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ORIGINAL RESEARCH

Efficacy and safety of dupilumab in the treatment of moderate-to-severe atopic dermatitis: a real-life study

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Abstract

Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease that occurs more frequently in children but can also manifest in adults. Approximately 15–20% of children are affected worldwide. Persistent AD may be present in approximately 50% of patients during childhood. Despite the pivotal studies, there are not enough real-life studies using dupilumab, especially in Latin American countries. This study was performed in Brazil and is essential for evaluating this population. The objective of the study was to understand the real-life efficacy and safety of using dupilumab in patients with moderate or severe AD.

Methods: Observational, descriptive study based on the biweekly evaluation of 100 patients using the immunobiological dupilumab in an infusion clinic for 16 consecutive weeks. Data collection was conducted from June 2020 to March 2022. To evaluate each sequential SCORing Atopic Dermatitis (SCORAD) value, a repeated measures analysis of variance was performed, with a value of $p<0.0001$.

Results: There was a significant decrease in SCORAD values from the second week of treatment. In 16 weeks, 80% of patients achieved SCORAD-50 and 37% achieved SCORAD-75. Regarding adverse effects, 22% of patients had conjunctivitis, 11% had facial erythema, 1% had herpes simplex and 1% had hypochromia at the application site. Regarding efficacy, the results showed a reduction in SCORAD value by 67.4% in 16 weeks, 72% of patients achieved SCORAD <25, that is, mild atopic dermatitis.

Conclusion: This study identified that dupilumab was effective in real life, even outside of the controlled environments of pivotal studies. Additionally, despite conjunctivitis being a common adverse event, no patient required treatment discontinuation.

Keywords: atopic dermatitis, skin diseases, data collection, weights and measures.

Citation

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that occurs most often in children but can also manifest in adults and has been increasing in recent decades.[1] Approximately 15–20% of children and up to 10% of adults are affected by AD worldwide.[2–4] Prevalence data show that around 52.1% of cases are mild, 37.7% are moderate and 10.2% are severe.[5–8]

Multiple factors, including skin barrier and immune system changes, are involved in the pathogenesis of AD. The higher the levels of cytokines predominant in T2 inflammation, such as IL-4 and IL-13, the lower the filaggrin expression, with a consequent decrease in stratum corneum lipids and increased tissue damage.[9–13]

Treatment of AD involves several actions to control pruritus, xerosis and inflammation. Initial treatment includes skin care focusing on skin hydration. In patients with mild AD, apart from the initial therapy, the use of topical corticosteroids and immunomodulators for the acute treatment of recurrences is widely indicated. In some cases of moderate AD and most severe cases, systemic therapies with immunosuppressants, immunobiologicals and JAK1 inhibitors are indicated.[14] Currently, the immunobiological dupilumab is indicated in patients with moderate

or severe AD over 12 years of age and in severe AD in patients over 6 months of age.[15]

Dupilumab is a monoclonal antibody that specifically binds to the IL-4 receptor subunit-α (IL-4Rα),[10] which is shared by IL-4 and IL-13; therefore, the use of dupilumab implies the inhibition of signalling of both interleukins. These are inflammatory cytokines of type 2/T helper 2 related to numerous allergic diseases, in which the eosinophil plays an important role.[16,17] The efficacy and safety of dupilumab were evaluated in three randomized, double-blinded, placebo-controlled pivotal studies (SOLO 1, SOLO 2 and CHRONOS) in 2,119 patients ≥18 years with moderate to severe AD.[15,18] In another study (LIBERTY AD CAFÉ), the efficacy of dupilumab in adult patients with AD that was not adequately controlled or who were intolerant to oral cyclosporine was evaluated.[19,20] The evaluation of adolescents (12–17 years of age) was performed through a multicentre, randomized, double-blinded, placebo-controlled study.[15]

In addition to pivotal studies, analyses closer to clinical practice are needed to better reflect the reality of the population receiving treatment. This makes real-life studies highly relevant. There are few real-life studies, especially in the Latin American population. Brazil is a developing country where public health does not yet make this immunobiological available to the population. Our study shows the clinical evolution and monitors adverse events over 16 weeks of follow-up of dupilumab use in Brazilian patients over 12 years of age with moderate or severe AD.

Methods

Adults and adolescents ≥12 years of age with moderate (SCORing Atopic Dermatitis (SCORAD) index value of between 25 and 50) or severe (SCORAD >50) AD and with refractoriness despite topical and/or systemic therapy and who did not reach SCORAD ≤25, and who had an indication and medical prescription of dupilumab were included.

An observational, descriptive study was performed based on the biweekly evaluation of 100 patients using the immunobiological dupilumab in an infusion clinic for 16 consecutive weeks. The study was approved by the Institutional Review Board of the Division of Clinical Immunology and Allergy, School of Medicine, University of São Paulo and all included patients signed the informed consent form.

To evaluate the evolution of AD, the patient-oriented SCORAD (PO-SCORAD) application was used, validated and developed based on SCORAD. Assessment of the severity of AD through this methodology includes analysis of the surface area of skin affected by eczema, skin xerosis, assessment of the severity of eczema over the past 3 days (redness of skin affected by eczema, oedema, oozing/crusting, excoriation and thickening), pruritus, and interference with sleep.[21] In all biweekly evaluations, PO-SCORAD was performed by the study's main author (MML) with the patient as well as questioning about adverse events. At the time of the study, the PO-SCORAD was the tool in use at the study clinic.

Table 1. Epidemiological data.

Characteristics *n*=100	**Results**
Age, median (variation)	22 (12–80)
Sex (male, %)	50% (50/50)
Initial SCORAD (variation)	61.9 (20.9–99.9)
Comorbidities *n*=50	**Frequency**
Rhinitis	76%
Allergic conjunctivitis	24%
Asthma	38%
Food allergy	38%
Eosinophilic esophagitis	4%
Previous immunosuppression (*n*=50)	**Frequency**
Cyclosporine	22%
Methotrexate	10%
Cyclosporine and methotrexate	14%

This real-life study aims to evaluate the efficacy and safety of immunobiological dupilumab in patients with moderate or severe AD. Specifically, the reduction in the mean SCORAD value was analysed at each biweekly evaluation during the 16 weeks of treatment as well as the adverse events presented. In addition, the rate of treated patients achieving mild severity score (SCORAD <25) as well as the individual impact on disease severity through the SCORAD-50 and SCORAD-75 metrics at 16 weeks of treatment were assessed.

Descriptive statistics of quantitative data (SCORAD) were initially used to analyse asymmetry and kurtosis. No outliers were found. The covariance equality test ($p>0.05$) and Levene test ($p>0.05$) were used to verify the homoscedasticity of the data.[22] A multivariate analysis (MANOVA four-way) was then performed to evaluate whether the weekly SCORAD values varied according to adverse events. The results of the multivariate analysis were interpreted by the Pillai trace test ($p>0.05$).[23] To evaluate whether sequential weekly SCORADs vary, repeated measures analysis of variance (ANOVA; $p<0.0001$) was

performed. To verify which groups were statistically different, the mean estimate with a 95% confidence interval was performed for analyses of multiple comparisons. A Kaplan–Meier[24] survival analysis with a 95% confidence interval was also performed to evaluate the odds ratio of achieving SCORAD ≤25 over the 16 weeks of treatment.

Results

One hundred patients were included in the study (50 men and 50 women), mostly young adults, with a mean age of 25 years, a median of 22, and a variation between 12 and 80 years. The mean initial SCORAD value was 61.9, ranging from 26.8 to 99.9 (Table 1). The difference between the various SCORAD values was significantly observed in the second week with increasing differences. A plateau in SCORAD values, with no reduction, was observed between weeks 6 and 14, with a new and significant reduction in SCORAD between weeks 14 and 16 (Figures 1 and 2).

Seventy-two patients (72%) achieved mild AD (SCORAD <25 at 16 weeks), and 22% had mild AD at 2 weeks

Figure 1. Sequence of mean SCORAD values over 16 weeks of treatment with dupilumab. 67.4% mean reduction in SCORAD after 16 weeks of treatment. Repeated measures ANOVA test value: $p<0.0001$. To check which groups are statistically different from each other, an estimate was performed with a 95% confidence interval.

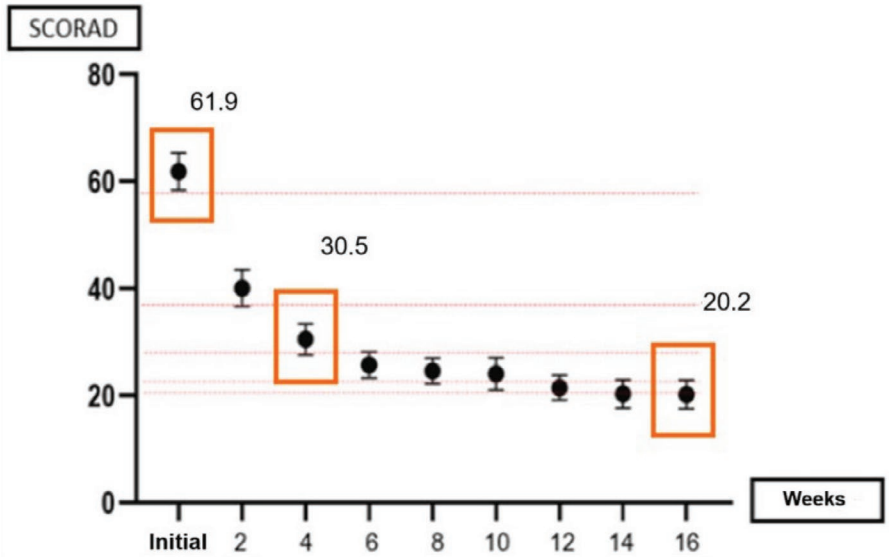
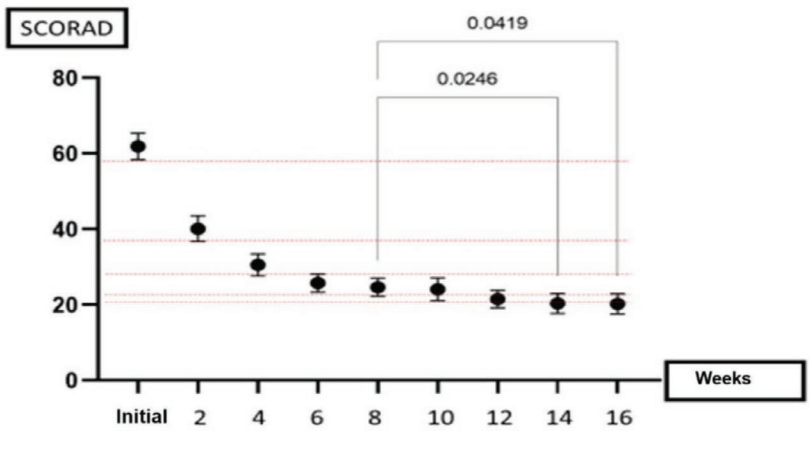


Figure 2. Mean graph with 95% confidence interval and Bonferroni test between 8 and 16 weeks. We confirmed the statistical significance between 14 and 16 weeks with the 8 week ($p<0.05$).



(Figure 3). The odds ratio of a patient having mild AD (SCORAD <25) throughout the treatment was cumulative and progressive, reaching 90.85 within 16 weeks (Figure 4). Amongst the 100 patients, 37% achieved SCORAD-75 and 80% achieved SCORAD-50 within 16 weeks of dupilumab treatment. Following 2 weeks of treatment, 3% had reached SCORAD-75 and 22% SCORAD-50 (Figure 5).

Information regarding prior use of immunosuppressants was retrieved retrospectively and was available

Figure 3. **Percentage of patients who reached SCORAD <25 during treatment. 72% of patients achieved SCORAD <25 at 16 weeks of treatment.**

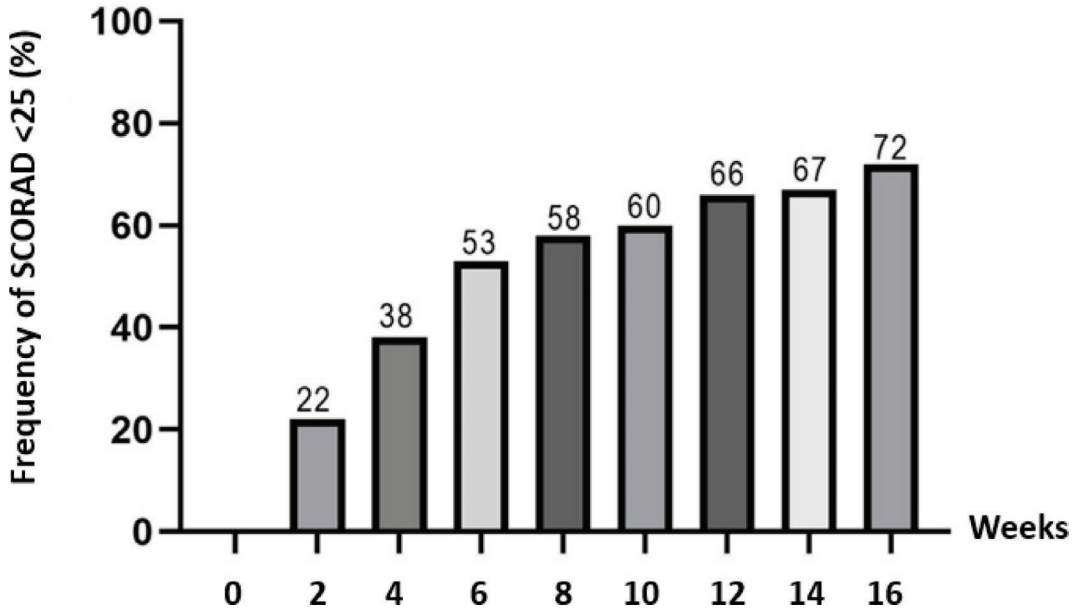
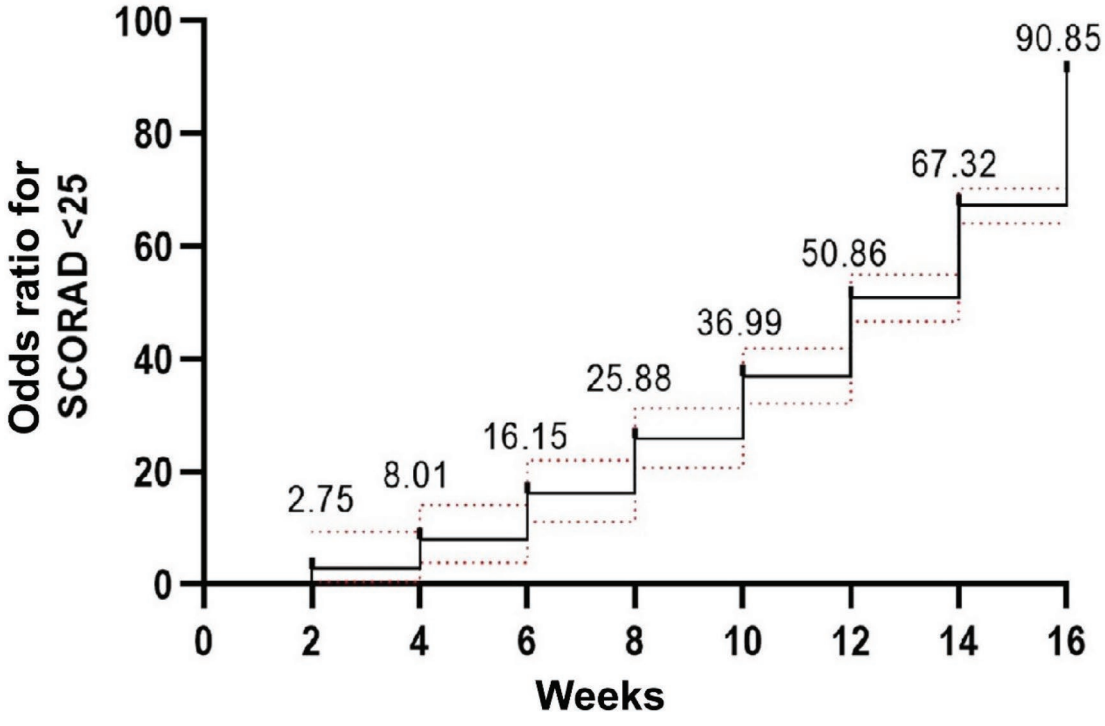


Figure 4. **Odds ratio of the patient reaching SCORAD <25. The odds ratio of a patient having mild disease, that is, SCORAD <25 throughout the treatment was cumulative and progressive, reaching 90.85 at 16 weeks of treatment.**



for 50 patients. In this subgroup of 50 patients, it was observed that the behaviour of AD was similar between the groups; there was a significant improvement over 16 weeks, and both achieved a similar SCORAD-50 but a higher percentage of those who had previously received immunosuppressant reached SCORAD-75 (Figure 6).

Adverse events

Amongst the 100 patients, none had to discontinue dupilumab due to adverse events. The most frequently observed adverse event was conjunctivitis (22%), followed by facial erythema (Table 2). Conjunctivitis manifested in 30% of patients after 4 weeks of treatment, with 5 out of 22 patients experiencing their first episode at 16 weeks. By the end of 16 weeks, 3 patients experienced a recurrence of symptoms after initial improvement. None of the adverse events required a delay or discontinuation of the medication.

Discussion

AD is a condition managed by immuno-allergologists that causes great damage to the quality of life of patients

Figure 5. Percentage of patients achieving SCORAD-50 and SCORAD-75 during treatment. Amongst the 100 patients studied, 80% achieved SCORAD-50, that is, 50% reduction in SCORAD, and 37% achieved SCORAD-75, that is, 75% reduction in SCORAD, at 16 weeks of treatment.

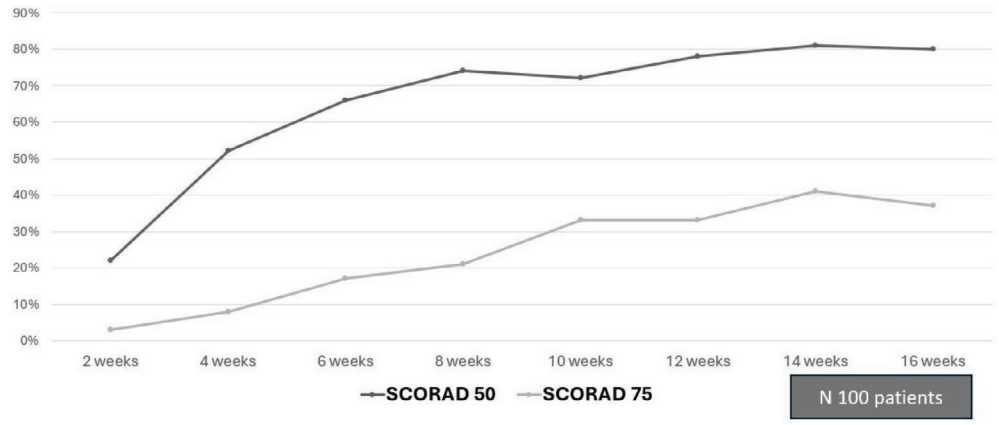


Figure 6. Percentage of patients who have and have not used a previous immunosuppressant and achieved SCORAD-50 and SCORAD-75 during treatment. In the subgroup of 50 patients, we observed that the behaviour was similar between the groups; there was a significant improvement over 16 weeks of treatment, both similarly reached SCORAD-50 but a higher percentage of those who had previously received immunosuppressant reached SCORAD-75.

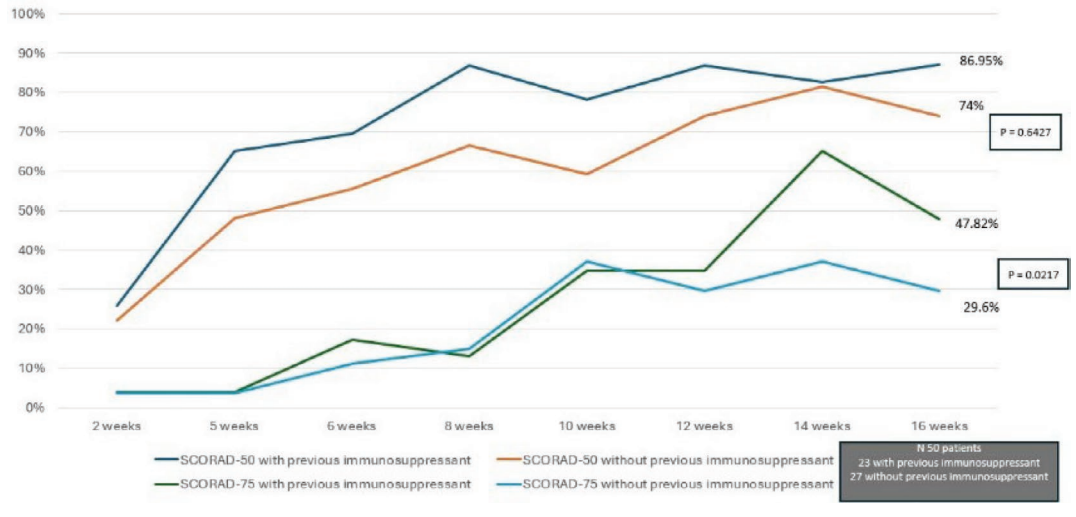


Table 2. Adverse events related to the use of dupilumab over 16 weeks of treatment.

Adverse events	Frequency (%)
Conjunctivitis	22
Facial erythema	11
Local reaction	1
Herpes simplex	1

and continues to be a major challenge for specialists. However, in recent years, with the development of this new therapeutic class of monoclonal antibodies, we have witnessed a significant advance in the treatment of patients with severe AD.

A real-life study refers to research that evaluates the efficacy and safety and even other inherent aspects of treatment with a new drug in conditions closer to clinical practice outside the controlled environment of extremely rigorous clinical trials. Our real-life study evaluated the effectiveness and safety of dupilumab (Dupixent®) on 100 Brazilian patients included in the analysis.

The SCORAD evaluation performed throughout our real-life study showed the impact of treating AD. The results showed a mean SCORAD reduction of 67.4% amongst the 100 patients evaluated during the 16 weeks of treatment with dupilumab (mean initial SCORAD was 61.9%). These results are in agreement with those of the pivotal study CHRONOS, which showed a mean reduction of 62.1% during the same period of use. This pivotal study had a mean initial SCORAD of 69.7% and followed its patients up to 52 weeks with a final mean reduction in SCORAD of 66.2.[19]

In our study, 80% of patients achieved SCORAD-50 within 16 weeks. The CHRONOS study evaluated SCORAD-50 after 52 weeks, and 70.8% of patients achieved this goal.[25] The pivotal LIBERTY AD CAFÉ study (mean initial SCORAD was 66.7%) demonstrated that, at 16 weeks of treatment, 66.4% of patients achieved SCORAD-50.[25] Comparing our real-life study with the pivotal studies that used dupilumab associated with topical therapy, our results showed that a higher percentage of patients reached SCORAD-50. SCORAD-75 was evaluated in our study but this metric was reached in only 37% of patients.

The original aim of this real-life study was the evaluation of SCORAD and side-effects in 100 patients using dupilumab. However, following the availability of more specific information, such as comorbidities and previous use of immunosuppressants, their assessment was added to the study. These data were collected retrospectively, and data were only available from 50 patients, making the comparison between groups that used or did not use immunosuppressants and the efficacy of the treatment limited to a smaller number of patients. Of these 50 patients, 23 had used at least one immunosuppressant and 27 patients were immunosuppressant naive. The comparison between these groups was significant regarding the percentage of patients who reached SCORAD-75. In the group that used immunosuppressants, 47.82% achieved SCORAD-75, whilst only 29.6% reached this goal amongst those whose dupilumab was the first systemic therapy. One of the possible justifications for this difference between the SCORAD-75 in the two groups may refer to the subjective scores of the part of the SCORAD that involves the perception of improvement in sleep quality and pruritus. Perhaps patients who have previously tried and failed immunosuppressant therapies have more expressive scores than those in whom dupilumab was the first systemic therapy and perhaps have created higher expectations regarding clinical improvement. We recognize the limitation concerning the number of participants for whom information on prior immunosuppressant use could be obtained. As a result, the generalization of these findings is limited. Future studies with larger cohorts will be essential to confirm and expand upon these observations.

Regarding efficacy, though all patients commenced treatment with a score corresponding to moderate or severe AD, 72% had SCORAD <25, indicating mild AD, by 16 weeks of treatment. The literature shows that, at 16 weeks, patients with previously severe AD improved to mild AD or were even without symptoms.[25,26] Whilst we would have liked to obtain longer-term data, a limitation of the study was the confinement to 16 weeks duration of treatment and follow-up due to guaranteed treatment by donation of the immunobiological drug by Sanofi through the 'Viva' programme for application in a supervised manner; however, this allowed the evaluation of SCORAD on a biweekly basis, always by the same researcher. Thus, following the 16 weeks, some patients continued their treatment independently with self-application, whilst others could not continue. Real-life studies with a longer follow-up time would be interesting to evaluate the possible increase in the percentage of patients who reach the parameters of mild AD.

Regarding safety, as in the literature, the most relevant adverse event was conjunctivitis, but real-life data in our population showed a higher incidence than in the previous series. The data from the literature showed 10.7% of conjunctivitis,[15] whereas our study showed 22%. We believe that the real-life evaluation, outside the controlled environment of clinical trials, contributed to the higher prevalence of conjunctivitis.

Conclusion

In this real-life study, we evaluated 100 Brazilian patients with moderate or severe AD who were indicated for dupilumab. These patients were followed up over 16 weeks of treatment with the immunobiological.

Regarding efficacy data, a significant reduction in SCORAD values was found during the study period. Although all patients started the study with a diagnosis of moderate or severe AD, more than 70 reached a SCORAD <25 (mild atopic dermatitis) after 16 weeks.

Another important finding was that 80% of patients reached SCORAD-50 (50% reduction in SCORAD) in 16 weeks of treatment and 37% reached SCORAD-75 (75% reduction in SCORAD) during this period. Despite the similarity of the metrics achieved in SCORAD-50 between the groups that had or had not used a previous immunosuppressant, SCORAD-75 was different between these groups, with a significantly higher percentage of patients achieving this metric in the group of patients who had previously used an immunosuppressant.

Regarding safety, the most common adverse event was conjunctivitis, with 22% of patients experiencing at least one episode during the study. The second most prevalent adverse event was facial erythema. None of them stopped treatment.

It is known that in real life, there are often limitations regarding access to immunobiological therapies due to the cost, especially when facing chronic diseases with prolonged treatment time or even continuous treatment. However, the prospects for innovative treatments with a good safety profile are already a reality in Brazil.

Contributions: Each author contributed individually and significantly to the development of this article: MML: Conceptualization, Data curation, Writing – Draft, Writing – Review & Editing; APMC: Data curation, Formal Analysis, Writing – Review & Editing; TMF: Data curation, Formal Analysis; JK: Validation, Writing – Review & Editing; ACY: Validation, Supervision; FMC: Conceptualization, Visualization, Supervision. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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