based on reactivation risk during antipsoriatic treatments. The risk assessment may be biased due to the different time periods when the cases occurred. At the time of TNF alpha introduction, TBC screening was not always done, leading to less testing and higher numbers of patients with latent TB being exposed to the respective drugs. In addition to the reported cases of TB reactivation, pathophysiological considerations of the immune response to TB favor the group of anti-IL-17 and anti-IL-23 as treatment options. IL-12 has been reported to play a role in the anti TB immune response. Recommendations for the treatment of psoriasis patients with latent TB are described in Table LXI.

Wish for child pregnancy: how should psoriasis patients with a wish for pregnancy in the near future or who are pregnant be managed?

Psoriasis commonly affects men and women planning conception and women who are pregnant, so understanding the risks of therapy during conception and pregnancy is crucial. Psoriasis is not known to have a significant impact on either male or female fertility. Although pregnancy has an unpredictable effect on psoriasis, limited evidence suggests that psoriasis usually improves; around 55% improve during pregnancy, 25% report no change, and 25% worsen.[350, 351] Conversely in the *post-partum* period, psoriasis is more likely to flare; around 65% worsen, 25% demonstrate no change and 10% improve. Maternal and fetal health outcomes are vital considerations when deciding on the optimal treatment for individuals with psoriasis who are planning conception or are pregnant. Although data are limited and not always consistent across studies,[352] untreated severe psoriasis in the mother may be detrimental for fetal well-being and pregnancy outcomes, for example

TABLE LX.—*LTBI screening indication based on different systemic treatments.*

Systemic treatments		SmPC	Comments
Conventional systemic agents	Acitretin	No	No cases of reactivation have been reported[340]
	Cyclosporine	No	Cases have been reported in organ transplant patients with high doses of CsA.[340]
	Fumarates	No	No cases of reactivation have been reported.[341, 342]
	Methotrexate	√	Cases of reactivation have been reported.[343]
Small molecules	Apremilast	No	Increased risk has not been reported.[344]
Anti-TNF alpha	Etanercept	√	Increased risk of reactivation has been reported.[345, 346]
	Infliximab	√	Increased risk of reactivation has been reported.[345, 346]
	Adalimumab	√	Increased risk of reactivation has been reported.[345, 346]
	Certolizumab	√	Increased risk of reactivation has been reported.[340, 345]
Anti-IL 12/23	Ustekinumab	√	Uncertain risk of reactivation (cases have been reported).[340, 347]
Anti-IL 17	Secukinumab	√	Increased risk has not been reported in clinical trials.[347]
	Ixekizumab	√	Increased risk has not been reported in clinical trials.[347]
	Brodalumab	√	Increased risk has not been reported in clinical trials.[347]
Anti-IL 23	Guselkumab	√	Increased risk has not been reported in clinical trials.[348]
	Tildrakizumab	√	Increased risk has not been reported in clinical trials.
	Risankizumab	√	Increased risk has not been reported in clinical trials.[349]

Reported cases need to be seen in correlation to approval date, especially with years and numbers of psoriasis patients exposed to the drug.

TABLE LXI.—*Recommendations for the treatment of psoriasis patients with latent TB.*

We **recommend against** TNF alpha antagonists as a treatment for patients with latent TB unless there are no other suitable treatment options	↓↓	STRONG CONSENSUS# 100% Agreement
We **recommend** remaining alert to signs and symptoms of tuberculosis activation or re-infection during therapy	↑↑	
We **suggest** acitretin, apremilast or fumarates or a treatment from the anti-IL-17 and anti-IL-23 group for patients with latent TB that require a systemic antipsoriatic treatment	↑	EXPERT CONSENSUS

#No abstentions due to personal-financial conflict of interest.

it has been shown to be associated with preterm birth and low birthweight babies.[353, 354] The risk of untreated psoriasis of the mother in pregnancy must therefore be weighed against any potential harm through drug exposure of the fetus. Other factors that may impact pregnancy outcomes include alcohol consumption, smoking and comorbidities such as obesity and depression (which are more prevalent in greater disease severity).[355] Despite the rapidly increasing number of medications available for the treatment of psoriasis, knowledge on their safety in pregnancy remains limited.

Non-biologic systemic drugs

Acitretin

Acitretin is teratogenic and is contraindicated in women of child-bearing potential, those planning pregnancy, breastfeeding or not capable of using contraception until three years after cessation of therapy.[356]

Apremilast

There are limited data about the use of the small molecule apremilast during pregnancy. Previous studies on animals did not show an increase in malformations with apremilast but have shown dose-related fetal loss and reduced birth weight. Apremilast is therefore contraindicated during pregnancy.[357] Women of child-bearing potential should use effective contraception to prevent pregnancy and continue this until at least four weeks after cessation of apremilast treatment.[357] Apremilast was detected in the milk of lactating mice at levels approximately 1.5-fold that of blood plasma samples.[358, 359] It is unknown whether apremilast or its metabolites are excreted in breast milk in humans, therefore apremilast should not be used whilst breastfeeding.[357, 359] No data are available regarding the influence of apremilast on fertility in humans.[357]

Cyclosporine

Cyclosporine crosses the placenta, but there is no evidence for teratogenicity.[360] Experience with solid organ transplant recipients indicates that ciclosporin increases the chance of pregnancy-specific complications such as pre-eclampsia and low birthweight. In pregnant women with plaque psoriasis receiving cyclosporine, the advantages and disadvantages of continuing cyclosporine should be considered. Cyclosporine should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus.[360] The ethanol content of the Sandimmun Neoral (Novartis International AG, Basel, Switzerland) formulations should also be considered in pregnant women. If necessary, cyclosporine treatment can be continued with close follow-up, preferably together with an obstetrician.[39,360] Cyclosporine is transferred into breast milk, therefore cyclosporine use is contraindicated during breastfeeding. There is limited data on the effect of ciclosporin on human fertility.

Dimethyl fumarate

Dimethyl fumarate is contra-indicated in women of child-bearing potential who are not using appropriate contraception.[361] Dimethyl fumarate should not be taken by women who are pregnant, breast-feeding or attempting conception. There are no published reports of patients becoming pregnant while on dimethyl fumarate.[362] No data are available on the effects of dimethyl fumarate on female fertility.[361] In patients with diarrhea during treatment with dimethyl fumarate, the effect of oral contraceptives can be reduced. Additional use of barrier methods of contraception is therefore recommended.[361] It is unknown whether fumarates or their metabolites are excreted in breast milk, therefore the use of fumarates is contraindicated during breastfeeding.[361]

Methotrexate

Methotrexate is a folic acid antagonist known to be teratogenic in humans. In a recent review, statistically significant higher proportions of microcephaly, craniosynostosis, tetralogy of Fallot, pulmonary valve atresia, limb reduction defects and syndactyly were found in new-born babies after maternal use of methotrexate in pregnancy.[363] Spontaneous abortions were observed more frequently in pregnant women receiving methotrexate (less than 30 mg/week) compared to women with comparable diseases treated with other medications (42.5% *versus* 22.5%).[364] Therefore, where relevant, women should be counselled about pregnancy and breastfeeding, and should not conceive whilst taking methotrexate.[364] Recent EMA guidelines recommend discontinuing methotrexate for 6 months before attempting conception, which is a change from the previous recommendations of 3 months.[365] No evidence pertaining to the standard dose of methotrexate (5-30 mg/week) for inflammatory diseases is cited for this change of recommendation. The practice of the guideline group differs from this in favor of a shorter period of discontinuation (3 months). It is recommended that sexually active women have a pregnancy test prior to starting therapy and use two methods of contraception throughout the period of methotrexate treatment. In the event of pregnancy during methotrexate therapy, immediate referral to an obstetrician

is required.[366] Methotrexate influences oogenesis and possibly can reduce fertility, especially in high doses. In most patients this is reversible after stopping methotrexate.[364] Methotrexate is excreted into breast milk and so should not be used when breastfeeding.

Recommendations (non-biologic systemic drugs)

When providing advice on use of systemic therapies in women planning conception or who are pregnant, prescribers are advised to use these recommendations with reference to the individual drug SmPC.

Recommendations for the treatment of psoriasis in women planning conception (non-biologic systemic drugs) are summarized in Table LXII.

Biologic drugs

Data from studies reporting pregnancy outcomes in women exposed to biologic treatments during conception and/or pregnancy were recently comprehensively reviewed as part of the British Association of Dermatologists guidelines for biologics use in psoriasis.[367] All of the biologic agents that are currently licensed for psoriasis except certolizumab pegol contain a human IgG1 Fc region and are actively transported across the placenta via neonatal Fc receptors.[368, 369] Active placental transfer is thought to be very low during the first trimester when organogenesis takes place, hence the theoretical risk of teratogenicity of biologics is low. Active transfer can, however, occur at around 13 weeks' gestation and increases significantly after 20 weeks' gestation. This increasing exposure to biologics during the second and third trimesters is hypothesized to adversely affect fetal development, leading to potential risk of neonatal immunosuppression and greater risk of neonatal infections.[370] Biologic therapies typically disappear from an infant´s serum within the first six months of life. In contrast, certolizumab pegol is the only PEGylated humanized antigen-binding fragment of a TNF antagonist and it lacks a Fc domain.[371] Certolizumab pegol therefore does not bind to the human neonatal Fc receptor and it is not actively transferred across the placenta. This was underscored by an analysis of 31 pregnancies exposed to infliximab, adalimumab and certolizumab pegol (for inflammatory bowel disease), in which the median levels of infliximab, adalimumab and certolizumab pegol in the cord blood of infants compared with that of mother were 160%, 153%, and 3.9%, respectively.[372] Infliximab and adalimumab could be detected in the infants for as long as 6 months. Postmarketing prospective pharmacokinetic research has confirmed no/minimal transfer of certolizumab pegol via the placenta (CRIB study, N.=16)[373] and into breast milk (CRADLE study, N.=19).[374] Population-based cohort studies that report pregnancy outcomes in women exposed to biologics during conception and/or pregnancy are limited to TNF antagonist exposure only (see the respective table).[375-387] No evidence was identified on the use of IL-12/IL-23p40, IL-17 or IL-23p19 inhibitor biologics. Overall, the available studies identified no clear evidence of drug-specific harm to the fetus following TNF antagonist exposure with respect to congenital malformations, live births, preterm births or neonatal infections.[375-387] One study (in inflammatory bowel disease) addressed maternal infection, indicating a potential increased risk to the mother following TNF antagonist exposure.[379] The evidence is overall limited since most studies involved small cohorts that may be underpowered to demonstrate small but significant risks associated with the treatments. Most of the evidence also relates to women with other chronic inflammatory conditions such as inflammatory bowel disease or arthritis rather than psoriasis specifically. Several of the outcomes were

TABLE LXII.—*Recommendations for the treatment of psoriasis in women planning conception (non-biologic systemic drugs).*

We **suggest** cyclosporine as a first line convention agent in women planning conception and when it is necessary to start systemic therapy during the 2nd and 3rd trimester of pregnancy	↑	STRONG CONSENSUS# 100% Agreement EXPERT CONSENSUS
Methotrexate and acitretin are contra-indicated in women planning conception. We **recommend against** using these	↓↓	
Fumarates and apremilast are contra-indicated in women planning conception. We **suggest against** using these	↓	
We **recommend** consultation and information sharing across specialties, including with an obstetrician with expertise in caring for pregnant women with medical problems	↑↑	
We **recommend** the collection of maternal exposure to medications and pregnancy outcome data in national safety registries where available	↑↑	

#No abstentions due to personal-financial conflict of interest.

poorly defined and heterogeneous, making it difficult to ascertain whether a pattern of specific birth defects was occurring. There is also a paucity of information on long-term outcomes for children born to women receiving biologics.

Recommendations (biologic drugs)

When providing advice on use of systemic therapies in women planning conception or who are pregnant, prescribers are advised to use these recommendations with reference to the individual drug SmPC. All biologic drugs currently licensed for psoriasis (except for certolizumab pegol) are actively transferred to the fetus during the second and third trimester, and the impact of this on neonatal development and risk of infection (to both mother and baby) has not been adequately studied. Recommendations for the treatment of psoriasis in women planning conception (biologic systemic drugs) are described in Table LXIII.

Necessity for continuing contraception immediately following biologic treatment cessation

There is no consensus on how long contraception needs to be continued after stopping treatment with a biologic. Table LXIV[380] gives an overview of the recommended minimum time lag between stopping a biologic treatment and conception, as stated in the respective SmPCs. For treatments with a good safety profile during pregnancy, continuation of contraception immediately following treatment cessation may not be as relevant as for treatments with an unknown or less favorable safety profile. It is worth noting, that active placental transfer of biologics starts to occur around 13 weeks' gestation and increases significantly after 20 weeks' gestation. The specific half-lives of the respective drugs impact the remaining drug level at these time points.

Paternal use

In men who are planning conception, the effects of systemic medications on both fertility and fetal development are important considerations. However, there is very limited data on the impact of paternal exposure to systemic medications, particularly with respect to teratogenicity and long-term sequelae. An overview of minimum time between stop of treatment and conception as given by respective SmPC is summarized in Table LXIV.[380]

TABLE LXIII.—*Recommendations for the treatment of psoriasis in women planning conception (biologic systemic drugs).*

We **suggest** certolizumab pegol as a first line choice when starting biologic therapy in women planning conception (when a biologic is considered essential to use in pregnancy) and when it is necessary to start a systemic therapy during the second or third trimester	↑	STRONG CONSENSUS# 100% Agreement EXPERT CONSENSUS
We **suggest** stopping biologic therapy in the second and third trimester (except certolizumab pegol) to minimise foetal exposure and limit potential infection risk to the neonate	↑	
We **suggest against** using live or live attenuated vaccines in infants (up to 6 months of age) whose mothers received biologic therapy beyond 16 weeks gestation, unless the benefit of the vaccination clearly outweighs the theoretical risk of administration	↓	
We **recommend** consultation and information sharing across specialties, including with an obstetrician with expertise in caring for pregnant women with medical problems	↑↑	
We **recommend** the collection of maternal exposure to medications and pregnancy outcome data in national safety registries where available	↑↑	

#No abstentions due to personal-financial conflict of interest.

TABLE LXIV.—*Overview of minimum time between stop of treatment and conception as given by respective SmPC.*

Infliximab	Adalimumab	Etanercept	Ustekinumab	Secukinumab	Apremilast*
6 months	5 months	3 weeks380	15 weeks	20 weeks	No information provided in SmPC, 28 days advised by Celgene
Ixekizumab	Certolizumab	Brodalumab	Tildrakizumab	Guselkumab	Risankizumab
10 weeks	5 months*	12 weeks	17 weeks	12 weeks	21 weeks

*Certolizumab is the suggested biologic treatment option, for women who are planning conception or are pregnant and require a systemic therapy, see also respective chapters.

Acitretin

Acitretin has no known effect on male fertility.[388] Traces of acitretin have been reported in the semen of men, however there is no evidence of teratogenicity at conception as the main at-risk period is 4-6 weeks later.[389] Although ongoing exposure via direct contact with semen during unprotected sexual intercourse after conception is of low risk, the barrier method of contraception postconception may be considered.[358]

Apremilast

There are no available data for the impact of paternal exposure to apremilast on male fertility or pregnancy outcomes. In animal studies in mice, no adverse effects on fertility were observed in males at exposure levels threefold clinical exposure.[18]

Cyclosporine

There is no evidence that paternal use of ciclosporin affects male fertility, however there are a paucity of studies on this.[358, 390, 391] Recent systematic reviews of cohort study data showed no impact on pregnancy outcomes.[358, 390] This includes data from a Danish registry study of 247 children conceived during paternal use of ciclosporin, which found no association between paternal exposure to ciclosporin and increased risk of congenital abnormalities.[392]

Fumarates

A recent European consensus meeting concluded that contraception for males receiving fumarates is not required, although there is a paucity of evidence.[361]

Methotrexate

Fertility.—A recent systematic review identified 48 male exposures to methotrexate,[390] of which there were two isolated case reports of oligospermia (one reversible and one irreversible).[393, 394] Another five publications comprising the remaining 46 exposures concluded that there was no impact of methotrexate on male fertility.[390] A case series of 26 men receiving methotrexate who had their semen examined using radioactive phosphorus for testicular histology and spermatogenic function showed no negative impact on fertility.[395] Another study compared semen parameters from ten men treated with methotrexate for severe psoriasis with those of ten men using topical steroids, and found that those taking methotrexate were significantly more likely to have normal semen parameters.[396]

Pregnancy outcomes.—Paternal methotrexate use has not been shown to cause teratogenicity or adverse pregnancy outcomes. A recent systematic review which reported 1511 peri-conception paternal methotrexate exposures concluded that there was no link between paternal methotrexate exposure and adverse pregnancy outcomes or congenital malformations.[390] The largest cohort studies, comprising national registry data[392, 397, 398] and longer-term outcomes,[399] showed no increased risk of paternal methotrexate exposure on pregnancy outcomes. Although the above data do not support the need for any washout period for methotrexate, further evidence is required before this can be recommended. Recent EMA guidelines recommend discontinuing methotrexate for six months before attempting conception, which is a change from the previous recommendations of three months.[365] No evidence pertaining to the standard dose of methotrexate (5-3 0mg/week) for inflammatory diseases is cited for this change of recommendation. The practice of the guideline group differs from this in favor of a shorter period of discontinuation (3 months).

Biologics

Although there is limited available data, cohort studies of TNF antagonists found no evidence for impairment in fertility during paternal use.[358, 391] A systematic review highlighted that sperm motility and vitality may even improve under TNF antagonist therapy, possibly due to a decrease in disease activity.[400] Cohort studies (total of 60 exposures with outcome events documented in 28 cases) involving a range of TNF antagonists (adalimumab, certolizumab pegol, etanercept, infliximab) also demonstrated no evidence for an association between impaired pregnancy outcomes and paternal use of TNF antagonist therapy at the time of conception.[358, 390, 400, 401] There are no studies which have assessed the potential impact of paternal exposure to other biologic agents including IL-12/IL-23p40 inhibitors, IL-17 inhibitors or IL-23p19 inhibitors on male fertility or pregnancy outcomes. Recommendations for men attempting conception are described in Table LXV.

Vaccinations: how should vaccinations in psoriasis patients on systemic treatment be managed?

In patients with psoriasis vaccination using dead vaccines and live vaccines can be performed at any time, unless a systemic treatment is given that necessitates a different strategy. Psoriasis on its own should not be considered a reason to deviate from standard vaccination recommen-

TABLE LXV.—*Recommendations for men attempting conception.*

It is **recommended** that men discontinue methotrexate 3 months before attempting conception*	↑↑	STRONG CONSENSUS# 100% Agreement
As a precaution, it is **suggested** that men taking acitretin use barrier forms of contraception post-conception to limit exposure via direct contact with semen during pregnancy	↑	
We **recommend** the collection of paternal exposure to medications during conception and pregnancy outcome data in national safety registries where available	↑↑	EXPERT CONSENSUS

*EMA recommends 6 months as a means of precaution, the practice of the guideline group differs from this; #No abstentions due to personal-financial conflict of interest.

dations. Before initiating a systemic treatment, vaccination status should be checked and completed if possible. Annual flu vaccination and vaccination against pneumococci (for those 60 and older) is particularly recommended. National recommendations for vaccinations should be followed.[402] When psoriasis patients receive any kind of systemic therapy dead vaccines can be given; however, vaccination responses may be decreased. Therefore, it is recommended to use inactivated vaccines 2 weeks, and attenuated live zoster vaccine 2-4 weeks prior to initiation of systemic therapy. If patients receiving systemic/immunosuppressive therapy inactivated vaccines should be given without treatment interruption.[403] Live vaccines (including measles-mumps-rubella, varicella) can be used in patients receiving acitretin, apremilast, fumarates, and methotrexate. Live vaccines are contraindicated in psoriasis patients treated with cyclosporine, TNF-α-antagonists adalimumab, certolizumab, etanercept and infliximab, and the interleukin 17A-antibodies ixekizumab and secukinumab, and interleukin 17RA-antibody brodalumab. Generally, before administration of a live vaccine after discontinuation of immunosuppressive therapy, the drug's half-life (specifically, the time of five half-lives) and mechanism of action should be taken into consideration. For the following medications, the respective SmPC provide recommendations regarding timing is available:

- guselkumab – wait two weeks after live vaccine, start vaccination 12 weeks after last dose;[404]
- risankizumab – wait four weeks after live vaccine, start vaccination 21 weeks after last dose;[95]
- ustekinumab – Wait two weeks after live vaccine, start vaccination 15 weeks after last dose;[405]
- tildrakizumab – wait four weeks after live vaccine, start vaccination 17 weeks after last dose.[104]

For live or live attenuated vaccines in infants (up to six months of age) whose mothers received biologic therapy beyond 16 weeks gestation see chapter pregnancy.

Immunogenicity of targeted therapies in psoriasis

A lack of fully comparable information on the formation of antidrug antibodies against targeted therapies in psoriasis has been identified during the guideline's development. Within the scope of this version of the guideline, a thorough systematic search of the available evidence has not been feasible and a consensus on consequent measures has not been achieved. The author group acknowledges that there is evidence of a beneficial effect of the combination of methotrexate with adalimumab from psoriasis patients and MTX with infliximab in rheumatoid arthritis or Crohn's disease patients to reduce the formation in ADA. The guideline group encourages research to pursue further investigations into the field of antidrug antibodies and to generate data that allows comparison between different drugs and that can lead clinically relevant recommendations. The authors encourage further opinion papers, narrative, or preferably systematic reviews to further advance the discussion on immunogenicity.[406-408]

COVID-19: guidance for systemic therapy of psoriasis during COVID-19 pandemic

A narrative review of the existing literature was conducted from the EurGuiDerm group in late April 2020. The most up to date version of this chapter can be found alongside the main guideline document on the EDF website.

The SIDeMaST actively supported the Italian dermatological community during the period of the pandemic by providing detailed information, specific recommendations for clinical practice and promoting observational studies on COVID-19 which are listed below with related links and/or references.

- Detailed information on COVID-19 for both patients and physicians are available from: https://www.sidemast.org/blog/coronavirus.[409]

• Micali G, Musumeci ML, Peris K; Board Members of the SIDeMaST. The Italian dermatologic community facing COVID-19 pandemic: recommendation from the Italian society of dermatology and venereology. G Ital Dermatol Venereol 2020;155:123-5.[410]
• Specific recommendations for clinical practice, namely the vademecum for patients with psoriasis and psoriatic arthritis on systemic treatment (available from: https://www.sidemast.org/blog/infezione-da-coronavirus-vademecum-per-i-pazienti-affetti-da-psoriasi-cutanea-e-o-artropatia-psoriasica).[411]
• The PSO-BIO-COVID is an observational, multicentric study, supported by SIDeMaST, aimed at evaluating the impact of SARS-CoV-2 infection on the management of patients with psoriasis in Italy, during the first year of the pandemic (available from: https://www.sidemast.org/blog/studio-n-1-pso-bio-covid). The results of this study have been published as follows. [412]

Management of biological therapies for chronic plaque psoriasis during COVID-19 emergency in Italy

A total of 12 807 psoriatic patients from 33 specialized dermatologic centres were included in the study. 328 patients (2.6%) stopped treatment during the observation period without consulting their dermatologist mainly because of fearing high contagious risk; 233 (1.8%) interrupted their therapy after consulting their dermatologist mainly because of suspected infection or contact with the SARS-CoV-2 as they were professional healthcare providers, or they have had a contact with SARS-CoV-2+ subjects (Talamonti M, Galluzzo M, Chiricozzi A, Quaglino P, Fabbrocini G, Gisondi P, *et al.*; PSO-BIO-COVID study group. Management of biological therapies for chronic plaque psoriasis during COVID-19 emergency in Italy. J Eur Acad Dermatol Venereol 2020;34:e770-e772).[413]

Characteristic of chronic plaque psoriasis patients treated with biologics in Italy during the COVID-19 pandemic: risk analysis from the PSO-BIO-COVID observational study

The aims of this study were: 1) to assess the prevalence and severity of COVID-19 in psoriatic patients treated with biologic agents during the first phase of the emergency (February 22 to April 22, 2020) in Italy; and 2) to report the clinical outcomes of patients who have been exposed to individuals with confirmed SARS-CoV-2 infection. We found that the incidence of COVID-19 observed in our cohort of psoriatic patients (0.2%) is similar to that seen in the general population (0.31%) in Italy. However, the course of the disease was mild in most patients. Biological therapies may likely lessen "cytokine storm" of COVID-19, which sometimes lead to multiple organ failure, ARDS, and death (Talamonti *et al.*).[414]

Finally, SIDeMaST recommendations for SarS-CoV-2 vaccines for patients on biological treatments as well as for adverse cutaneous and mucous reactions from SarS-CoV-2 vaccines have been published as follows.

SarS-CoV-2 vaccines and biological treatments: dermatological perspectives

Although the evidence is limited in quality and quantity and further studies are required to understand the safety and effectiveness of SARS-CoV-2 vaccine in people who take medications that interact with the immune system, SIDeMaST, along with other dermatologic societies and task forces, strongly recommends vaccination in all subjects affected by chronic inflammatory skin diseases; only in selected patients with potential contraindications, the decision to do the vaccination should be personalized and shared between the patient and the physician (Stingeni L, Bianchi L, Peris K, Fabbrocini G, Micali G, Calzavara-Pinton P, *et al.*; Board Members of SIDeMaST. SARS-CoV-2 vaccines and biological treatments: dermatological perspectives. Ital J Dermatol Venerol 2021;156:118-120).[415]
The Italian Society of Dermatology (SIDeMaST) elaborated the following recommendations to help the healthcare personnel to conduct a risk-assessment before planning for anti-SARS-CoV-2 vaccination.
In order to guarantee a vaccination without risks, it is necessary to consider: 1) family history of allergies and atopy (allergic rhinoconjunctivitis and asthma, atopic dermatitis); 2) personal history of atopy (allergic rhinoconjunctivitis and asthma, atopic dermatitis); 3) maculo-papular eruptions or acute urticaria-angioedema syndrome of documented biotic origin; 4) controlled asthma or chronic urticaria-angioedema syndrome; 5) allergen-specific immunotherapy; 6) therapy with biological drugs and small molecules; 7) NECD: NSAID-exacerbated cutaneous disease; NERD: NSAID-exacerbated respiratory disease; NIUA: NSAID-induced urticaria-angioedema; 8) if there are documented allergic reactions to clearly defined hymenoptera poisons, foods and drugs; and 9) local (non-systemic) reaction at the injection site of other vaccinations and other injectable drugs.
Important recommendations to achieve a major security include a normal execution of vaccination as per vaccination schedule and postvaccine observation (15 minutes).

On the contrary, a vaccination with increased risks may occur in case of: 1) reported anaphylaxis to previous vaccinations; 2) maculo-papular eruption or acute urticaria-angioedema syndrome after the first administration of anti-SARS-CoV-2 vaccine; 3) reported maculo-papular eruption or acute urticaria-angioedema syndrome of unclear etiology and pathogenetic mechanism; 4) reported maculo-papular eruption, acute urticaria-angioedema syndrome or anaphylaxis by drug, especially injective, not adequately investigated; 5) reported serious cutaneous-mucosal adverse drug reactions: Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome, AGEP (Acute Generalized Exanthematous Pustulosis), DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome; 6) known idiopathic anaphylaxis; 7) anaphylaxis with severe cardiovascular and respiratory symptoms by hymenoptera or food; 8) cutaneous and systemic mastocytosis; and 9) chronic urticaria-angioedema syndrome or asthma, not in clinical control. The action recommended in these cases are postvaccine observation for at least 1 hour (for immediate reactions), re-evaluation at 24 and 48 hours (for delayed reactions), evaluation of the allergy risk to excipients and preservatives contained in the anti-SARS-CoV-2 vaccines (to be evaluated in individual cases after a dermatologic or allergologic evaluation) and, in patients suffering from cutaneous and systemic mastocytosis and in the other conditions to individually evaluate, premedication with antihistamine (cetirizine oral drops 10 mg: 24h before the vaccination day, in the vaccination day, and in the following 5 days).

Vaccination is contraindicated in case of: 1) severe anaphylaxis on first administration of SARS-CoV-2 vaccine; 2) history of severe immediate reactions (urticaria-angioedema syndrome, anaphylaxis) and/or delayed reactions (maculo-papular eruptions, severe adverse drug reactions) to drugs containing polyethylene glycols, polysorbate 80 or 20, and tromethamine; and 3) documented immediate and/or delayed allergy to polyethylene glycols, polysorbate 80 or 20, and tromethamine.

In these cases, it is recommended not to vaccinate with the vaccine containing the incriminated excipients, it is better to establish a dermatologic and/or allergologic evaluation and to identify the vaccine without the above incriminated excipients (Stingeni L, Bianchi L, Zalaudek I, Pigatto PD, Peris K, Patruno C, *et al.*; Board Members of SIDeMaST. Adverse cutaneous and mucous reactions from anti SARS-CoV-2 vaccines: recommendations from the Italian Society of Dermatology (SIDeMaST). Ital J Dermatol Venerol 2021;156:115-7).[416]

Limitations of the study

The general recommendations and treatment algorithm are evidence-and consensus-based and they were developed in cooperation with Sbidian *et al.*,[34] which meant that the most-up-to-date systematic review and network meta-analysis was used and that the methods applied in the development of this review were rigorous – as detailed in the Cochrane Handbook – and peer reviewed independently though the Cochrane Skin Group. While this allowed for an inclusion of newer treatment options, one limitation of this guideline is the absence of recommendations beyond induction treatment, as this was not covered by the review. Another focus of this guideline is the explicit reporting on management and monitoring recommendations for patients receiving the different treatments. However, while these were developed taking the SmPCs and clinical practice in many European countries into account, the recommendations are often not evidence based as there typically is no evidence available.

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SUPPLEMENTARY DIGITAL MATERIAL 1

Supplementary Table I.—Abbreviations.

AAD	American Academy of Dermatology
ADA	Anti-drug antibodies
ADR	Adverse drug reactions
AE	Adverse event
ANA	Antinuclear antibodies
BCG	Bacillus Calmette-Guérin
BID	Twice daily
BIW	Twice weekly
BSA	Body surface area
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CS	Consensus statement
CSF	Cerebrospinal fluid
CsA	Ciclosporin
DMF	Dimethylfumarate
DLQI	Dermatology Life Quality Index
DMARD	Disease-modifying antirheumatic drugs
EDF	European Dermatology Forum
EMA	European Medicines Agency
EOW	Every other week
FUM	Fumarates
GFR	Glomerular filtration rate
GL	Guideline
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B virus

HCV	Hepatitis C virus
HDL	High-density lipoprotein
HPV	Human papilloma virus
HOMA	Homeostasis Model Assessment
HRQoL	Health-Related Quality of Life
IBD	Inflammatory bowel disease
IFPA	International Federation of Psoriasis Associations
IGRA	Interferon-gamma-release assay
LDL	Low-density lipoprotein
LTBI	Latent tuberculosis infection
MACE	Major adverse cardiac event
MEF	Monoethylfumarate
MI	Myocardial infarction
MID	Minimal important difference
MS	Multiple sclerosis
MTX	Methotrexate
NMA	Network meta-analysis
NMSC	non-melanoma skin cancer
NSAID	Nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
OR	Odds ratio
PASI	Psoriasis Area and Severity Index
PBO	Placebo
PGA	Physician's Global Assessment
PIINP	Procollagen type III N-terminal peptide
PML	Progressive multifocal leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
PsA	Psoriatic arthritis
PUVA	Psoralen plus UV-A
PY	Person years
Q2W	Every 2 weeks

Q4W	Every 4 weeks
QD	Once daily
QUICKI	Quantitative Insulin Sensitivity Check Index
QW	Once weekly
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
RPLS	Reversible posterior leukoencephalopathy syndrome
RR	Risk ratio
SAE	Serious adverse event
SmPC	Summary of product characteristics
SR	Systematic review
SUCRA	Surface under the cumulative ranking curve
TB	Tuberculosis
TNFi	TNF inhibitor
TST	Tuberculin skin test