ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA
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Dupilumab in the treatment of chronic rhinosinusitis with nasal polyps in adolescents

Dupilumabe no tratamento de rinossinusite crônica com pólipo nasal em adolescente

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ABSTRACT

The use of the monoclonal antibody dupilumab in adults has allowed the control of chronic inflammation, significantly reducing the size and recurrence of new polyps, improving nasal symptoms, and, consequently, quality of life. We report a successful case of dupilumab use in an adolescent for the treatment of chronic rhinosinusitis with nasal polyps.

Keywords: Sinusitis, asthma, monoclonal antibody.

RESUMO

O uso do anticorpo monoclonal dupilumabe em adultos tem possibilitado o controle da inflamação crônica, reduzindo significativamente o tamanho e a recorrência de novos pólipos, melhorando os sintomas nasais e, consequentemente, a qualidade de vida desses indivíduos. Relatamos o caso de uma adolescente que evidencia a eficácia de dupilumabe no tratamento da rinossinusite crônica com pólipo nasal.

Descritores: Sinusite, asma, anticorpo monoclonal.

Introduction

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease of the nasal mucosa and paranasal sinuses, presenting with or without nasal polyps (CRSwNP and CRSsNP, respectively).[1] Polyps are benign inflammatory masses that appear in the upper airways, often manifesting as nasal obstruction and hypo/anosmia.[2] The clinical diagnosis of CRSwNP is confirmed by the presence of sinonasal symptoms for more than 12 weeks and by the visualization of polyps in the nasal cavity by nasal endoscopy or computed tomography (Table 1).[2] Up to 60% of patients have lower airway involvement, coexisting with adult-onset asthma.[3,4] However, its association with childhood asthma is less common and, if present, cystic fibrosis and other secondary causes of CRS should be investigated.[5]

In most cases of CRSwNP, treatment is performed with topical corticosteroids and nasal lavage with saline solution. In addition to these, severe symptomatic patients require cycles of corticosteroids and systemic antibiotic therapy for prolonged periods, and endoscopic nasal polypectomy (ENP) is indicated for refractory cases.[6]

Cases resistant to steroid therapy and with recurrent polyps progress with progressive worsening of quality of life (assessed by the SNOT-22, Sino-Nasal Outcome Test),[7] requiring treatment with specific

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Submitted: 02/02/2022, accepted: 02/19/2022.
Arq Asma Alerg Imunol. 2022;6(2):295-9.

http://dx.doi.org/10.5935/2526-5393.20220031

Table 1
Diagnostic criteria for chronic rhinosinusitis with nasal polyposis (two or more, with at least one main plus one additional criterion)

Main clinical criteria	Secondary clinical criteria	Complementary criteria
Nasal obstruction/congestion	Facial pain/pressure	Endoscopic signs of nasal polyposis (polyps and/or nasal discharge from the middle meatus and/or swelling with middle meatus obstruction)
Nasal discharge (anterior or posterior)	Hypo or anosmia	Tomographic evidence of nasal polyps (alterations of the nasal mucosa compromising the osteomeatal complex and/or the paranasal sinuses)

immunobiologicals. Such specificity is determined by the pathophysiological/immunological mechanism involved in the formation of polyps, and the type 2 immune response is found in almost 90% of cases.[8]

In this context, the first immunobiological agent approved for the treatment of uncontrolled CRSwNP in adults (≥ 18 years) was dupilumab (use authorized by the FDA in 2019, and by ANVISA in 2020), a human monoclonal antibody, immunoglobulin (Ig)G4, whose target is the subunit α interleukin (IL)-4 receptor (IL-4Rα), which is also common to the IL-13 receptor. Thus, the signaling of both fundamental cytokines in the development of the type 2 immune response is blocked.[8-10]

Case report

Female patient, 17 years old, student, with a history of asthma since childhood, controlled with the use of salmeterol xinafoate + fluticasone propionate (25 µg/125 µg; 1 inhalation 1x/day). Five years ago, he developed recurrent nasal obstruction and hyposmia. Initially, she was evaluated by the team from the Otorhinolaryngology Service, who performed a computed tomography scan of the paranasal sinuses (NSCT), which showed bilateral nasal polyps, left septal deviation and pansinus opacification, compatible with the diagnosis of CRSwNP. ENP was indicated and performed, whose histopathology was compatible with allergic inflammatory polyp. In the immediate postoperative period, he presented edema and hematoma in the right maxillary sinus, in addition to a positive nasal secretion culture for *Enterobacter* spp., with a satisfactory response to intranasal budesonide 400 µg/day associated with nasal lavage with mupirocin (5 times/day). After four months, there was a recurrence of polyps that extended beyond the middle meatus, being submitted to a new ENP. In the etiological investigation, sweat and genetic tests for cystic fibrosis were performed, both negative. Referred to the Immunology Department, sensitization to *Dermatophagoides pteronyssinus* and *Blomia tropicalis*, eosinophilia (1,103/mm^3), total IgE = 460 IU/mL, and low levels of IgM (P3-P10) were confirmed. After an oligosymptomatic period (about 24 months), it evolved with episodes of exacerbation of rhinosinusitis, refractory to conventional drug treatment, complicating with pneumonia and exacerbation of asthma. Clinical treatment for asthma and rhinosinusitis was optimized with formoterol fumarate dihydrate + beclomethasone dipropionate (6 µg/100 µg; 2 inhalations 12/12 h), in addition to montelukast sodium (10 mg; 1 tablet 1x/day) and nasal wash with glycerin budesonide solution 500 mL/day. Recently, even using nasal medications and, despite the new ENP, he still had an exacerbation of symptoms, with recurrent need for antibiotic therapy and frequent use of systemic corticosteroids (six cycles of 7-14 days in six months). In the last year,

the patient was symptomatic, with a predominance of nasal symptoms, refractory to treatment, in addition to complete veiling of the paranasal sinuses and ethmoid cells, extending to the nasal cavities, with progressive worsening of quality of life, when the use of dupilumab was indicated, despite not being licensed for CRSwNP in this age group. Started with 300 mg subcutaneously (SC) every two weeks. After eight weeks, the patient evolved with a significant improvement in the SNOT-227, VAS (visual analogue scale)[11] and NPS (nasal polyp score)[12] scores, maintaining asthma controlled by the ACT (asthma control test)[13] (Table 2 and Figure 1).

Discussion

About 90% of patients have CRSsNP mediated by type 2 immune response, with eosinophilia and IgE formation, in addition to significant eosinophilic infiltration of the mucosa and nasal polyps. There is synthesis of high levels of type 2 cytokines such as eosinophilic cationic protein, eotaxin, IL-4, IL-5 and IL-13. These interleukins play an important role in the pathophysiological mechanism of associated comorbidities, including asthma, which affects up to two thirds of patients with CRSwNP, impairing clinical control and worsening the quality of life of these patients.[14-15]

In clinical practice, evidence of inflammation of type 2 are the association with late-onset asthma and/or aspirin-exacerbated respiratory disease (ARD), in addition to greater severity in the presentation of CRSwNP itself, with recurrence of polyps after oral corticosteroid therapy and/or polypectomy. Other parameters are eosinophilia, high levels of serum IgE and eosinophilic infiltrate at the histopathology of polyps.[16,17]

The conventional therapeutic approach to CRSwNP aims to control the nasal inflammatory process. Topical intranasal corticosteroids and repeated courses of systemic corticosteroids may be necessary for more severe cases, leading to side effects from prolonged use. In addition, surgical treatment is more frequent due to the recurrence of polyps.[16,17]

Recently, the use of immunobiological agents have been indicated in patients with severe CRSwNP who have evidence of type 2 inflammation (tissue eosinophilia ≥ 10 cells/HPF or blood eosinophilia ≥ 250 cells/mcL or total IgE ≥ 100 IU/mL). In this context, patients with CRSwNP who need frequent courses of systemic corticosteroid therapy, with hypo/anosmia, association with asthma and significant reduction in quality of life. Dupilumab, as an anti-IL-4/IL-13 antibody, has a precise indication for CRSwNP. It is worth emphasizing that it is an IgG4, whose target is IL-4Rα, shared by IL-4 and IL-13, blocking their signaling and, consequently, attenuating the inflammatory response.[17-19]

In 2016, Bachert et al. evaluated the efficacy of dupilumab in CRSwNP, in subjects over 18 years of age, treated with a loading dose of 600 mg SC followed by 300 mg every two weeks. Patients showed

Table 2
Scores for clinical and nasal endoscopic assessment pre-dupilumab and at each application (2-week interval) up to 8 weeks of treatment

Scores	Pre-dupilumab	2 weeks	4 weeks	6 weeks	8 weeks
EVE	7.5	–	–	–	5
SNOT-22	41	50	41	44	27
ACT	25	25	25	25	25
NPS	6	8	–	–	6

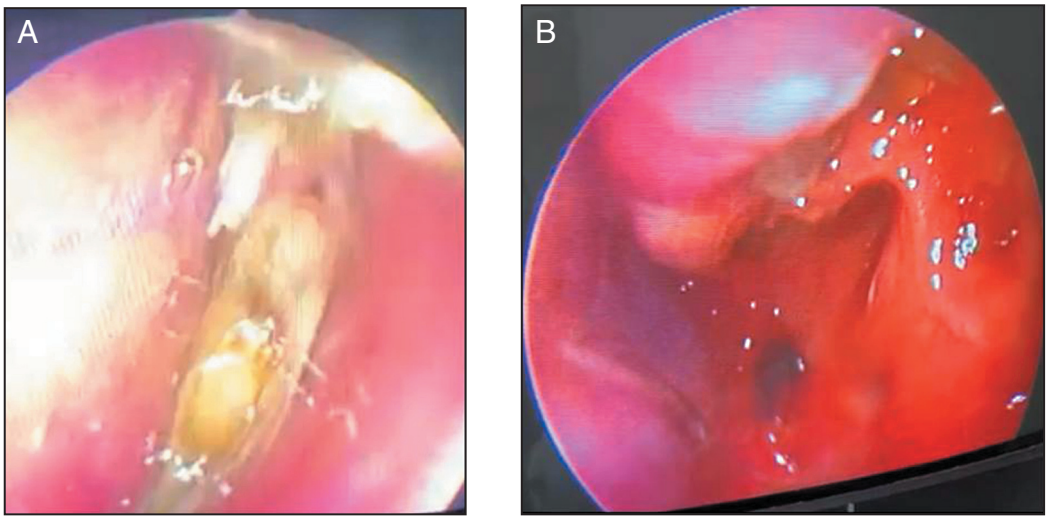

Figure 1
Nasal endoscopy pre-dupilumab (A) and after 8 weeks of treatment (B)

significant improvement in SNOT-22, endoscopic score and tomographic nasal polyp score (NPS and Lund-Mackay sinus – LMS, respectively). In addition, the use of dupilumab improved lung function and asthma control (ACT) in the subgroup of patients with asthma.[19]

Based on the positive results of this study, two other multicenter studies were carried out, SINUS-24 and SINUS-52 (with 24 and 52 weeks of follow-up, respectively), which also demonstrated that the use of dupilumab in adults ≥ 18 years with severe CRSwNP significantly reduced SNOT-22, NPS and LMS scores, with an increase in ACT, when compared to placebo. Thus, they evidenced the effectiveness of dupilumab in patients with CRSwNP refractory to clinical and surgical treatments, including those with associated asthma.[20]

In the case reported, the patient had all the clinical and laboratory criteria established for the diagnosis of CRSwNP with type 2 inflammation (Table 1, Figure 1).[16] He evolved with progressive clinical worsening, characterized by the recurrence of polyps, refractory to clinical and surgical treatments, coexistence of uncontrolled asthma, resulting in a significant loss of his quality of life. Considering the severity of the clinical picture, especially due to the recurrence of polyps and frequent use of systemic corticosteroids, it was decided to start dupilumab, 300 mg SC every two weeks, in an attempt to control the nasal inflammatory process. After eight weeks, the patient evolved with significant clinical improvement, corroborated by the SNOT-22, VAS and NPS scores, keeping the asthma controlled by the ACT (Table 2).

The dupilumab has been shown to be safe and clinically effective in the treatment of diseases with a type 2 immune response, including CRSwPN in adults. We report the case of an adolescent patient (17 years old), with severe CRSwNP, who achieved significant clinical control after eight weeks of use of dupilumab, at the dosage licensed for adults above 18 years old. Therefore, there is a need for further studies to show such efficacy in other age groups, avoiding future risks such as the development of osteoporosis and bone necrosis due to the frequent use of systemic corticosteroids.

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No conflicts of interest declared concerning the publication of this article.

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