DOI: https://dx.doi.org/10.29021/spdv.79.2.1318

ORIGINAL ARTICLE

Dupilumab Treatment in Atopic Dermatitis: Real-World Evidence from a Portuguese Tertiary Center

Tratamento de Dermite Atópica com Dupilumab: Evidência de um Centro Português Terciário

Received/Recebido
2020/12/06

Accepted/Aceite
2021/01/17

Published/Publicado
2021/06/30

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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.

RESUMO – ***Introdução:*** *O dupilumab é um anticorpo monoclonal totalmente humano que bloqueia a interleucina-4 e a interleucina-13, elementos chave da resposta inflamatória mediada por células T auxiliares tipo 2 (Th2). Foi o primeiro tratamento biológico aprovado para doentes adultos com dermatite atópica (DA) moderada a grave, inadequadamente controlada. A colheita contínua de dados de prática clínica diária é importante para avaliar a real eficácia e segurança do tratamento com dupilumab.*
Métodos: *Neste estudo de coorte observacional, foram incluídos prospectivamente todos os doentes adultos com DA moderada a grave tratados com dupilumab no Centro Hospitalar Lisboa Central de julho de 2019 a abril de 2020. Os dados clínicos iniciais foram recolhidos e a eficácia e segurança do tratamento foram avaliadas após 16 semanas.*
Resultados: *Vinte e cinco doentes foram incluídos e todos tinham sido previamente tratados com imunossupressores sistêmicos. O EASI médio inicial diminuiu de 27,8 no início do estudo para 8,8 à semana 16 (+/- 4 semanas). Uma resposta ΔEASI 75 foi alcançada em 58,3% dos doentes (ΔEASI 90 - 29,1%). A conjuntivite foi o principal efeito adverso registado, afetando 20,8% dos pacientes.*
Discussão: *O nosso estudo mostrou uma redução significativa do EASI durante as primeiras 16 semanas de tratamento com dupilumab em pacientes adultos com DA. Apesar de sua segurança geral, os dados da prática diária tendem a relatar um risco maior de conjuntivite do que o esperado anteriormente e, por isso, recomendamos que os doentes sejam informados especificamente sobre esse possível efeito adverso.*
PALAVRAS-CHAVE – *Anticorpos Monoclonais Humanizados/uso terapêutico; Dermite Atópica/tratamento farmacológico; 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.[1] 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%.[2] 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[3] and increased awareness about the importance of Th2 inflammatory cells in these conditions[4] 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.[5-7]

Although dupilumab has emerged in these trials as a breakthrough therapy,[8] 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. Appointments 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 analysed 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 cyclosporine 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 revaluation 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)).

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

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

Table 2 - Efficacy and safety outcomes at week 16.

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

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.

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).[9] 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 naive 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

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 receptors, were used in dupilumab development and explain the significant 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 significant increase of EASI 50 responses, reinforcing what has already been suggested by some early "real-life" data[12,13]: dupilumab is effective in most AD adult patients treated under daily-practice conditions.

However, our results have also highlighted that there is a considerable 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 dupilumab seems to be of the utmost importance. However, practical predictors of its effectiveness are still under investigation. While initial studies[5,12-15] suggested baseline EASI, IgE, lactate dehydrogenase (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 validation of these predictive biomarkers, in order to allow a better patient 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 between dupilumab and placebo groups.[5] In fact, these trials underlined 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 adverse effect is still unknown, some authors proposed that ocular comorbidities are dependent on disease severity, prior conjunctivitis history or certain biomarkers such as thymus and activation-regulated chemokine (TARC) or IgE.[17] Hence, we tend to agree that intrinsic differences in the analysed cohorts - namely regarding conjuntivitis' 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 treatment. However, this clinical intervention was not systematically recorded 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 orientation 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 efficacy 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 - 1º Congresso Virtual de Dermatologia e Venereologia - 20-21 November 2020".

Conflicts of Interest: The authors have no conflicts of interest to declare. **Financing Support**: This work has not received any contribution, grant or scholarship. **Confidentiality of Data**: The authors declare that they have followed the protocols of their work center on the publication of data from patients. **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). **Provenance and Peer Review**: Not commissioned; externally peer reviewed.

__Conflitos de Interesse:__ Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho. __Suporte Financeiro:__ Não existiram fontes externas de financiamento para a realização deste artigo. __Confidencialidade dos Dados:__ Os autores declaram ter seguido os protocolos da sua instituição 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 Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial. __Proveniência e Revisão por Pares:__ Não comissionado; revisão externa por pares.

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