ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Response to dupilumab in severe atopic dermatitis without prior use of systemic immunosuppressive agents during the COVID-19 pandemic

Resposta ao dupilumabe na dermatite atópica grave sem uso prévio de imunossupressor sistêmico durante a pandemia de COVID-19

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ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense itching and recurrent eczema. It mainly affects childhood but has become quite prevalent in adolescents and even adults. Despite being generally non-fatal, it has an important psychosocial burden for patients and their families. AD treatment involves skin hydration and anti-inflammatory medications. In severe cases, systemic therapy with immunosuppressive agents such as cyclosporine, methotrexate, and azathioprine may be necessary. More recently, some biologicals are being developed to control AD. Dupilumab is a monoclonal antibody with anti-IL-4/IL-13 dual-action, approved for the treatment of children from 6 years of age with severe AD and adolescents/adults with moderate to severe AD. This article aimed to report a case series of adolescent and adult patients with severe AD and their response to dupilumab during the COVID-19 pandemic. These are four patients (three female), with a significant worsening of AD during the year 2020. All had a history of AD since childhood, with complementary exams showing IgE-mediated sensitization to mites. They had already undergone several topical and systemic treatments, including courses on oral corticosteroids. None of them had received systemic immunosuppressive agents, but they were refusing this type of treatment due to fear of the pandemic. All had a good response to dupilumab, evidenced by a reduction in the number of skin lesions and pruritus, with few side effects. Two patients had symptoms suggestive of COVID-19 during treatment with dupilumab (one confirmed by PCR) with a good outcome.

RESUMO

A dermatite atópica (DA) é uma doença inflamatória crônica da pele, caracterizada por intenso prurido e eczema recorrente. Acomete principalmente a infância, mas tem se tornado bastante prevalente em adolescentes e até em adultos. Apesar de ser geralmente não fatal, apresenta uma carga psicossocial importante para os pacientes e seus familiares. O tratamento da DA envolve a hidratação cutânea e medicações anti-inflamatórias. Em casos graves, pode haver necessidade de terapia sistêmica com imunossupressores como ciclosporina, metotrexato e azatioprina. Mais recentemente, alguns imunobiológicos estão em desenvolvimento para controle da DA. O dupilumabe é um anticorpo monoclonal com ação dupla anti-IL-4/IL-13, liberado para tratamento de crianças a partir de 6 anos com DA grave e adolescentes/adultos com DA moderada a grave. O objetivo deste artigo foi relatar uma série de casos de pacientes adolescentes e adultos com DA grave e sua resposta ao dupilumabe durante a pandemia do COVID-19. Trata-se de quatro pacientes (três do sexo feminino), com piora significativa da DA durante o ano de 2020. Todos tinham história de DA desde a infância, com exames complementares evidenciando sensibilização IgE-mediada para ácaros. Já haviam sido submetidos a diversos tratamentos tópicos e sistêmicos, inclusive a cursos de corticosteroides orais. Nenhum deles havia recebido imunossupressor sistêmico, porém estavam recusando este tipo de tratamento devido ao medo da pandemia. Todos apresentaram boa resposta ao dupilumabe, evidenciada pela redução do número de lesões cutâneas e prurido, com poucos efeitos colaterais. Dois pacientes apresentaram sintomas

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In conclusion, patients with severe AD have a great impact on quality of life and, during the COVID-19 pandemic, many had a significant worsening of their dermatological condition. In this context, dupilumab proved to be an effective and safe therapeutic option for the treatment of these patients.

Keywords: Atopic dermatitis, monoclonal antibodies, immunosuppressive agents, quality of life, COVID-19.

sugestivos de COVID-19 durante o tratamento com dupilumabe (um com confirmação por PCR), com boa evolução. Concluindo, os pacientes com DA grave possuem grande impacto na qualidade de vida e, durante a pandemia de COVID-19, muitos apresentaram piora significativa do seu quadro dermatológico. Nesse contexto, o dupilumabe se mostrou uma opção terapêutica eficaz e segura para tratamento destes pacientes.

Descritores: Dermatite atópica, anticorpos monoclonais, imunossupressores, qualidade de vida, COVID-19.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense itching and recurrent eczema.[1] It mainly affects children, but it has become quite prevalent in adolescents and even adults.[2] Despite being generally non-fatal, it has an important psychosocial burden for patients and their families.

The severity of AD can be assessed using a score called Scoring Atopic Dermatitis (SCORAD).[3] The index considers the extent of the disease, the severity of the lesion, and the presence of subjective symptoms such as itching and sleep loss. The SCORAD is an objective measure that allows the assessment of the patient over time and comparison between different studies.[1]

The impact on the quality of life (QoL) of patients with AD can be measured using different instruments.[4] One of the most used is the Quality of Life Index in Dermatology Questionnaire (DLQI-BRA).[5] The risks to QoL arising from AD have been recognized, but this impact is still little explored in the adult population.[6-8]

AD treatment involves skin hydration and anti-inflammatory medications.[4] Among the anti-inflammatory drugs, the most used are topical corticosteroids and calcineurin inhibitors.[4] In severe cases, there may be a need for systemic therapy with immunosuppressants such as cyclosporine, methotrexate, and azathioprine.[4] More recently, some immunobiologicals are being developed to control AD.[9] Dupilumab is a monoclonal antibody with anti-IL-4/IL-13 dual-action, approved for the treatment of children from 6 years of age with severe AD and adolescents/adults with moderate to severe AD.[9]

The aim of this article was to report a case series of adolescent and adult patients with severe AD and their response to dupilumab during the COVID-19 pandemic.

Case report

Case 1

I.B.P., 28 years old, male, with AD since 5 years old. He had partially controlled asthma using combined therapy (inhaled corticosteroids and long-acting beta-agonists), allergic rhinitis, allergy to shrimp, and amoxicillin-clavulanate. He reported a significant worsening of the skin lesions in 2020. He was under regular use of bilastine (double dose), moderately potent topical corticosteroids (mometasone), topical tacrolimus on the eyelids, skin moisturizer, in addition to frequent use of topical and systemic antibiotics and corticosteroids systemic. Exams (09/22/2020): Total IgE: 4588 KU/L; *Blomia tropicalis* specific IgE > 100 KU/L; *Dermatophagoides pteronyssinus* > 100 KU/L; *Dermatophagoides farinae* > 100 KU/L; dog epithelium 1.98 KU/L; cat epithelium 0.16 KU/L; *Aspergillus fumigatus* 0.36 KU/L; shrimp 48 KU/L. The DLQI-BRA was applied, totaling 15 points out of a maximum of 30 points, which indicates a high compromise in the patient's quality of life, and the initial SCORAD of 74 on 09/22/2020 was calculated, which indicates severe dermatitis. He had already been submitted to specific immunotherapy with mites on previous occasions. The patient refused to start treatment with a systemic immunosuppressant for fear of the side effects of the drugs and a possible more serious evolution of COVID-19 during the pandemic. Considering the severity of the AD picture and the impact on QoL, in addition to partially controlled

asthma, it was decided to start dupilumab in December 2020. The patient returned on 01/26/21, after 4 applications of dupilumab, with a SCORAD of 24,2 and significant improvement in pruritus. Regarding side effects, reported only occasional mild facial erythema and ocular pruritus. He maintains the use of dupilumab and is currently with her asthma controlled using combination therapy. He was suspected of having COVID-19 during the use of dupilumab (suggestive symptoms, in addition to intra-household contact with positive PCR), but no PCR was collected. He had a good evolution, with no need for hospitalization.

Case 2

M.M.S.R, 19 years old, female, with AD since she was 6 months old. She had rhinitis but had no other allergic comorbidities. She reported a significant worsening of the skin lesions in 2020. She was under regular use of bilastine (double dose), moderately potent topical corticosteroids (mometasone), topical tacrolimus on the eyelids, skin moisturizer, in addition to frequent use of topical and systemic antibiotics and corticosteroids systemic. Exams (11/08/2020): Total IgE 5000 KU/L; *Dermatophagoides pteronyssinus* specific IgE > 100 KU/L; *Dermatophagoides farinae* > 100 KU/L. The DLQI-BRA was applied, totaling 15 points out of a maximum of 30 points, which indicates a high compromise in the patient's quality of life, and the initial SCORAD of 62.6 on 08/04/2020 was calculated, which indicates severe dermatitis. She had already been submitted to specific immunotherapy with mites on previous occasions. She refused the use of systemic immunosuppressants due to possible side effects. It was decided to start dupilumab in January 2021 due to the severity of the condition and the patient's QoL, even without the use of systemic immunosuppressants. The patient returned on March 31, 21, after 5 applications of dupilumab, with a SCORAD score of 18.5, with substantial improvement in skin itching (approximately 90%). In June 2021, the patient complained of conjunctivitis after applying duplilumab, being prescribed eye drops with lubricants, and being referred to Ophthalmology. Repeated the DLQI-BRA in August 2021, totaling 2 points. It was decided to start dupilumab in January 2021 due to the severity of the condition and the patient's QoL, even without the use of systemic immunosuppressants. The patient returned on March 31, 21, after 5 applications of dupilumab, with a SCORAD score of 18.5, with substantial improvement in skin itching (approximately 90%). In June 2021, the patient complained of conjunctivitis after applying duplilumab, being prescribed eye drops with lubricants, and being referred to Ophthalmology. The DLQI-BRA was repeated in August 2021, totaling 2 points. It was decided to start dupilumab in January 2021 due to the severity of the condition and the patient's QoL, even without the use of systemic immunosuppressants. The patient returned on March 31, 21, after 5 applications of dupilumab, with a SCORAD score of 18.5, with substantial improvement in skin itching (approximately 90%). In June 2021, the patient complained of conjunctivitis after applying duplilumab, being prescribed eye drops with lubricants, and being referred to Ophthalmology. The DLQI-BRA was repeated in August 2021, totaling 2 points. the patient complained of conjunctivitis after the application of duplilumab, being prescribed eye drops with lubricants, and referred to ophthalmology. The DLQI-BRA was repeated in August 2021, totaling 2 points. the patient complained of conjunctivitis after the application of duplilumab, being prescribed eye drops with lubricants, and referred to ophthalmology. The DLQI-BRA was repeated in August 2021, totaling 2 points.

Case 3

M.S.S.A.A., 19 years old, female, with AD since 6 years old, without other allergic comorbidities (asthma, rhinitis, or food allergy). She reported a significant worsening of the skin lesions in 2020. She was under regular use of bilastine (double dose), moderately potent topical corticosteroids (mometasone), skin moisturizer, in addition to frequent use of topical and systemic antibiotics and systemic corticosteroids. Exams (11/12/2020): Total IgE: 897 KU/L; *Dermatophagoides pteronyssinus* specific IgE 56.8 KU/L; *Dermatophagoides farinae* 54.8 KU/L; *Blomia tropicalis* 10.5 KU/L; ant 4.7 KU/L; dog epithelium; cat and negative fungi. The DLQI-BRA was applied, totaling 29 points out of a maximum of 30 points, which indicates a very serious compromise in the patient's quality of life, and the initial SCORAD of 83.5 was calculated, which indicated severe dermatitis on 01/06/2021. She had already been submitted to specific immunotherapy with mites in 2020, with worsening of the lesions, being suspended after two series. She refused the use of systemic immunosuppressants due to possible side effects and fear of progressing to severe COVID-19. It was decided to start dupilumab due to the seriousness of the condition and the impact on

the patient's quality of life, even without the use of systemic immunosuppressants. The patient returned on March 24, 21, after 4 applications of dupilumab, with a SCORAD score of 21. She had many residual hypertrophic lesions, especially in the lower limbs, and was seeking treatment with Dermatology.

Case 4

M.E.T.N.O., 16 years old, with AD since 2 months of age. She had asthma and allergic rhinitis. She reported a significant worsening of the skin lesions in 2020. She was in regular use of phototherapy (no response). In addition, she was already using bilastine (double dose), moderately potent topical corticosteroids (mometasone), and skin moisturizer. She frequently used topical and systemic antibiotics and systemic corticosteroids. Exams (12/17/2020): Total IgE: 875 KU/L; (06/24/2018): total IgE 279 KU/L; *Dermatophagoides pteronyssinus* specific IgE 15.2 KU/L; *Dermatophagoides farinae* 7.31 KU/L; *Blomia tropicalis* 32.1 KU/L; ant 1.13 KU/L; negative dog and cat epithelium. The DLQI-BRA was applied, totaling 29 points out of a maximum of 30 points, which indicated a very high compromise in the patient's quality of life, and the initial SCORAD of 76.3 was calculated. which indicated severe dermatitis on 03/02/2021. She had already been submitted to specific immunotherapy with mites in 2018, with worsening of the lesions, and was suspended. She refused the use of systemic immunosuppressants due to possible side effects. It was decided to start dupilumab due to the severity of the condition and the impact on the patient's QoL, even without the use of systemic immunosuppressants. Dupilumab started in May 2021 with SCORAD falling to 24.9 in August 2021, as shown in Figures 1, 2, and 3. Repeated the DLQI-BRA in August 2021, totaling 3 points. She had mild COVID-19 in July 2021, confirmed by PCR, without the need to go to the Emergency Room or hospital. She report that during the picture she only presented odynophagia. Delayed

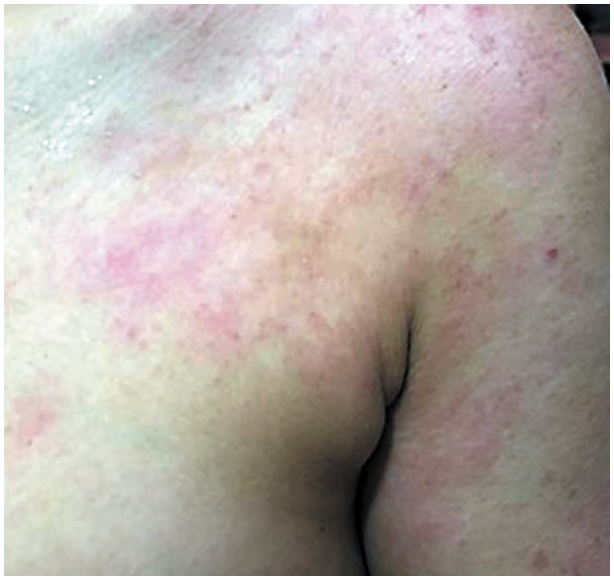

Figure 1
Case 4: left shoulder (before starting dupilumab).

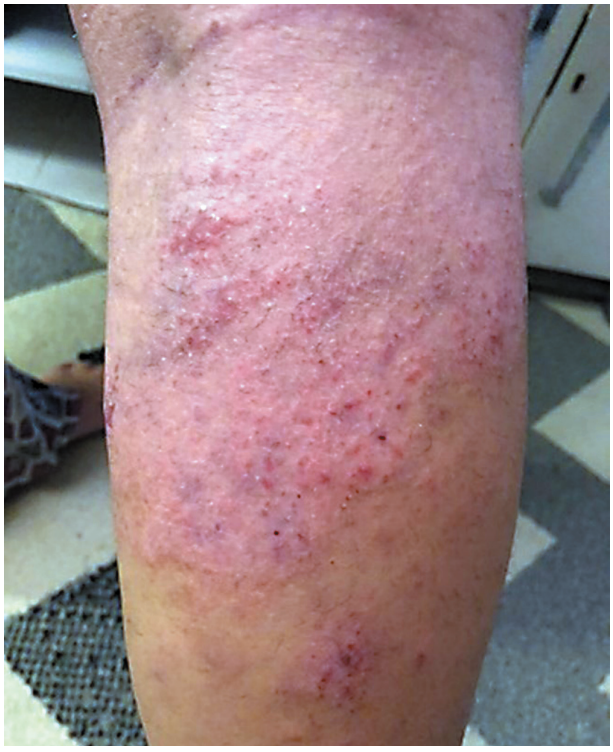

Figure 2
Case 4: popliteal region (before starting dupilumab).

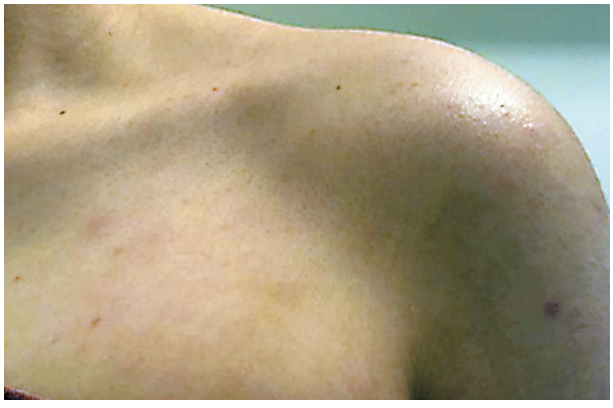

Figure 3
Case 4: left shoulder (after starting dupilumab).

the application of dupilumab due to the condition of COVID-19.

Discussion

In all reported cases there was a significant worsening of AD during 2020, coinciding with the COVID-19 pandemic period, highlighting the importance of the emotional agent as an aggravating factor in AD cases.[1] On the other hand, after starting dupilumab there was a substantial improvement in the patients' QoL as evidenced by the DLQI-BRA.[4] Thus, it is clear that the use of different instruments can be useful to better measure the impact of AD on patients' lives.

Another important aspect is the long evolution of the disease, with a severe condition, all with SCORAD above 50. The SCORAD is a widely used tool to assess the severity of AD, as it considers the extent of the disease, the intensity of the lesions, and the presence of subjective symptoms.[1,3] All patients had significant improvement in SCORAD after starting dupilumab, both in subjective criteria such as pruritus and in the intensity and extension of the lesions. Other tools can be used to measure the severity of AD, such as the EASI and the IGA.[1] We chose to use SCORAD because it is the simplest, with measurement through an application.

The frequent use of systemic corticosteroids to control AD exacerbations was observed in all reported cases, and it is a very common practice in our country. On the other hand, it should be noted that it increases the risk of infections, in addition to serious, often irreversible, side effects. A meta-analysis (10 studies, n = 6,548 patients) has already shown that the use of corticosteroids in patients with Influenza pneumonia was associated with higher mortality, longer intensive care unit stay, and a higher rate of secondary infection.[10] Thus, especially in times of COVID-19 pandemic, the use of oral corticosteroids should be avoided, always making gradual and slow reduction if the patient is with prolonged use, being careful with the risk of adrenal insufficiency in abrupt withdrawal.

Finally, the discussion on the scaling of treatment steps deserves to be highlighted. Topical therapy is usually sufficient to manage patients with mild to moderate AD. However, in moderate to severe cases, especially when there is a refractory disease, it may be necessary to introduce therapy with systemic immunosuppressants. Cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil have shown positive results in the treatment of patients with severe AD. On the other hand, they are medications that cannot be used for a long time due to their potential toxic effects. Furthermore, many of these drugs are not licensed for use in AD in Brazil and are not distributed free of charge by the health network. Methotrexate and cyclosporine are among the most used drugs, but both are associated with an increased risk of infections. The BIOBADADERM registry (Spanish Registry of Adverse Events for Biological Therapy in Dermatological Disease), which included 2,153 patients with psoriasis, showed a higher infection rate for cyclosporine versus methotrexate of 58%.[11] In a comparison of methotrexate (n = 50) versus cyclosporine (n = 47) in adults with moderate to severe AD, infection rates were 32% and 24%, respectively.[12] Another consideration is the potential impact of these immunosuppressants on the susceptibility/severity of SARS-CoV2 infection. Patients in our series refused to use immunosuppressants for fear of side effects. These are effects that can be controlled and monitored through periodic examinations. Before starting to use this type of medication, we need patients' consent. Benefits versus risks must be explained so that we can make a shared decision.

Dupilumab is a monoclonal antibody that inhibits IL-4 and IL-13 by binding to IL-4 subunits α and IL-13α-1 of the receptor, inhibiting the JAK-STAT signaling pathway.[13] Thus, there is a reduction in the production of Th2 cytokines, IgE, and an improvement in the skin barrier function.[13] It was the first biologic approved for use in AD, with proven efficacy in patients with moderate to severe AD, as observed in our patients. An analysis of seven randomized controlled trials showed that adult AD patients treated with dupilumab had a lower risk of serious infections, skin infections, and herpetic infections (eczema herpeticum or herpes zoster) compared to placebo.[14] Furthermore, through the concomitant treatment of asthma, in theory, there would be better evolution during an infection in the COVID-19 pandemic.

The side effects observed in our series were conjunctivitis and facial erythema. These effects are similar to those described in the literature and generally do not prevent the continued use of the medication. The reason why dupilumab causes conjunctivitis is still not completely known.[13] In any case, it remains a much safer therapeutic option when compared to systemic immunosuppressants

that can lead to pancytopenia, hepatotoxicity, or renal failure.[13] It is important to consider that during treatment with dupilumab, there is a contraindication for the application of vaccines with live components, but vaccines with inactivated components, such as those of SARS-CoV2 can be applied.

There are few studies on the evolution of COVID-19 in patients using dupilumab. In our sample, one patient had an unconfirmed suspicion of infection and evolved well, with no need for hospitalization. Another patient had confirmed infection with good evolution. A recent publication showed a series of 71 adult AD patients in Lombardy using dupilumab and only 2 had infection confirmed by COVID-19 (one of these patients had comorbidities and needed to be hospitalized, but did not have sequelae).[15] In Milan, among 245 patients using dupilumab, only 2 developed COVID-19 (without complications).[16] In a retrospective study in Toronto, of 162 patients using duplilumab, only 1 had to discontinue treatment due to patient concerns, but not because of infection.[17]

In conclusion, patients with severe AD have a great impact on QoL and, during the COVID-19 pandemic, many had a significant worsening of their dermatological condition. In this context, duplilumab proved to be an effective and safe therapeutic option for the treatment of these patients. Further studies are needed to assess the safety and efficacy of immunosuppressants compared to immunobiologicals, such as dupilumab, during the COVID-19 pandemic.

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