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ORIGINAL ARTICLE

Estimation of patients with psoriasis potentially eligible and currently untreated with biological drugs in Italy

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ABSTRACT

BACKGROUND: Psoriasis (PSO) patients can benefit from the growing availability of novel biological agents, that are often underused or discontinued. This real-world analysis estimated PSO patients potentially eligible and currently untreated with biologics in Italy.

METHODS: An observational analysis was performed on administrative databases of a pool of healthcare entities, covering 11.3% of Italian population. During the inclusion period (2010- 2020), patients were identified by: 1) at least one prescription of topical drugs for PSO; or 2) active exemption for PSO; or 3) at least one PSO hospital discharge diagnosis. The index-date was the first PSO identification across inclusion period. Eligibility for biologics was evaluated prior to index-date (characterization period) through two not-mutually exclusive criteria: Criterion A, failure of at least one systemic treatment, and/or Criterion B, onset of psoriatic arthritis (PsA). Data were re-proportioned to the Italian population.

RESULTS: The study sample showed a PSO prevalence of 2%. Projection to 2020 national population (N=59,236.213) estimated 1.43 million Italian patients affected by PSO: 95% treated with conventional therapies, 4% with biologics, and 1% untreated. Among those non-treated with biologics, 3.8% of overall PSO patients met one or both eligibility criteria for biologics, specifically 25% met criterion A (failure to conventional treatments), 68% criterion B (PsA co-diagnosis), and 7% met both. About half of them had 1 or 2 comorbidities and 30% above 3.

CONCLUSIONS: These findings from real clinical practice estimated about 4% PSO patients potentially eligible for biologics, but still untreated, with nearly one-third exhibiting a complex comorbidity profile.

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KEY WORDS: Biological therapy; Psoriasis; Observational study.

Psoriasis (PSO) is a chronic nontransmissible and disabling skin disease with a negative impact on patients' quality of life (QoL). Although the disease can occur at any age, the most commonly involved age range is between 50 and 69 years.[1] The last WHO report estimated about 100 million individuals affected by PSO worldwide, with a variable prevalence across the different countries ranging between 0.09% and 11.4%.[2, 3] In Italy, the overall estimated prevalence of PSO is 1.8-3.1%, but a broader range (0.8-4.5%) was found when investigating specific regions.[4] Up to now, the underlying causes have not been fully clarified. It has been postulated a genetic predisposition and suggested a possible autoimmune etiology, but no responsible autoantigens have been identified yet. However, it is known that the disease can be exacerbated by several triggers (*i.e.* mild trauma, stressing conditions, sunburn, infections, systemic drugs) and further burdened by comorbidities, including arthritis, metabolic syndrome, cardiovascular disease, and inflammatory bowel disease.[5-7]

Moreover, the clinical presentation, symptoms and course over time are often unpredictable, making therapeutic interventions a still open clinical challenge. Depending

on disease severity, the treatment options include topical drugs, conventional medications including acitretin, cyclosporin, methotrexate and dimethyl fumarate, phototherapy and photochemotherapy, and biologics, namely monoclonal antibodies targeted against specific immune molecules, like TNF, IL-17 and IL12/23.[8-10] A consensus report by dermatologists from 33 European countries defined a scale to classify disease severity as "mild" when affecting less than 10% of body surface area (BSA), and "moderate-to-severe psoriasis" with more of 10% of BSA involvement.[11] Current national and international guidelines recommend topical therapies as the mainstay for mild-to-moderate PSO and systemic therapy (biologic or non-biologic) for the more severe forms.[12, 13]

Evidence from real-life clinical settings has shown indeed that, in front of the large and growing availability of novel anti-psoriatic agents, many subjects affected by PSO are unsatisfied and remain untreated or under-treated.[14] In particular, in Italy biologics appear to be often underused or discontinued among PSO patients, feasibly in view of the higher costs and the still poor real-world evidence in support of the recourse to early biologic treatment.[15, 16]

In this framework, the present analysis was aimed at estimating the number of patients with PSO potentially eligible to biological therapy in an Italian setting of real-world clinical practice.

Materials and methods

Data source

This retrospective observational study was carried out using data retrieved from administrative databases of a sample of geographically distributed Italian Entities, covering 11.3% of the Italian population. The following databases were browsed: 1) demographic database, containing patients' demographic data, namely gender, age and death; 2) pharmaceuticals database, for collecting information on medicinal products reimbursed by the Italian National Healthcare Service (INHS), as the Anatomical Therapeutic Chemical (ATC) code, number of packages, number of units per package, unit cost per package, and prescription date; 3) hospitalization database, which includes all hospitalizations data, such as the discharge diagnosis codes classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), Diagnosis Related Group (DRG) and DRG-related charge (provided by the Italian Health System); 4) outpatient specialist services (OSS) database, which reports all information about visits and diagnostic tests (date and type of prescription, description of activity and laboratory test or specialist visit charge); 5) payment exemption database, which gathers data of exemption codes by which patients are exempt from paying the contribution charge for services/treatments when specific diseases are diagnosed.

An anonymous univocal numeric code was given to each study subject to guarantee privacy, in full compliance with the European General Data Protection Regulation (GDPR) (2016/679). The patient code in each database allowed the electronic linkage between the various databases. All the results of the analyses were produced as aggregated summaries, which are not attributable, either directly or indirectly, to individual patients.

The data collected on the sample of patients in this study were then reproportioned to the whole Italian population.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local Ethics Committees of the healthcare departments involved.

Identification of study population

Between January 2010 and December 2020 (inclusion period) patients with PSO with available data were included. Diagnoses of PSO were identified by the presence of one of the following criteria: 1) at least one prescription of topical antipsoriasic drugs (ATC code: D05A); or 2) active exemption code for PSO (code 045.696.1); or 3) at least one PSO hospitalization with the ICD-9-CM 696.1 code indicated at each level among the discharge diagnoses, throughout the period of data availability in the database.

Among the patients meeting at least one of the above inclusion criteria, the index-date was defined as the most recent date in the database, considering the availability of the data for at least a 12-month follow-up period and during the whole time of characterization (pre-index-date).

Definition of treated and untreated patients for PSO and criteria of potential eligibility for biologics

Patients were defined as treated or untreated in the presence or absence, respectively, of at least one prescription of the medications and treatments indicated for PSO, listed in Table I according to drug category: topical drugs, conventional systemic drugs/treatments and biological drugs. Eligibility criteria to biological therapies were the following:[13, 17] 1) Criterion A: failure of at least one systemic conventional drug, defined by patients with PSO, not on biological treatment with at least 1 previous treatment with conventional systemic drugs, namely acitretin (ATC code D05BB02), cyclosporin (ATC code L04AD01), methotrexate (ATC codes L01BA01, L04AX03), dimethyl fu-

TABLE I.—*Drugs and treatments used as first prescription during the available period (2010-2020).*

Topical drugs:	Biological drugs:
Topical antipsoriatic drugs (ATC code D05A)	• Adalimumab (ATC code L04AB04), class TNF inhibitor
Conventional systemic drugs/treatments:	• Apremilast (ATC code L04AA32), class PDE4 inhibitor
• Acitretin (ATC code D05BB02)	• Brodalumab (ATC code L04AC12), class TNF inhibitor
• Cyclosporin (ATC code L04AD01)	• Certolizumab (ATC code L04AB05), class TNF inhibitor
• Methotrexate (ATC codes L01BA01, L04AX03)	• Etanercept (ATC code L04AB01), class TNF inhibitor
• Dimethyl fumarate (ATC code L04AX07)	• Guselkumab (ATC code L04AC16), class TNF inhibitor
• Phototherapy [PUVA (procedure code 99.82.2) and narrowband UVB (procedure code 99.82.1)]	• Infliximab (ATC code L04AB02), class TNF inhibitor
	• Ixekizumab (ATC code L04AC13), class IL17 inhibitor
	• Risankizumab (ATC code L04AC18), class TNF inhibitor
	• Secukinumab (ATC code L04AC10), class IL17 inhibitor
	• Tildrakizumab (ATC code L04AC17), class TNF inhibitor
	• Ustekinumab (ATC code L04AC05), class IL12/23 inhibitor

marate (ATC code L04AX07); 2) Criterion B: patients with onset of psoriatic arthritis (PsA) before or after the diagnosis of PSO, identified by 1) presence of at least one hospitalization for PsA in which the ICD-9-CM code 696.0 code indicated at each level among the discharge diagnoses; and/or 2) presence of an active exemption code for PsA (exemption code 045.696.0).

Analysis of clinical characteristics and previous disease history of study population

All the patients with PSO included and in those stratified by treatment, previous diseases were recorded during the pre-inclusion time (characterization period). Specifically, the search was focused on autoimmune diseases and neurodegenerative disorders.

Among autoimmune diseases, the following were computed: rheumatoid arthritis ICD-9-CM code 714, exemption 006; ankylosing spondylitis ICD-9-CM code 720, exemption 054; PsA ICD-9-CM code 696.0, exemption 045.696.0; Crohn's disease ICD-9-CM code 555, exemption 009.555; ulcerative colitis ICD-9-CM code 556, exemption 009.556; uveitis ICD-9-CM code 364).

Concerning neurodegenerative disorders, the following were searched: amyotrophic lateral sclerosis ICD-9-CM code 335. 20, exemption RF0100; multiple sclerosis ICD-9-CM code 340, exemption 046; alemtuzumab (ATC code L04AA34), daclizumab (L04AC01), dimethyl fumarate (N07XX09), fingolimod (L04AA27), glatiramer acetate (L03AX13), interferon-beta-1a (L03AB07), interferon-beta-1b (L03AB08), mitoxantrone (L01DB07), natalizumab (L04AA23), ocrelizumab (L04AA36), peginterferon beta-1a (L03AB13), teriflunomide (L04AA31), cladribine (L01BB04), Guillain-Barré Syndrome ICD-9-CM code 357.0, exemption RF0183; optic neuritis ICD-9-CM code 377.30; multifocal motor neuropathy ICD-9-CM code 357.8, exemption RF0181; peripheral neuropathy ICD-9-CM code 356.0, 356.8; myasthenia gravis ICD-9-CM code 358.00, 358.01, exemption RFG101, 034, pyridostigmine (ATC N07AA02).

The patients were also evaluated by the Charlson Comorbidity Index (CCI), an assessment system developed in 1987 which assigns a score for each concomitant disease: an index score of 0 indicates no comorbidity, while higher scores indicate a greater level of comorbidities.[18]

Moreover, the presence and frequency of comorbidities were collected in patients potentially eligible for treatment with biological drugs. In particular, patients' clinical history was investigated for the presence of: 1) hypertension and cardiocirculatory diseases at least one hospitalization for hypertension (ICD-9-CM code: 401) or at least one prescription for antihypertensive drugs (ATC codes: C02, C03; C07; C08; C09); at least 1 hospitalization for ischemic heart disease (ICD-9-CM codes: 411, 413, 414), heart failure (ICD-9-CM codes: 428), cerebrovascular disease (ICD-9-CM codes: 430, 431, 432, 433, 434, 435, 436, 437, 438), atherosclerosis (ICD-9-CM codes: 440-442) and other peripheral vascular disease (ICD-9-CM codes: 443); 2) dyslipidemia [at least one hospitalization for dyslipidemia (ICD-9-CM code: 272) or at least one prescription of hypolipidemic drugs (ATC code: C10); 3) diabetes (at least one prescription for anti-diabetic drugs [ATC code: A10]); inflammatory bowel diseases (at least one hospitalization for inflammatory bowel disease with ICD-9-CM codes 555, 556 or exemption codes: 009.555, 009.556); 4) liver diseases (at least one hospitalization for hepatitis [ICD-9-CM codes 573.1, 573.2, 573.3], chronic liver disease/cirrhosis/NAFLD [ICD-9-CM code 571]); 5) kidney diseases/renal failure (at least one hospitalization for renal diseases [including renal insufficiency] with ICD-9-CM codes 580-589; 593.8; 593.9); 6) lung fibrosis and chronic obstructive pulmonary disease (COPD) (at least one hospitalization for lung fibrosis with ICD-9-CM codes

515 and 516.3; at least one hospitalization for COPD, ICD-9-CM codes 490-496) or at least two prescriptions for drugs with ATC code R03); and 7) specific conditions: transplantation (exemption code 052 and/or at least one hospitalization [ICD-9-CM V42.0-42.1-42.6-42.7-42.8-42.9-42.5]); cancer history (exemption code 048 and/or at least one hospitalization [ICD-9-CM codes 140-239]).

Statistical analysis

Continuous variables are reported as mean±standard deviation (SD), and categorical variables as frequencies and percentages. The proportion of patients potentially eligible for biological therapy was determined referring to the number of patients with one or more criteria of eligibility for biologic treatment but not treated with biologics. All analyses were performed using STATA SE, version 17.0 (StataCorp LLC, College Station,TX, USA).

Results

Epidemiology data

Within the study sample covering approximately 11.3% of the overall Italian population, 161,650 patients with a diagnosis of PSO were identified during the period of data availability in the database, corresponding to an estimated overall prevalence of 2% in the study sample and 2.4% in adults (Figure 1).

Estimates of the potential eligibility for biological drug treatment

Of the 161,650 patients with a diagnosis of PSO found in the analysis, up to 99% (N=160,124) were treated with drugs indicated for PSO, about 4% (N=6371) of them with biologics and 96% (N=153,753) with non-biological drugs. About 1% of the confirmed PSO patients (N=1526) did not receive any drug indicated for PSO. Applying the eligibility criteria, 6098 PSO patients (approximately 4% of the total study population) result as potentially eligible for treatment with biologic drugs.

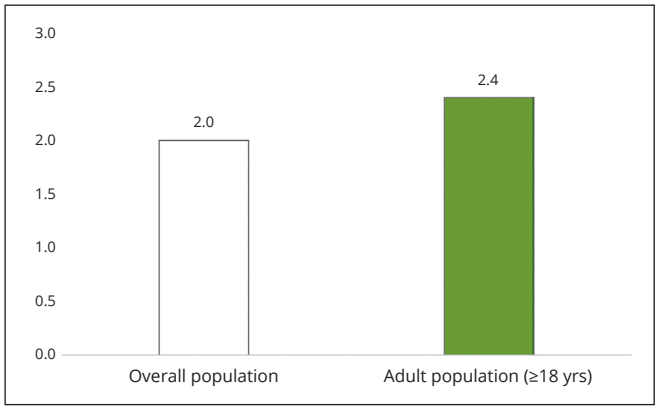

Figure 1.—Estimated prevalence of PSO in the overall study population of PSO patients and in adults.

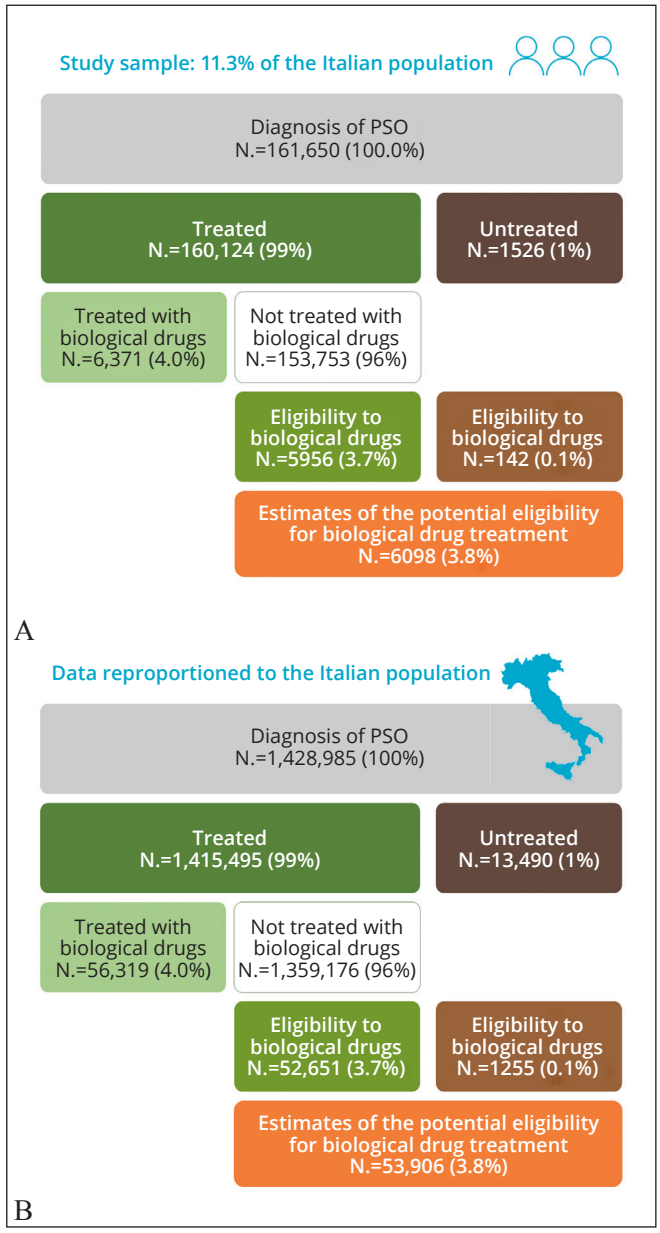

Figure 2.—Schematic representation of treatment patterns and eligibility to biologics in the study sample of PSO patients (A) and projection on the Italian population (B).

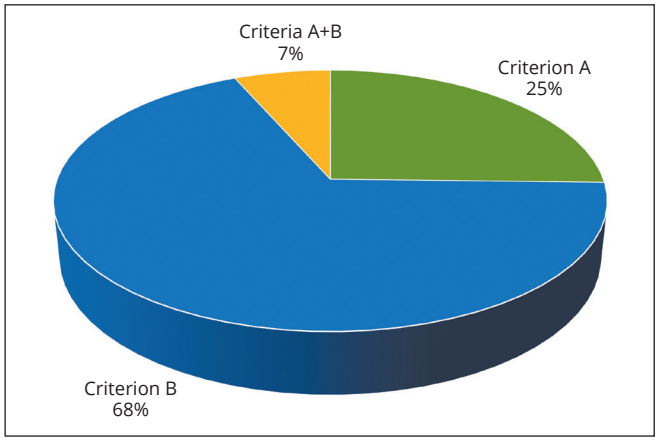

Figure 3.—Distribution of PSO patients who met one or both eligibility criteria for treatment with biologics.

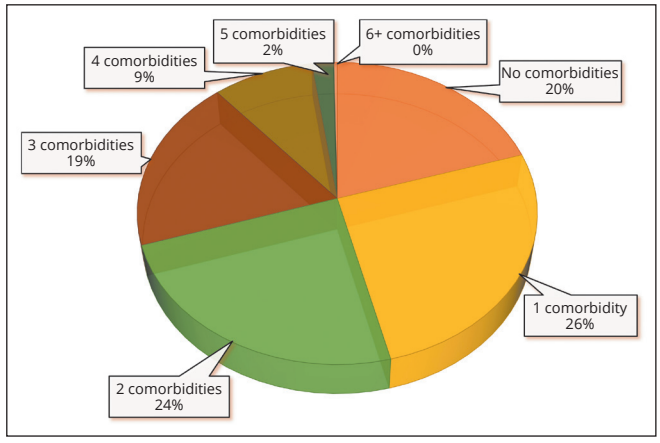

Figure 4.—Distribution of PSO patients by the presence of comorbidities.

These data were reproportioned to the entire national population. A schematic representation of treatment patterns in the study sample and the projection on the Italian population is provided in Figure 2A, B, respectively.

The detailed proportion of PSO patients who meet one or both eligibility criteria is shown in Figure 3. Specifically, of the 6098 PSO patients identified as potentially eligible for biological therapy: 25% met the eligibility criterion A, meaning at least one failure to conventional systemic treatments, 68% met the eligibility criterion B, namely concurrent diagnosis of PsA, and 7% met both eligibility criteria A and B.

The pattern of comorbidities in PSO patients potentially eligible for biological therapy revealed that 20% of patients had no comorbidity analyzed here, 26% and 24% had 1 or 2 comorbidities, respectively, 19% had 3 comorbidities, 9% had 4 comorbidities, and 2% had 5 comorbidities (Figure 4).

Table II details the demographic and clinical features and the distribution of comorbidities in the overall study

TABLE II.—*Demographic and clinical features and the distribution of comorbidities in the overall study population and in patients stratified according to the type of treatment for PSO received (or not). Continuous variables are reported as mean±SD, categorical variables as frequencies with percentages in brackets.*

	PSO patients (N=161,650)	Untreated (N=1526)	Treated (N=160,124)	Bio-treated (N=6371)	Non-bio-treated (N=153,753)
Age, years	58.4±17.9	54.0±19.1	58.5±17.9	55.2±14.5	58.6±18.0
Male gender	82,696 (51.2%)	770 (50.5%)	81,926 (51.2%)	3608 (56.6%)	78,318 (50.9%)
CCI before index date	0.3±0.6	0.3±0.7	0.3±0.6	0.7±0.8	0.3±0.6
Autoimmune diseases					
• Rheumatoid arthritis	1438 (0.9%)	17 (1.1%)	1421 (0.9%)	433 (6.8%)	988 (0.6%)
• Ankylosing spondylitis	372 (0.2%)	13 (0.9%)	359 (0.2%)	152 (2.4%)	207 (0.1%)
• PsA	6780 (4.2%)	142 (9.3%)	6638 (4.1%)	2231 (35.0%)	4407 (2.9%)
• IBD	1399 (0.9%)	20 (1.3%)	1379 (0.9%)	310 (4.9%)	1069 (0.7%)
• Crohn's disease	713 (0.4%)	7 (0.5%)	706 (0.4%)	215 (3.4%)	491 (0.3%)
• Ulcerative colitis	829 (0.5%)	15 (1.0%)	814 (0.5%)	156 (2.4%)	658 (0.4%)
• Uveitis	77 (0.05%)	0 (0%)	77 (0.05%)	12 (0.2%)	65 (0.04%)
Neurodegenerative disorders					
• Amyotrophic lateral sclerosis	44 (0.03%)	<4	43 (0.03%)	<4	41 (0.03%)
• Multiple sclerosis	449 (0.3%)	8 (0.5%)	441 (0.3%)	17 (0.3%)	424 (0.3%)
• Guillain-Barré syndrome	50 (0.03%)	<4	48 (0.03%)	<4	46 (0.03%)
• Optic neuritis	9 (0.01%)	0 (0%)	9 (0.006%)	<4	8 (0.005%)
• Multifocal motor neuropathy	84 (0.1%)	0 (0%)	84 (0.1%)	4 (0.1%)	80 (0.1%)
• Peripheral neuropathy	16 (0.01%)	0 (0%)	16 (0.01%)	<4	14 (0.009%)
• Myasthenia gravis	230 (0.1%)	4 (0.3%)	226 (0.1%)	5 (0.1%)	221 (0.1%)

Bio-treated: treated with biological drugs; CCI: Charlson Comorbidity Index; IBD: inflammatory bowel disease; Non-bio-treated: not treated with biological drugs; PsA: psoriatic arthritis; PSO: psoriasis; SD: standard deviation.

population (N=161,650) and in patients stratified according to the type of treatment for PSO received (or not): untreated (N=1526), treated (N=160,124), treated with biologics (N=6371), and not treated with biologics (N=153,753).

Discussion

Over the last decades, pharmaceutical research has largely broadened the therapeutic options for the treatment of PSO with the introduction of novel biological agents, above all monoclonal antibodies inhibiting TNF, IL-17 and IL-12/23.[10, 19]

In this analysis, we investigated the current state-of-art of pharmacoutilization of biological drugs among patients with PSO in an Italian real-life setting of clinical practice. Besides, in our patients' sample corresponding to the 11.3% of the whole national population, epidemiological data revealed a 2% prevalence of PSO (rising to 2.4% in the adults), in line with previous published data. A recent systematic review by Prignano *et al.* reported that the prevalence of PSO in the Italian general population ranges between 1.8% and 3.1%.[4] Previous reports have highlighted that biological therapy is underused in PSO patients, maybe in view of the elevated costs and the poorly available data from real world evidence studies.[8-10]

The original European S3-Guideline on the systemic treatment of PSO vulgaris, firstly released in 2015,[12] have been updated over the years in view of the growing availability of newly introduced biological agents[20] and adapted at national level in the various countries. In general, the current national and international guidelines share a sequential therapeutic path indicating the use of topical drugs in mild forms and systemic treatments for moderate-severe forms. In patients not achieving an adequate response to conventional treatments, biological drugs are recommended.[12]

Here, we browsed the administrative databases of a sample of Italian healthcare entities to provide an overview of PSO patients' therapeutic management in Italy, in order to estimate the proportion of patients untreated or treated with conventional therapies who might be eligible for biologics and not currently using with these novel drugs. The criteria of eligibility for biologics were a previous failure of at least one systemic conventional drug, and a co-diagnosis of PsA before or after the diagnosis of PSO. These two criteria were not mutually exclusive since a portion of patients met both of them. Applying the abovementioned criteria, we found that around 4% of the sample population (6,098 patients) were potentially eligible for biological treatment. When projecting these data on national scale, it can be postulated that around almost 54 thousand Italian PSO patients comply the criteria to receive biologics but are not currently treated with them.

In a nutshell, our findings seem to confirm that there is still much room to increase the recourse to biological drugs for PSO. The reasons beyond such underuse observed in this analysis are partly still unclarified and might vary across the countries in view the different rules of healthcare systems.[14, 15, 21, 22] If one possible explanation for the still limited recourse to biologics might lie in the higher costs, it also true that according to our pharmacoeconomic analysis, all other healthcare expenses related to the management of PSO tended to be lower in biologically treated patients compared to eligible but still untreated patients. Moreover, increasing age and the presence of autoimmune and neurogenerative comorbidities resulted in a substantial rise in healthcare expenditures per patient.

Limitations of the study

These findings must be taken with caution in view of some limitations, above all the observational retrospective design and the fact that data were extrapolated from administrative databases. In front of the advantage of such real-life approach that reflects daily clinical practice of a sample of health-assisted individuals, administrative databases might lack some information, mainly inherent to disease severity, comorbidities, use of OTC drugs and other potential confounders. Regarding this, it should be also considered that primary care and private care data could not be could not be captured, because administrative databases collect information only on healthcare resources reimbursed by INHS. Hence, all out-of-pocket topical treatments or other therapies not covered by the INHS were missed.

Moreover, there might have been an underestimation of PSO patients potentially eligible for biologics according to criterion B (co-diagnosis of PsA) in the case of a PSO patient who might have an underlying PsA without having received a clear PsA diagnosis yet. A certain degree of inaccuracy is an intrinsic and unavoidable flaw of data extraction through administrative databases, and anyhow beyond investigators' control. These limitations prevent us from indicating with certainty all the reasons for the underuse of biological drugs in PSO management.

Conclusions

In conclusion, this real-world data analysis conducted on a sample of healthcare entities in Italy, provided an es-

timation of patients with a diagnosis of PSO and found that about 4% of those who comply the criteria to access biological therapies, are untreated with them. These data, reproportioned at the national scale, might imply that almost 54 thousand Italian PSO patients result to be potentially eligible to biologics and there is still an unmet medical need in the Italian general clinical practice for managing PSO.

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Conflicts of interest

Francesca Prignano served as advisory board member and consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Leo Pharma, Lilly, Janssen, Novartis, Biogen and Sanofi Genzyme. The author has no conflicts of interest to declare for the present manuscript. All the other coauthors have no competing interest to disclose.

Authors' contributions

Luca Degli Esposti, Valentina Perrone, Francesca Prignano: conceptualization, supervision, original draft reviewing; Melania Dovizio: original draft preparation, reviewing and editing, methodology; Diego Sangiorgi: data analysis, methodology; Antonella Di Cesare, Elia Rosi, Ketty Peris: investigation; methodology; supervision. All authors read and approved the final version of the manuscript.

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