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Case Report

Dupilumab in Children and Adolescents with Severe Atopic Dermatitis and Severe Asthma: A Case Series

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Abstract: The increasing incidence and common specific inflammatory type 2 intracellular pathways have recently allowed for the rise of new biologic therapies in two inflammatory chronic diseases in children: atopic dermatitis (AD) and severe asthma. Such therapies aim at relieving symptoms and reducing inflammation by treating the underlying molecular causes. Dupilumab is a monoclonal antibody indicated in children with moderate–severe AD and severe asthma ineffectively responsive to standard treatments. Here, we report a case series of seven consecutive children with moderate–severe AD, with three of them also affected by asthma and treated with dupilumab. The children experienced a reduction in the extent and severity of lesions and decreased intensity of symptoms, leading to better asthma control, a general improvement in sleep and quality of life (QoL), with a good safety profile. Notwithstanding the observed clinical improvement, further larger prospective studies are needed to better tailor the treatment duration and the potential preventive and long-lasting effects.

Keywords: atopic dermatitis; severe asthma; endotypes; dupilumab; sleep; quality of life; safety profile

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1. Introduction

Asthma and atopic dermatitis (AD) are common chronic diseases in children. The prevalence of AD reaches up to 20% of the pediatric population worldwide, while asthma affects around 14% [1]. AD and asthma represent an enormous burden for patients and families in terms of quality of life (QoL), missed school days and treatment costs [1]. Asthma and AD often represent a continuum of the so-called "atopic march", beginning from AD, followed by food allergies and then airway diseases [2]. In this regard, it is well established that children who develop AD early on may have a higher probability of developing asthma throughout childhood [2]. In fact, environmental exposure and complex genetic interactions often lead to the activation of the common T-helper type 2 (Th2) response, with the subsequent release of IgE and inflammatory molecules, such as interleukin (IL)-4, IL-13 and IL-5. The release of these molecules leads to several effects, such as the development of cutaneous eczematous lesions in AD and airway remodeling with narrowing of the bronchial walls in asthma (predominantly T2-high endotype in children) [3–5]. The consequences of this chronic inflammation include symptoms, such as skin itching, eczema, scratch lesions and a higher risk of developing asthma with cough, wheezing and respiratory distress. In recent years, the identification of common pathogenetic mechanisms and specific molecular targets has led to the production of individualized biological drugs for children with severe AD and/or severe asthma [6–11]. Dupilumab, a fully human monoclonal antibody, binds to the alpha subunit of the heterodimeric IL-4 receptor (IL-4Ra), blocking both IL-4 and IL-13

signaling pathways and, as a consequence, the inflammatory reaction mediated by Janus family protein kinases (JAKs) [12,13]. Recent findings in children affected by severe asthma treated with dupilumab have provided a significant improvement in asthma symptoms and QoL [14] and a drastic reduction in asthma attacks with a strong safety profile [15]. Here, we report seven pediatric cases with moderate–severe AD, three of them with asthma as well, successfully treated with dupilumab in terms of an improvement in symptoms and QoL.

2. Materials and Methods

Data for children and adolescents aged 11–17 years, affected by moderate-to-severe AD and/or severe asthma treated with dupilumab, were collected through standardized questionnaires and scores. Lung function testing was acquired from our Pediatric Allergy and Pulmonology Unit in Chieti. AD and asthma diagnoses were formulated by a pediatrician based on clinical presentation, personal history and spirometry according to the U.K. working party's diagnostic criteria for AD and Global Initiative for Asthma (GINA) guidelines [3,16]. The U.K. working party's diagnostic criteria require an itchy skin condition with three or more of the following: history or visible flexural involvement, a history of asthma/allergic rhinitis, a history of generalized dry skin or onset of rash under the age of 2 years [16]. GINA guidelines require two pivotal elements: a history of variable respiratory symptoms and demonstration of variable expiratory airflow limitation [3]. Dupilumab was administered subcutaneously [SC] according to the disease and the weight of the patients. Patients continued using moisturizers, topical and/or systemic treatments for AD and inhaled corticosteroids (ICSs) associated or not with long-acting beta-agonists (LABAs) or leukotriene receptor antagonists for asthma. The following data were collected for a descriptive analysis: age, gender, medical history, clinical phenotype of AD, asthma clinical and spirometric parameters, comorbidities (atopic and non-atopic), other ongoing treatments and adverse events (AEs). Disease severity was assessed at baseline and after week 12 (12W) of dupilumab using, for AD: EASI (Eczema Area and Severity Score) with range 0–72 and SCORAD (Severity Scoring of Atopic Dermatitis) with range 0-103, both describing the extent (area) and severity of AD; P-NRS (Pruritus Numerical Rating Scale (P-NRS) and sleep (S)-NRS) with range 0–10; c-DLQI score (Children's Dermatology Life Quality Index) with range 0–30; for asthma: ACT (asthma control test), ranging from 5 (poor control of asthma) to 25 (complete control of asthma), with higher scores reflecting greater asthma control; spirometric parameters, such as FVC (forced vital capacity) and FEV1 (forced expiratory volume in the first second).

3. Cases

3.1. Case 1

A 15-year-old girl was evaluated for severe AD and moderate-to-severe asthma. Her family history was positive for atopy, and she had atopic dermatitis, allergic rhinitis and food allergies from the age of 2. Despite an initial first-line treatment with TCs followed by subsequent add-on of SCs, the child experienced several exacerbations of AD that greatly affected her school performance and quality of sleep. She, therefore, started oral cyclosporine A for a total of 6 months, without reporting significant positive effects. At the age of 10, she was started on controller therapy for asthma with inhaled fluticasone, according to the GINA guidelines for a total of 5 years, nonetheless experiencing multiple exacerbations throughout the years [3]. Finally, at the age of 15, she was started on dupilumab (400 mg (SC) at baseline and then 200 mg every two weeks), with a quick improvement in AD symptoms and better control of asthma and QoL already after the first few doses. She reduced the use of TCs and SC antihistamines as well. About 8 weeks after the introduction of dupilumab, the girl reported a slight headache and mild conjunctivitis and no further AEs, justifying the interruption of the therapy. We observed a progressive minor extent and severity of the skin lesions already after the first four administrations. The patient continued follow-up for a total of six months, in which she reported a further

improvement in itching and sleep quality. She concurrently complained of fewer asthma exacerbations, with an overall significant improvement in asthma control.

3.2. Case 2

From the age of 3, a 12-year-old female patient reported AD symptoms, followed by a later appearance of allergic rhinitis and food allergy. Her AD was generalized, involving the folds of the arms and legs, neck, shoulders and face as well, and was associated with intense and constant daily itch affecting her quality of sleep. First-line therapies with moisturizers and topical steroids had poor efficacy; thus, dupilumab was started at 400 mg on day (D)1, followed by 200 mg every two weeks. Visible clinical improvement was noted already after 4 weeks in terms of a reduction in pruritus, clinical skin symptom scores and need of TCs. The treatment is currently ongoing, with the patient reporting further improvements in pruritus and QoL.

3.3. Case 3

A 12-year-old girl was evaluated for severe AD with skin lesions involving eyelids, forehead, folds and arms. Like the previous patients, she also had a positive family history for atopy and allergic comorbidities. Furthermore, she was diagnosed with celiac disease at the age of 5. The patient had numerous relapses after attempts to stop TCs, which severely affected her life activities and school performance. Therefore, she started dupilumab at an induction dose of 400 mg, followed by 200 mg every two weeks. After the first three administrations, the patient had a considerable improvement in the skin lesions and QoL and suspended the use of TCs.

3.4. Case 4

A seventeen-year-old girl was evaluated because of a mild form of AD from the age of one and a half, with the subsequent development of severe allergic asthma. Conventional therapies for atopic dermatitis, such as emollients, TCs and TCIs, allowed for a good control of AD, which presented with a predominantly flexural phenotype. On the other hand, her asthma remained poorly controlled despite a controller therapy with ICS-LABA and bronchodilators as needed. After the introduction of dupilumab, the patient experienced a marked improvement in terms of a reduction in asthmatic relapses and the use of LABA, with a better control of asthma already after the first few administrations. Mild and transient injection site reaction was recorded after the first two doses of dupilumab.

3.5. Case 5

A 16-year-old male patient presented AD from the early stages of life, controlled with first-line conventional topical therapies, followed by the inception of severe allergic asthma with several exacerbations requiring reliever therapy. Asthma was poorly controlled despite medium-dose ICS-LABA and leukotriene receptor antagonist. Indeed, the child complained of multiple episodes of bronchospasm, which significantly impacted on his QoL. Therefore, dupilumab was started on an induction dose of 600 mg, followed by 300 mg every two weeks. After 12 weeks of treatment, he experienced a reduction in asthma relapses and a decrease in the use of systemic therapies. Although the patient needed to continue antihistamines and ICS-LABA, doses were progressively tapered. The patient also had asymptomatic SARS-CoV-2 infection, which did not affect the patient's overall condition and did not stop him from regularly continuing dupilumab [17].

3.6. Case 6

From the age of 4, a 13-year-old male patient presented severe AD localized to his face, folds of the arms and legs, and back, with a progressive rise in hyperkeratosis and excoriations. The boy complained of intense itching, which became extremely disabling and negatively impacted his QoL. In fact, the boy no longer left his house, had no social relationships and developed school problems. First-line therapies had a small effect on

controlling his AD; therefore, according to GINA guidelines and to his weight [3], we started dupilumab dosing of 600 mg at time 0 and 300 mg SC every 15 days, which reversed his AD. He experienced a significant reduction in itching and a clear improvement in the quality of sleep that positively influenced every aspect of his adolescent life. The treatment, with the exception of mild conjunctivitis and isolated hypereosinophilia, was free from side effects.

3.7. Case 7

The last case was an 11-year-old male patient, with severe AD characterized by skin lesions on his face, hands and genitals, inducing considerable discomfort and poor QoL. Similar to previous patients, he also had positive family history for atopy. Despite moisturizers and TCs, the patient experienced no improvement in pruritus or skin lesions. Therefore, dupilumab 300 mg every two weeks was administered, with a recorded improvement after only 4 weeks of his AD and without AEs.

4. Results and Conclusions

Seven children with AD (three males (43%) and four females (57%)) were treated with dupilumab during the reference period. Of these, three were also affected by severe asthma. Patients' demographic and clinical baseline characteristics are reported in Table 1. From the data obtained, a reduction in the EASI score, SCORAD, P-NRS, S-NRS and c-DLQI was observed at 12 weeks of treatment with dupilumab in all patients. These successful clinical results also led to an improvement in the quality of sleep, with better school performance and social relationships. In all cases, we recorded a reduction in the value of IgE. Additionally, we observed a lower use of SCs and TCs. In the three asthmatic children, despite stable spirometric values before and after dupilumab, there was a general improvement in symptoms and a reduction in the use and/or dosage of ICS. Indeed, in one of them, after 3 months of dupilumab, the administration of antihistamines was suspended (case 1); in another one, LABA was suspended (case 4); in case 5, the patient continued to use antihistamines and ICS-LABA but at a lower dosage. Of the seven patients, three of them experienced mild side effects: case 6 and case 1 developed a mild conjunctivitis (this later developed into headache as well), successfully treated with topical TCs, and one patient (case 4) developed a mild and transient injection site reaction. In only one case, we recorded a marked increase in the eosinophil count, as also reported in the literature [18]. Asymptomatic SARS-CoV-2 infection occurred in one child (case 5), but he regularly continued dupilumab treatment, as suggested by the guidelines [19]. None of the patients discontinued dupilumab. Our data seem to confirm the effectiveness of dupilumab in both AD and asthma in children, in terms of a reduction in the extent and severity of skin lesions, intensity of symptoms, sleep, QoL and a general increase in asthma control, with a good safety profile.

These encouraging results stimulate us to expand the use of dupilumab in atopic children. In this evolving field, Paller et al. [20] recently conducted the first randomized, double-blind, placebo-controlled, phase three trial involving 162 patients aged six months to six years, with moderate-to-severe AD. The authors showed a significant reduction in AD signs and symptoms, in terms of the Investigator Global Assessment (IGA) and EASI–75 without significant differences in AEs between dupilumab and placebo groups, except for a higher incidence of conjunctivitis in the dupilumab group compared to the placebo group (5% vs. 0%). Due to this pivotal trial, dupilumab is the first ever biologic medicine for people living with AD from infancy to adulthood. Considering its good safety profile and effectiveness, dupilumab has the potential to alleviate the multidimensional burden that asthma and moderate-to-severe AD place on infants, toddlers and their families [11,21].

Table 1. General characteristics of the study population.

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**
Age (years)	15	12	12	17	16	13	11
Sex	F	F	F	F	M	M	M
Coexisting allergic diseases	Allergic asthma, food allergy	Food allergy	Food allergy	Allergic asthma	Allergic asthma	Food allergy	None
Pretreatment total serum IgE, KU/L	5000	1199	2073	505	1632	3366	600
Post-treatment total serum IgE, KU/L	4794	480	925	99	1020	3330	150
Pretreatment blood eosinophil count, cells/mm^3	2.41	0.45	0.16	0.14	0.25	0.49	0.36
Post-treatment blood eosinophil count, cells/mm^3	0.16	0.12	0.13	0.37	0.11	1.95	0.65
Pretreatment AD clinical scores							
EASI	33	12.2	30.1	11.6	6	38.4	29.8
SCORAD	50	52.5	68.4	16	12	70.4	53
P-NRS	6	6	10	8	4	9	10
S-NRS	7	0	0	0	0	10	10
cDLQI	19	19	10	12	0	22	6
Post-treatment AD clinical scores							
EASI	18	0	9.3	0	4	19.8	7.4
SCORAD	33	22.8	28.4	6	8	19	36
P-NRS	3	3	1	2	2	5	7
S-NRS	4	0	0	0	0	7	0
cDLQI	6	5	5	4	0	4	3

Table 1. *Cont.*

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**
AD treatment before dupilumab	Moisturizers, TCs, TCIs, SCs, CsA	Moisturizers, TCs	Moisturizers, TCs	Moisturizers, TCs, TCIs	Moisturizers, TCs, TCIs, SCs	Moisturizers, TCs	Moisturizers, TCs
AD treatment after 3 months	Moisturizers, TCIs	Moisturizers, TCIs	Moisturizers	Moisturizers	Moisturizers	Moisturizers, TCs	Moisturizers, TCs
Asthma evaluation before dupilumab							
FVC (L)	2.44	/	/	3.00	6.07	/	/
FVC z score	1.40	/	/	−1.45	1.80	/	/
FEV1 (L)	2.12	/	/	2.70	4.60	/	/
FEV_1 z score	1.29	/	/	−1.97	0.61	/	/
ACT	19	/	/	20	21	/	/
Asthma evaluation after 3 months							
FVC (L)	2.76	/	/	3.70	4.92	/	/
FVC z score	0.95	/	/	−0.07	−0.75	/	/
FEV1 (L)	2.50	/	/	2.95	3.60	/	/
FEV_1 z score	1.24	/	/	−0.95	−1.78	/	/
ACT	23	/	/	25	25	/	/
Treatment for asthma before dupilumab	ICS, antihistamines	/	/	ICS-LABA, antihistamines	ICS -LABA, antihistamines	/	/
Treatment for asthma after 3 months	ICS	/	/	ICS, antihistamines	ICS-LABA, antihistamines	/	/
Side effects of dupilumab	Headache, conjunctivitis	None	None	Injection site reaction	None	Conjunctivitis	None

Abbreviations: AD: Atopic dermatitis; cDLQI, Children's Dermatology Life Quality Index; EASI: Eczema Area and Severity Score; SCORAD: Severity Scoring of Atopic Dermatitis; TCS: topical corticosteroids; TCI: calcineurin inhibitors; CS: corticosteroids; CsA: cyclosporine. FVC: forced vital capacity; FEV1: forced expiratory volume in the 1st second; ACT: Asthma Control Test; ICS: Inhaled Corticosteroid (ICS); ICS-LABA: Inhaled Corticosteroid and Long-Acting Beta-Agonist.

In addition, recent evidence has suggested new potentially preventive functions of dupilumab [22]. An early administration of dupilumab from the first months of life may play a pivotal role in slowing or interrupting the progression of the atopic march towards asthma [20]. In this regard, a meta-analysis of 12 clinical trials including 3525 patients (mean age, 35 years; range, 12–88 years) sought to define the risk of developing new or worsening allergic events for dupilumab compared to placebo in patients with AD. The authors observed a marked reduction in both the incidence of new allergies and the worsening of pre-existing allergic conditions in patients, especially children with an early-onset AD (2 years), treated with dupilumab compared to controls [22].

In our case series, patients with AD and asthma receiving dupilumab (cases 1, 4 and 5) started treatment at 15, 17 and 16 years, respectively. In accordance with the new treatment indications starting from 6 months of age [20], it would be interesting to evaluate, in the future, the effects of an early administration of dupilumab in children with AD and/or severe asthma. Our study presents some limitations, such as the small numerosity and the lack of long-term follow-up for all patients, yet this is a real-life and timely case series that showed clinical improvements. Further larger and longer longitudinal studies are needed to better investigate the treatment duration and the potential preventive and long-lasting effects of dupilumab in children.

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