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ORIGINAL ARTICLE

Dupilumab in pediatric atopic dermatitis: real-world evidence from two national centers

Experiência com dupilumab na dermatite atópica em idade pediátrica: dados do mundo real de dois centros nacionais

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Abstract

Objective: The use of dupilumab in children with atopic dermatitis (AD) demonstrated clinical efficacy in clinical trials. Nevertheless, real-world evidence is still limited. We aim to provide data on this matter regarding a Portuguese pediatric population. **Methods:** Retrospective analysis of patients with AD below the age of 18 treated with dupilumab in two Portuguese hospitals. Data regarding previous therapies, activity scores, and adverse reactions were collected. **Results:** Thirty patients were included in the analysis (19 male patients, 63%), with a median age of 14 years (2-17 years). The median follow-up after starting treatment was 80 weeks. The median baseline Eczema Area and Severity Index (EASI) score was 32.3. Sixty percent of patients achieved EASI-90 and 77% EASI-75 at week 16 (n = 30); 79% EASI-90 and 92% EASI-75 at week 52 (n = 24); 64% EASI-90 and 82% EASI-75 at week 104 (n = 11); and 75% EASI-90 and 100% EASI-75 at week 132 (n = 4). Regarding adverse reactions, four patients (12%) presented facial erythema and two patients had eosinophilia above 2000/μL and conjunctivitis. In five patients (17%), there was a need for a dose increase, with treatment failure occurring in two patients (7%). **Conclusion:** Our data corroborated the evidence from clinical trials, highlighting the maintained efficacy and adequate safety profile of dupilumab in this age group.

Keywords: Atopic dermatitis. Dupilumab. Monoclonal antibody. Pediatrics. Real world.

Resumo

Objetivo: O uso de dupilumab em crianças com dermatite atópica (DA) demonstrou eficácia clínica em ensaios clínicos. No entanto, a evidência do mundo real é ainda limitada. Este trabalho pretende fornecer dados relativos a este domínio, numa população pediátrica portuguesa. **Métodos:** Análise retrospetiva de doentes com DA com idade inferior a 18 anos, tratados com dupilumab, em dois hospitais portugueses. Foram recolhidos dados sobre terapêuticas prévias, *scores* de atividade e reações adversas. **Resultados:** Trinta doentes foram incluídos na análise (19 doentes do sexo masculino, 63%), com uma mediana de idades de 14 anos (2-17 anos). O seguimento mediano após o início do tratamento foi de 80 semanas.

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O *score* EASI basal mediano foi de 32,3. Sessenta por cento dos doentes alcançaram EASI-90 e 77% EASI-75 na semana 16 (n = 30); 79% EASI-90 e 92% EASI-75 na semana 52 (n = 24); 64% EASI-90 e 82% EASI-75 na semana 104 (n = 11); 75% EASI-90 e 100% EASI-75 na semana 132 (n = 4). Em relação a reações adversas, 4 doentes (12%) apresentaram eritema facial e 2 doentes eosinofilia superior a 2000/μL e conjuntivite. Em 5 doentes (17%), houve necessidade de aumento de dose, com falência do tratamento em 2 doentes (7%). **Conclusão:** O tratamento com Dupilumab na DA em idade pediátrica num ambiente de mundo real corroborou os dados dos ensaios clínicos, destacando a eficácia mantida e o perfil de segurança adequado neste grupo etário.

Palavras-chave: Dermatite atópica. Dupilumab. Anticorpo monoclonal. Pediatria. Mundo real.

Introduction

The introduction of dupilumab, a monoclonal IgG4 antibody that inhibits the action of both interleukin (IL)-4 and IL-13, constituted a revolutionary milestone in the management of atopic dermatitis (AD). In adulthood, approval in Europe and the United States occurred in 2017, with its efficacy initially demonstrated in three phase III trials: LIBERTY AD SOLO1 and SOLO2[1,2], versus placebo, and LIBERTY AD CHRONOS[3], with the addition of topical corticosteroids in both dupilumab and placebo groups. In addition, an extension of the SOLO 1 and II trials (LIBERTY AD SOLO-CONTINUE)[4] revealed a maintained clinical efficacy of up to 36 weeks, but there are data already supporting the persistence of this effect up to 76 weeks[5], 3 years (LIBERTY AD OLE)[6], and 4 years[7].

Regarding the pediatric population, there has also been consistent progress in the use of the drug. Evidence from the LIBERTY AD ADOL (12-17 years)[8] and LIBERTY AD PEDS (6-11 years)[9] trials allowed for extrapolation of efficacy and safety data from the adult population to this age group, culminating in FDA and EMA approval for the use of dupilumab from 12 years of age in 2019 and from 6 years of age in 2020. More recently, favorable data from the LIBERTY AD PRESCHOOL[10] trial served as the basis for FDA approval in 2022 and EMA approval in March 2023 for the use of the drug from 6 months of age. In adolescents, data on the extension of dupilumab use up to 52 weeks are additionally available, with the achievement of Eczema Area and Severity Index (EASI)-75 in 81% of the recruited individuals[11].

At present, we witness the emergence of so-called real-world evidence regarding the efficacy of dupilumab in patients with AD. While in the adult population, there is already significant evidence devoted to this matter[12], in the pediatric population, the number of publications is still limited. A prospective multicenter Italian study including 139 adolescents with AD displayed a mean EASI reduction of 79.8% at week 16[13], a result superior to that observed in clinical trials. A Chinese publication, including 15 children with AD, observed a significant reduction of the mean EASI score from 19.2 to 1.69 at up to 6 months of follow-up[14]. A study from the United States featuring 23 children and adolescents with AD who received dupilumab for 1 year or more revealed an achievement of EASI-75 in all patients and EASI-90 in 60.8% of them[15]. Finally, a Dutch publication involving 61 children and adolescents with AD, described, at 28 weeks of therapy, 75.4%, 49.2%, and 24.6% of patients reaching EASI-50, EASI-75, and EASI-90, respectively[16].

Although these data already hint at a favorable performance of dupilumab in pediatric populations in a real-world setting, there is a visible need for additional evidence, namely in what pertains to longer periods of follow-up. We aim to provide real-world data on this matter in a Portuguese pediatric population.

Methods

Retrospective analysis of clinical charts of patients with AD below the age of 18 treated with dupilumab under follow-up in two Portuguese tertiary hospitals. Data regarding comorbidities, previous therapies, activity scores (EASI, NRS-pruritus, and DLQI), and adverse reactions were collected.

Statistical analysis was performed using IBM SPSS Statistics 28. Categorical variables are reported as proportions and/or percentages. Continuous variables are reported as mean (± SD) or median (range) values, depending on normal distribution. The correlation between categorical variables was obtained by performing a Chi-square test.

Results

Thirty patients were included in the analysis (19 male patients, 63%), with a median age of 14 years (IQR 8.5-16 years, min-max 2-17 years). Information on patient's allergic comorbidities is available in table 1.

Table 1. Patients' previous therapies, allergic comorbidities, and observed adverse reactions

Previous therapies	
≤ 1 immunosuppressant	6 (20)
≥ 2 immunosuppressants	24 (80)
Oral corticosteroids	28 (93)
Cyclosporine	23 (77)
Methotrexate	5 (17)
Azathioprine	5 (17)
Mycophenolate mofetil	4 (13)
Omalizumab	1 (3)
Atopic comorbidities	
Allergic rhinitis	15 (50)
Asthma	14 (47)
Conjunctivitis	1 (3)
Adverse reactions	
Facial erythema	4 (13)
Eosinophilia (> 2000/μL)	2 (7)
Conjunctivitis	2 (7)
Herpes virus infections	1 (3)
Injection-site reaction	0 (0)
Skin infections	0 (0)

The previously most used immunosuppressants were oral corticosteroids (28 patients, 93%), cyclosporine (23 patients, 77%), methotrexate, and azathioprine (both in five patients, 17%). The median follow-up after starting treatment with dupilumab was 80 weeks (IQR 52-104 weeks). Median baseline EASI score was 32.3 (IQR 25.7-40). Sixty percent of patients achieved EASI-90 and 77% EASI-75 at week 16 (n = 30); 62% EASI-90 and 79% EASI-75 at week 28 (n = 29); 79% EASI-90 and 92% EASI-75 at week 52 (n = 24); 78% EASI-90 and 78% EASI-75 at week 72 (n = 18); 64% EASI-90 and 82% EASI-75 at week 104 (n = 11); and 75% EASI-90 and 100% EASI-75 at week 132 (n = 4). In five patients (17%), there was a need for a dose increase, with treatment failure occurring in two patients (7%) – one primary and one secondary failure. In two patients (7%), there was a worsening of the EASI score during therapy with dupilumab after an initial favorable response, with a subsequent reattainment of disease control while maintaining therapy. Ninety-seven percent of patients (n = 29) achieved an EASI score below 7, 97% (n = 29) EASI-50, and 93% (n = 28) EASI-75 and EASI-90 at some point of follow-up. Complete results are shown in table 2. Ninety-three percent of patients (n = 28) achieved at some point a reduction superior to 4 points in the NRS pruritus scale and of more than 6 points in the DLQI questionnaire. Regarding the most common adverse reactions, four patients (12%) presented facial erythema, two (7%) patients asymptomatic eosinophilia above 2000/μL, and two (7%) patients mild conjunctivitis (Table 1). All events were manageable or transient and there was no need to stop treatment.

Discussion

Our results suggest that treatment outcomes with dupilumab in pediatric AD in a real-world setting corroborate those observed in clinical trials, even surpassing them in some cases.

Our data reports 77% of patients achieving EASI-75 at week 16, a value higher than those observed in pediatric trials: in the LIBERTY AD ADOL (12-17 years)[8] trial, achieved by 42% of patients in the every-2-week regimen and 38% in the every-4-week regimen; in the LIBERTY AD PEDS (6-11 years)[9] trial, achieved by 67% of patients in the every-2-week regimen and 70% in the every-4-week regimen; and in the LIBERTY AD PRESCHOOL[9] trial (6 months-5 years), achieved by 53% of patients. Comparing our data with other real-world evidence studies, the value EASI-75 at week 16 observed in 77% of our patients also surpasses the available evidence, with reported values ranging from 43 to 65%[13,15,16]. Regarding long-term outcomes, our results fall in line with the reported literature, with the LIBERTY AD PED-OLE[11] trial in adolescents providing evidence on the extension of dupilumab use up to 52 weeks, with EASI-75 in 81% of recruited individuals, whereas a real-world study from the United States featuring 23 children and adolescents with AD who received dupilumab for 1 year or more revealed an achievement of EASI-75 in all patients[15]. In our case, 93% of patients achieved EASI-75 and EASI-90 at some point of follow-up, being noteworthy that our cohort displays a median follow-up of 80 weeks, with patients followed up to 132 weeks. Our cohort also provides relevant data in what concerns the significant reduction of the NRS pruritus score and DLQI in the vast majority of our patients, highlighting the impact of treatment, not only in disease activity scores but also on the quality of life reported by patients, as already stressed by other real-world publications[16]. An additional novel information added by our data regards the specific treatment outcomes of need for dose increase and treatment failure, with the former occurring in 17% and the latter in 7%. In addition, the fact that, in two patients, there was a worsening of the EASI score during therapy with dupilumab after an initial favorable response, with subsequent reattainment of disease control with maintained therapy, strengthens the rationale of not suspending the treatment at the first signs of clinical deterioration.

Table 2. Eczema Area and Severity Index (EASI) score at different follow-up points

	Timepoint					
Disease activity	**Week 16 (n = 30)**	**Week 28 (n = 29)**	**Week 52 (n = 24)**	**Week 72 (n = 18)**	**Week 104 (n = 11)**	**Week 132 (n = 4)**
Median EASI	3 (1-8.2)	2 (1-6)	1 (0-3)	1.5 (0-3.8)	2 (0-6.1)	4.5 (0-8.9)
EASI 75	23 (77)	23 (79)	22 (92)	14 (78)	9 (82)	4 (100)
EASI 90	18 (60)	18 (62)	19 (79)	14 (78)	7 (64)	3 (75)

Regarding safety and adverse reactions, pediatric clinical trials revealed no serious events, with conjunctivitis and injection-site reactions as the most common occurrences[8,9], whereas, in real-world pediatric studies, conjunctivitis, flushing, joint pain, and headache featured among the most reported[13,14-16]. In our cohort, conjunctivitis was also present, but facial erythema and asymptomatic eosinophilia were additionally noted. No serious events occurred, corroborating the previously observed safety of dupilumab.

Our study presents both strengths and limitations. On the one hand, our sample is composed of a significant number of pediatric patients, originating from two different centers, featuring detailed data on their evolution across a substantial time span. On the other hand, data were collected retrospectively, with expectable shortcomings, and two-thirds of the patients were above the age of 11, a fact that might constitute the source of certain biases, making our data particularly applicable to this age group.

Overall, treatment with dupilumab in pediatric AD in a real-world setting corroborated the data from clinical trials, highlighting its maintained efficacy and adequate safety profile in this age group.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016;375:2335-48.
2. Gooderham MJ, Hong HC, Eshtiaghi P, Papp KA. Dupilumab: a review of its use in the treatment of atopic dermatitis. J Am Acad Dermatol. 2018;78(3 Suppl 1):S28-36.
3. Blauvelt A, De Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet. 2017;389: 2287-303.
4. Worm M, Simpson EL, Thaçi D, Bissonnette R, Lacour JP, Beissert S, et al. Efficacy and safety of multiple dupilumab dose regimens after initial successful treatment in patients with atopic dermatitis: a randomized clinical trial. JAMA Dermatol. 2020;156:131-43.
5. Deleuran M, Thaçi D, Beck LA, De Bruin-Weller M, Blauvelt A, Forman S, et al. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. J Am Acad Dermatol. 2020;82:377-88.
6. Beck LA, Thaçi D, Deleuran M, Blauvelt A, Bissonnette R, De Bruin-Weller M, et al. Dupilumab provides favorable safety and sustained efficacy for up to 3 years in an open-label study of adults with moderate-to-severe atopic dermatitis. Am J Clin Dermatol. 2020; 21:567-77.
7. Beck LA, Deleuran M, Bissonnette R, De Bruin-Weller M, Galus R, Nakahara T, et al. Dupilumab provides acceptable safety and sustained efficacy for up to 4 years in an open-label study of adults with moderate-to-severe atopic dermatitis. Am J Clin Dermatol. 2022;23: 393-408.
8. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. JAMA Dermatol. 2020;156:44-56.

9. Paller AS, Siegfried EC, Thaçi D, Wollenberg A, Cork MJ, Arkwright PD, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: a randomized, double-blinded, placebo-controlled phase 3 trial. J Am Acad Dermatol. 2020;83:1282-93.
10. Paller AS, Siegfried EC, Simpson EL, Cork MJ, Lockshin B, Kosloski MP, et al. A phase 2, open-label study of single-dose dupilumab in children aged 6 months to <6 years with severe uncontrolled atopic dermatitis: pharmacokinetics, safety and efficacy. J Eur Acad Dermatol Venereol. 2021;35:464-75.
11. Blauvelt A, Guttman-Yassky E, Paller AS, Simpson EL, Cork MJ, Weisman J, et al. Long-term efficacy and safety of dupilumab in adolescents with moderate-to-severe atopic dermatitis: results through week 52 from a phase III open-label extension trial (LIBERTY AD PED-OLE). Am J Clin Dermatol. 2022;23:365-83.
12. Kamata M, Tada Y. A literature review of real-world effectiveness and safety of dupilumab for atopic dermatitis. JID Innov. 2021;1:100042.
13. Stingeni L, Bianchi L, Antonelli E, Caroppo ES, Ferrucci SM, Ortoncelli M, et al. Moderate-to-severe atopic dermatitis in adolescents treated with dupilumab: a multicentre Italian real-world experience. J Eur Acad Dermatol Venereol. 2022;36:1292-9.
14. Yang DY, Li L, Lu T, Jing WW, Liu X, Li XL. Efficacy and safety of dupilumab in pediatric patients with moderate to severe atopic dermatitis: a real-world study. Arch Dermatol Res. 2023;315:467-72.
15. Pagan AD, David E, Ungar B, Ghalili S, He H, Guttman-Yassky E. Dupilumab improves clinical scores in children and adolescents with moderate to severe atopic dermatitis: a real-world, single-center study. J Allergy Clin Immunol Pract. 2022;10:2378-85.
16. Kamphuis E, Boesjes CM, Loman L, Bakker DS, Poelhekken M, Zuithoff NP, et al. Dupilumab in daily practice for the treatment of pediatric atopic dermatitis: 28-week clinical and biomarker results from the BioDay registry. Pediatr Allergy Immunol. 2022;33:e13887.