ABSTRACT – Introduction: Dupilumab is a fully human monoclonal antibody that blocks interleukin-4 and interleukin-13, key drivers of type 2 helper T-cell (Th2)-mediated inflammatory response. It was the first biologic treatment approved for adult patients with inadequately-controlled moderate-to-severe atopic dermatitis (AD). Continuous collection of daily data practice is important in order to evaluate the real effectiveness and safety of dupilumab treatment.

Methods: In this observational cohort study, we prospectively included all adult patients with moderate to severe AD treated with dupilumab in our Portuguese dermatology center from July 2019 to April 2020. Baseline clinical data was initially collected and treatment effectiveness and safety were assessed after 16 weeks.

Results: Twenty-five patients were included. All patients had been previously treated with systemic immunosuppressants. The estimated mean Eczema Area and Severity Index Score (EASI) decreased from 27.8 at baseline to 8.8 at week 16 (+/- 4 weeks). A ΔEASI 75 response was achieved by 58.3% of patients (ΔEASI 90 - 29.1%). Conjunctivitis was the main reported side-effect, affecting 20.8% of patients.

Discussion: Our study showed a significant EASI reduction during the first 16-weeks of dupilumab treatment in adult patients with AD. Despite its overall safety, daily-practice data tend to report a higher risk of conjunctivitis than previously expected and we hence recommend that patients should be specifically informed about this possible side-effect.

KEYWORDS – Antibodies, Monoclonal, Humanized/therapeutic use; Dermatitis, Atopic/drug therapy; Dupilumab.

INTRODUCTION

Atopic dermatitis (AD) is an exceedingly common inflammatory skin disorder that typically presents with pruritic eczematous lesions with a chronic and relapsing course. The prevalence of AD in the adult population is not fully characterized, but some authors suggested a lifetime prevalence that ranged from 3.0% to 17.7%. Moderate to severe AD usually requires long-term systemic therapy with classic agents such as cyclosporine, azathioprine, methotrexate or systemic corticosteroids, often associated with severe side-effects and variable efficacy.

AD is deeply associated with other diseases within the atopy spectrum and increased awareness about the importance of Th2 inflammatory cells in these conditions allowed dupilumab, a fully human monoclonal antibody that targets the shared IL-4Rα subunit of heterodimeric IL-4 and IL-13 receptors, to be approved as the first biologic treatment for adult patients with inadequately controlled moderate-to-severe AD. In phase 3 clinical trials, 16-week dupilumab treatment significantly improved clinical parameters and symptoms of AD, while maintaining an acceptable safety profile.

Although dupilumab has emerged in these trials as a breakthrough therapy, continuous data collection in the postmarketing phase
is needed in order to validate its efficacy and safety performance in the real-world clinical setting. As such, we aim to describe our daily-practice experience with dupilumab, providing further evidence for its clinical use.

**MATERIAL AND METHODS**

In this observational cohort study, we prospectively included all adult patients with moderate to severe AD who initiated dupilumab in our Portuguese tertiary care hospital, from July 2019 to April 2020. Our dermatology team was instructed to initially register the patient’s epidemiologic data; comorbidities; previous treatments; and Eczema Area and Severity Index (EASI).

A 600 mg loading dose of dupilumab was injected subcutaneously at baseline, followed by an injection of 300 mg dupilumab every other week. The need for other ongoing systemic treatments was clinically assessed and recorded. Topical anti-inflammatory agents and moisturizers usage was recommended but not systematically described.

Patients were re-evaluated after 16 weeks of treatment and EASI, adverse events and treatment interruptions were assessed. Appointment between week 12 and 20 of treatment - motivated by physicians or patient agenda constraints - were also considered suitable for inclusion. At the end of the study, data was reviewed by the authors and patients with non-compliant clinical records were excluded. Statistical analysis was performed using SPSS 24.0 (IBM, Armonk, NY, U.S.A.).

**RESULTS**

Our study analyzed 32 patients but 7 were excluded due to incomplete clinical records. Of the 25 included patients (Table 1), most were male (64%); 16 of 21 with a mean age of 32 years (20-60). Asthma (36%) and allergic rhinitis (20%) were the most frequent comorbidities. All patients had been previously treated with oral corticosteroids; 96% (24 of 25) with oral cyclosporine; 60% with phototherapy (n=15); 36% with methotrexate (n=9); 24% with mycophenolate mofetil (n=6); and 20% with azathioprine (n=5).

The mean EASI score at week 0 was 27.8, ranging from 11 to 51. Concomitant treatment was initially maintained in 32% of patients (n=8), with three patients medicated with corticosteroids and others with mycophenolate mofetil; oral prednisolone; narrow-band UVB; azathioprine with oral prednisolone; or cyclosporine with oral prednisolone.

At week 16 (+/- 4 weeks), one patient missed the reevaluation assessment, voluntarily abandoned therapy against clinical decision and was excluded from the study. The mean EASI score at week 16 was 8.8 (68.6% reduction), ranging from 0 to 50 (Table 2). EASI 50 (defined by an EASI score improvement of at least 50%) was achieved in 87.5% of patients (n=21); 58.3% (n=14) reached EASI 75; 29.1% (n=7) EASI 90; and 16.6% (n=4) EASI 100. However, 8.3% (n=2) of patients did not respond to dupilumab therapy.

When evaluating patients with no concomitant systemic treatment (n=16), the mean initial EASI was 25.9 and EASI at week 16 was 6.8 (73.8% reduction); EASI 50 in 93.7% of patients (n=15); EASI 75 in 68.7% of patients (n=11); EASI 90 in 31.2% of patients (n=5); EASI 100 in 18.7% of patients (n=3); 6.2% of patients with no response (n=1).

**DISCUSSION**

In AD, barrier-disrupted keratinocytes produce immunoregulatory cytokines (alarmins) such as thymic stromal lymphopoietin or IL-33, activating group 2 innate lymphoid cells (ILC2s). These activated ILC2s produce type 2 cytokines, which cause further skin barrier disruption and allow the entry of various antigens into the skin, leading to the differentiation of antigen-specific naïve T cells into effector Th2 cells. These cells produce IL-4 and IL-13, known to be involved in several proinflammatory pathways of AD, such as down-regulation of filaggrin expression in keratinocytes (further increasing epidermal

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**Table 1 - Epidemiological and clinical characteristics of our cohort population.**

<table>
<thead>
<tr>
<th>Epidemiological and clinical characteristics at baseline</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Age at the start of dupilumab treatment (years)</td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>32 (20 - 60)</td>
</tr>
<tr>
<td>Previous use of conventional systemic immunosuppressants, n (%)</td>
<td></td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>25 (100%)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>24 (96%)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Previous use of phototherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 (60 %)</td>
</tr>
<tr>
<td>Atopic/allergic conditions, n (%)</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Food allergy</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>EASI at week 0</td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>27.8 (11 - 51)</td>
</tr>
</tbody>
</table>

**Table 2 - Efficacy and safety outcomes at week 16.**

<table>
<thead>
<tr>
<th>Efficacy and safety outcomes (week 16)</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EASI</td>
<td></td>
</tr>
<tr>
<td>Mean score (range)</td>
<td>8.8 (0-50)</td>
</tr>
<tr>
<td>Mean reduction</td>
<td>68.6%</td>
</tr>
<tr>
<td>EASI 50, % (n)</td>
<td>87.5% (21)</td>
</tr>
<tr>
<td>EASI 75, % (n)</td>
<td>58.3% (14)</td>
</tr>
<tr>
<td>EASI 90, % (n)</td>
<td>29.1% (7)</td>
</tr>
<tr>
<td>EASI 100, % (n)</td>
<td>16.6% (4)</td>
</tr>
<tr>
<td>Non-responders, % (n)</td>
<td>8.3% (2)</td>
</tr>
<tr>
<td>Adverse-events, % (n)</td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis, % (n)</td>
<td>25% (6)</td>
</tr>
<tr>
<td>Eyelid eczema</td>
<td>20.8% (5)</td>
</tr>
<tr>
<td></td>
<td>4.2% (1)</td>
</tr>
</tbody>
</table>

Outcomes are a comparison between baseline and follow-up at week 16 (+/- 4 weeks), EASI, Eczema Area and Severity Index; EASI 50, EASI score improvement of at least 50%; EASI 75, EASI score improvement of at least 75%; EASI 90, EASI score improvement of at least 90%; EASI 100, EASI score improvement of 100%.

Dupilumab-associated conjunctivitis (DAC) was the main reported side-effect, affecting 20.8% (n=5) of patients. Another patient presented with eyelid eczema (4.2%). No patient had to discontinue dupilumab due to an adverse-event.
barrier dysfunction); amplification of IL-31-induced and histamine-
induced pruritus; stimulation of B cells to produce immunoglobulin
E (IgE) which binds to mast cells and induces their degranulation
upon binding to allergens; or increased production of CCL17,
CCL22 and CCL26, that together with IL-5 can further recruit Th2
cells and eosinophils.10, 11

These key-functions of IL-4 and IL-13 in AD immune response,
together with evidence of a common component shared by their re-
ceptors, were used in dupilumab development and explain the sig-
ificant clinical improvement of AD patients treated with this drug. In
phase 3 clinical trials, 16-week treatment with dupilumab (300 mg
q2w) lead to a 70.07% mean EASI reduction, with 61% of patients
reaching EASI 50; 50.2% EASI 75; and 31.8% EASI 90.5

Our study showed a similar mean EASI reduction and a sig-
ificant increase of EASI 50 responses, reinforcing what has alre-
dy been suggested by some early “real-life” data12,13: dupilumab is
effective in most AD adult patients treated under daily-practice con-
ditions.

However, our results have also highlighted that there is a con-
siderable individual variability in the effectiveness of dupilumab,
with some patients displaying an extraordinary treatment response
(29.1% reaching EASI 90), while others failed to respond (8.3%).

Based on these data, predicting treatment response with dupi-
umab seems to be of the utmost importance. However, practical
predictors of its effectiveness are still under investigation. While ini-
tial studies5,12-15 suggested baseline EASI, IgE, lactate dehydrogena-
se (LDH), eosinophilia, allergic comorbidities or early-onset AD as
possible predictive markers of treatment response, there are still no
validated guidelines for treatment eligibility based on these possible
predictors.

We believe that future studies should be focused on proper vali-
dation of these predictive biomarkers, in order to allow a better pa-
tient selection, a realistic setting of treatment goals and an improved
management of our patient’s expectations.

Regarding the safety profile of dupilumab, phase 3 clinical trials
showed that the overall incidence of adverse events was similar be-
tween dupilumab and placebo groups.6 In fact, these trials under-
lined that placebo-treated patients had a higher-risk for a serious
adverse event (mainly AD exacerbation), although conjunctivitis
(9.7%) and injection-site reactions (16.7%) were more common in
the dupilumab-treated group.

Daily-practice early data, however, showed that DAC’s incidence
rate was significantly higher.5,16 While the mechanism for this adver-
se effect is still unknown, some authors proposed that ocular comor-
bidities are dependent on disease severity, prior conjunctivitis history
or certain biomarkers such as thymus and activation-regulated che-
mokine (TARC) or IgE.17 Hence, we tend to agree that intrinsic di-
ferences in the analysed cohorts - namely regarding conjunctivitis’
proposed risk-factors - are a likely explanation for the discrepancy
between clinical trials and real-life data, and that the true incidence
of conjunctivitis-induced by dupilumab was initially underestimated.
Currently, there is no standard treatment to prevent and manage
DAC, although topical corticosteroids, topical calcineurin inhibitors,
cyclosporin eye drops, hyaluronic acid eye drops or artificial tears
have been successfully used in several patients.18 In our study, some
of our physicians used artificial tear drops in the beginning of treat-
ment. However, this clinical intervention was not systematically re-
corded and therefore we cannot evaluate its efficacy on preventing
DAC, nor recommend its usage just based on our data. As such, we
believe that future studies should properly address this question in
order to produce solid evidence that can support a clinical orienta-
tion guideline for the prevention of DAC.

Finally, we acknowledge that our study has some limitations.
Dupilumab’s efficacy on pruritus reduction and its overall impact on
patients’ quality of life are among other important key-metrics that
should be considered when dupilumab is prescribed, and they were
not included in our study. Besides, by narrowing dupilumab’s effica-
sy and safety assessment to a solo 16-week EASI revaluation - and
by not including an earlier week 4-8 observation - we missed the
opportunity to determine its onset of action (or of its complications)
in a real-life setting.

CONCLUSION

Our study corroborates dupilumab as an effective treatment for
AD in the real-world clinical setting, with some individual variances
that should be further explored in a near future. No serious events
were reported but conjunctivitis is a common side-effect that should
be specifically mentioned to all patients.

Presentations/Apresentações

This paper was partially presented at the “SPDV - 1st Congresso Virtual
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Human and Animal Subjects: The authors declare that the procedures followed
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committee and with those of the Code of Ethics of the World Medical Association
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acerca da publicação dos dados de doentes. Proteção de Pessoas e Animais:
Os autores declaram que os procedimentos seguidos estavam de acordo com os
regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clí-
nica e Ética e de acordo com a Declaração de Helinskia da Associação Médica
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