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USE OF DUPILUMAB IN CHRONIC RHINOSINUSITIS WITH DIFFICULT TO MANAGE NASAL POLYPOSIS: CASE REPORT

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Abstract: Introduction: The present study aims to report a clinical-surgical case of a patient with aspirin-exacerbated respiratory disease (ASR), with chronic rhinosinusitis with nasal polyposis (CRSwNP) that is difficult to control and its evolution with the use of dupilumab in the city of Santa Maria, Rio Grande do Sul. It also intends to review the pathophysiological mechanisms of the disease and the current and future perspectives in relation to the treatment of the pathology. Clinical case: Male patient, 53 years old, sought specialized care in Otorhinolaryngology in 2017 due to chronic nasal obstruction. He had already undergone two sinonasal endoscopic surgeries without improvement in his clinical condition. After the diagnosis of CRSwNP and DREA was established, several therapeutic alternatives were tried, again without effective improvement and the patient was recommended to start immunobiological therapy with dupilumab. Discussion: Treatment with dupilumab resulted in significant clinical improvement, reduction in nasal symptoms, improvement in the SNOT-22 score and Lund-Mackay score in the patient subject of this report. Despite a temporary interruption in the supply of the medication, which led to the patient's clinical worsening, the resumption of treatment resulted in a further improvement in symptoms. Final considerations: Despite the high costs, the use of dupilumab proved to be beneficial and effective in significantly improving endoscopic, radiological and clinical parameters of patients with severe CRSwNP, reducing the need for surgery and the use of systemic corticosteroids as rescue treatment. The drug demonstrated to be an effective therapeutic alternative for patients with severe CRSwNP.

Keywords: Chronic Rhinosinusitis with Nasal Polyposis; Respiratory Disease Exacerbated by Aspirin; Dupilumab; Immunobiological Therapy in CRSwNP.

INTRODUCTION

Chronic Rhinosinusitis (CRS) in adults is a clinical syndrome, defined as inflammation of the mucosa of the nose and paranasal sinuses lasting at least 12 weeks (ROSENFELD et al, 2015). It is a multifactorial pathological process with genetic, environmental, bacterial and immunological contributions, among other etiologies (MARCUS et al, 2019).

CRS is characterized as one of the most prevalent chronic pathologies worldwide, with an estimated incidence of 12.3% in the USA, 10.9% in Europe and 13% in China (ALBU, 2020). It is also a disease that leads to a significant reduction in patients' quality of life and generates high costs for society. The direct costs associated with CSR in the US are estimated to be around US$10 to 13 billion per year, in addition to indirect costs from lost workdays, absenteeism and lost productivity, which are estimated to exceed US$ 20 billion per year (RUDMIK, 2017; BHATTACHARYYA, 2011).

Historically, CRS has been divided into two main phenotypes: CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP). In recent decades, however, it has been seen that within these phenotypes there are still certain endotypes, which define the predominant type of inflammatory reaction of the disease and, therefore, help in choosing the most appropriate treatment for each case (GURROLA et al, 2017).

Aspirin-Exacerbated Respiratory Disease (ARD) consists of the association of the following three conditions: severe asthma, CRSwNP and non-allergic hypersensitivity to cyclooxygenase-1 (COX-1) inhibitor drugs, with consequent exacerbation of respiratory symptoms after the use of these drugs. (WANGBERG; WHITE, 2020).

DREA affects approximately 0.3-0.9% of the general population in the US and approximately 7% of total asthmatic patients. According to a European study, it is rare in children, the average age of onset is 35 years and affected patients usually present with severe asthma.

Asthma is commonly non-atopic or weakly atopic and begins after adolescence, CRSwNP is the most important clinical feature of the disease and nasal symptoms commonly develop several years before the onset of ASD (TANIGUCHI et al, 2019).

GOALS

The main objective of the study was to report a clinical-surgical case of a patient with Disease Exacerbated by Aspirin, with Chronic Rhinosinusitis with Nasal Polyposis that is difficult to control and its evolution with the use of dupilumab in the city of Santa Maria, Rio Grande do Sul, in addition to reviewing the pathophysiological mechanisms of the pathology and addressing current and future perspectives regarding the treatment of the disease.

REVIEW OF LITERATURE

DEFINITION AND PATHOPHYSIOLOGY OF CRSwNP

CRS in adults is diagnosed based on the presence of two or more of the following symptoms: nasal obstruction/congestion, anterior/posterior nasal secretion, facial pain/pressure and reduced sense of smell for a period of at least 12 consecutive weeks; the presence of at least one of the following is mandatory: nasal obstruction/congestion and anterior/posterior nasal secretion, without the need for additional examination (FOKKENS et al, 2020).

CRS is further classified into genotypes, phenotypes and/or endotypes. Genotypic classification subdivides based on genetic polymorphisms and can identify related monogenic conditions, but has had limited utility (KATO et al., 2021).

The phenotypic classification subdivides the disease according to clinically observable characteristics into two main types: CRSwNP and CRSsNP (AHERN; CERVIN, 2019). In patients without previous sinus surgery, the definition is given by the presence of bilateral polyps visualized endoscopically in the middle meatus for the CRSwNP group and by the absence of polyps visible in the middle meatus endoscopically for the CRSsNP group, after use of topical decongestant. In those with previous sinus surgery, the diagnosis of CRSwNP is made in the presence of endoscopically visualized polyps, defined as bilateral pedunculated lesions as opposed to granulosa, for a period of more than 6 months after surgery, and in patients with any other mucosal change without polyps evident, considered within the RSCsPN group (FOKKENS et al, 2020).

The endotype refers to the type of immune response predominant in the disease, with three types being characterized: non-type 2 inflammation correlated with the CRSsNP phenotype; moderate type 2 inflammation with both phenotypes and severe type 2 inflammation with the CRSwNP phenotype (AHERN; CERVIN, 2019).

Type 2 inflammation aims to promote protection at mucosal barriers, particularly in defense against extracellular parasites and in response to allergens (LLOYD; SNELGROVE, 2018). The type 2 inflammatory reaction is characterized by the predominance of the action of T helper 2 cells (Th2), extensive tissue eosinophilia, increased number of group 2 innate lymphoid cells (ILC2), tissue mast cells, local immunoglobulin E (IgE) and increased production of Th2 cytokines; IL-4, IL-5 and IL-13; produced by Th2 cells, mast cells and group 2 innate lymphoid cells.

Interleukin-5 is an important factor for the differentiation, maturation and activation of eosinophils, in addition to reducing their degree of apoptosis and, consequently, increasing their degree of survival, while interleukin-4 and interleukin-13 contribute to fibrosis and remodeling by increasing collagen production; they also cause hyperplasia of goblet cells, hyperproduction of mucus and induction of the class change of B lymphocytes to the production of IgE (LAIDLAW; BUCHHEIT, 2020).

It is believed that type 2 inflammation leads to the formation of nasal polyps by promoting fibrin deposition, plasma protein retention and edema (KATO et al, 2021).

Computed tomography (CT) is the imaging test of choice for evaluating patients with CRSwNP. It is essential, above all, in the planning of endoscopic sinus surgery, as it provides information on the anatomy of the sinuses, the presence of liquid, the degree of mucosal thickening and the presence of bone dehiscence or osteitis. To evaluate the extent of the inflammatory process in these patients through CT, the Lund-Mackay score is commonly used, which evaluates each paranasal sinus separately (maxillary, anterior ethmoid, posterior ethmoid, sphenoid and frontal) using a score of 0 to 2, depending on the degree of opacification of each one (0 without abnormality, 1 with partial opacity and 2 total opacification). It also evaluates the osteomeatal complex with a score from 0 to 2 (0 being no occlusion and 2 being occluded). The final score ranges from 0 to 24, with 0 equivalent to no abnormality of any sinonasal structure and 24 equivalents to total opacification of all sinonasal structures. (BRESCIA et al, 2022)

DEFINITION AND TREATMENT OF DREA

DREA is a chronic disease with high resistance to treatment, defined by the concomitant presence of CRSwNP, bronchial asthma and non-allergic hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit COX-1 (RODRÍGUEZ-JIMÉNEZ et al, 2018).

The disease is not yet fully understood; however, studies have characterized it as the result of a dysregulation in arachidonic acid metabolism (STEVENS et al, 2021). Arachidonic acid makes up the plasma membrane of all cells in the body; Whenever cell injury occurs, the enzyme phospholipase A2 is released and removes arachidonic acid from the cell membrane.

From this, it can be acted upon by two enzymes: lipoxygenase (LOX) and cyclooxygenase (COX), generating the production of several pro-inflammatory substances. The COX pathway generates the production of prostaglandins, prostacyclin and thromboxane, while LOX generates the production of leukotrienes (GUYTON; HALL, 2017). It is believed that patients with DREA have greater activity of the LOX enzyme and consequently higher levels of leukotrienes. When using a drug that inhibits COX-1 and, consequently, inhibits the production of Prostaglandin E2, which is an inhibitor of the synthesis of leukotrienes, there is an even greater accentuation of the action of the latter, generating an increase in mast cell degranulation and, therefore, exacerbation of respiratory symptoms in these patients (XU et al, 2013).

The treatment of DREA aims to control upper and lower respiratory tract symptoms and commonly includes the use of corticosteroids and ant leukotrienes. Sinonasal endoscopic surgery is also commonly used to reduce nasal polyps and increase topical penetration of nasal saline solution and corticosteroids (PETERS et al, 2014). Furthermore, there are protocols for desensitization therapy to oral and nasal aspirin, which consists of using increasing doses of acetylsalicylic acid (ASA) progressively, until desensitization to the drug occurs (AGONDI, 2018).

In general, patients tend to undergo numerous treatments and repeated surgeries, resulting in higher healthcare costs and a worsening of their quality of life. Treating this disease is, therefore, a challenge (FOKKENS et al, 2020).

MONOCLONAL ANTIBODIES

Köhler and Milstein, in 1975, developed the first monoclonal antibody based on methods that isolated antibodies from hybridoma cells; resulting from the fusion between two cells with distinct genetic characteristics; generated from mice previously immunized with the antigen of interest, to be used as a drug or directed to any part of the human organism, aiming to target a single tissue or cell type (MARQUES, 2005).

The first monoclonal antibody with therapeutic function was generated as OKT3 by Ortho Biotech in 1984, with the aim of preventing kidney transplant rejection in transplant patients (NORMAN, 1995).

The monoclonal antibody is generated from the fusion of myeloma cells with B lymphocytes isolated from mice whose immune systems have been stimulated by a specific antigen (DE GROOT; SCOTT, 2007). It has unique specificity, is derived from a single B cell clone and, consequently, its physicochemical and biological properties are identical (NELSON et al, 2000).

The first clinical results regarding cancer therapy based on monoclonal antibodies, however, were negative. Because they are of murine origin, they led to the development of an immune response by the body against the

monoclonal antibody itself, with consequent rapid elimination of the drug and a suboptimal capacity in its interaction with the human immune system in order to combat cancer. However, the development of techniques that allowed the genetic modification of murine monoclonal antibodies into chimeric or humanized mouse-human antibodies provided therapeutic success, with less propensity for the drug to be recognized by the immune system as a foreign antigen and with a similar half-life. to human IgG (WEINER, 2015). Current monoclonal antibodies have high specificity, few side effects and are an alternative for diseases that require aggressive clinical or surgical treatment (SANTOS et al, 2002).

USE OF DUPILUMAB IN CRSwNP

Dupilumab is a fully human monoclonal antibody that targets the IL-4 alpha (α) receptor. Because this unit is present in both IL-4 and IL-13 receptors; cytokines that orchestrate type 2 inflammation, its administration leads to the blocking of signaling of both (Figure 3) and, consequently, causes a decrease in type 2 inflammatory response (BACHERT et al, 2016).

Ultimately, there is a reduction in the production of nasal secretion, a reduction in the production of IgE in the blood, a reduction in the production of local IgE in the polypoid tissue, a reduction in nasal polyps and an improvement in the symptoms of CRSwNP (YANG et al, 2022).

The treatment of CRSwNP aims to control tissue inflammation and commonly includes the use of nasal corticosteroids, nasal saline irrigation and antibiotics or short-term systemic corticosteroids. In patients in whom polyps persist despite clinical treatment, surgical excision is considered (FOKKENS et al, 2020). Recurrence of the disease after surgery, however, approaches 50% in patients with tissue eosinophilia and resolution of symptoms is generally incomplete (VLAMINCK et al, 2014). Thus, it was seen that dupilumab may be indicated in patients with bilateral polyps undergoing paranasal sinus surgery or who are unfit for surgery and who present three of the following characteristics: evidence of type 2 sinonasal inflammation (eosinophils in the tissues ≥ 10/HPF or blood eosinophils ≥ 250 or total IgE ≥ 100), need for at least two courses of systemic corticosteroids/continuous use of systemic corticosteroids (long-term use for more than 3 months; at low dose)/contraindication for use of systemic corticosteroids, significantly impaired quality of life, anosmia verified in a smell test and/or diagnosis of asthma requiring regular inhaled corticosteroids (FOKKENS et al, 2020). Dupilumab is contraindicated in patients with known hypersensitivity to the drug or any excipient contained in it (``*Sanofi Medley Farmacêutica Ltda*``., 2020).

Dupilumab is the first immunobiological treatment approved for use in CRSwNP by the United States Food and Drug Administration (FDA, 2019) and by Anvisa in Brazil (ANVISA, 2020).

In a double-blind study carried out in 2013, involving 60 individuals with CRSwNP refractory to nasal corticosteroids, 2 groups were divided to compare dupilumab and placebo. Initially, all patients underwent 4 weeks of use of Mometasone Furoate nasal spray and, afterwards, they were randomly divided into 2 groups of 30 people, one of which underwent the use of dupilumab (dose of 600 mg followed by 15 weekly doses of 300 mg) and the other on placebo (also for a period of 16 weeks), both groups maintaining the use of the nasal spray.

As a result, it was seen that the use of dupilumab was associated with significant improvements in endoscopic, clinical, radiographic examinations through the

Lund-Mackay score and pharmacodynamic outcomes after 16 weeks; A significant improvement in patients' quality of life was also reported through the Sinus Nasal Outcome Test-22 (SNOT-22) questionnaire and in the main symptoms, such as smell, nasal obstruction and nighttime awakenings. No serious adverse events were reported. (BACHERT et al, 2016).

Additionally, in 2 international phase 3 follow-up studies, Liberty NP SINUS-24 and Liberty NP SINUS-52, 276 and 448 patients, respectively, were randomized to receive dupilumab or placebo. In SINUS-24, individuals received dupilumab at a dose of 300 mg or placebo every two weeks. In SINUS-52, patients were divided into 3 groups, the first group received dupilumab at a dose of 300 mg every 2 weeks for 52 weeks, the second group received the drug at a dose of 300 mg every 2 weeks for 24 weeks and, after, 300 mg every 4 weeks for 28 weeks and the third group received placebo every 2-3 weeks for 52 weeks; all groups in both studies also used Mometasone Furoate spray throughout the period.

At the end of 24 weeks, the SINUS-24 study demonstrated that 57% of patients in the dupilumab group had an improvement in the level of nasal obstruction compared to 19% in the placebo group; 33% of patients in the dupilumab group had a reduction in the nasal polyp score versus a 7% increase in the score in the placebo group; 60% of patients in the dupilumab group achieved an improvement in quality of life compared to 18% improvement in the placebo group. There was also a 73% reduction in rescue treatments with systemic corticosteroids or sinonasal surgery in the dupilumab group compared to placebo during this period. In the SINUS-52 study, at the end of 52 weeks, an improvement in sinus opacification visualized on paranasal sinus CT scans was observed in 37% of patients in the dupilumab group versus only 2% of patients in the placebo group; an improvement in quality of life in 58% of patients in the dupilumab group versus 14% in the placebo group and a 76% reduction in rescue treatments compared to placebo. (BACHERT et al, 2019).

It is important to note, however, that not all patients with treatment-refractory CRSwNP benefit from treatment with dupilumab, as around 40% of participants in the SINUS-24 study and around 49% of participants in the SINUS-52 study did not show an improvement in quality of life, according to SNOT-22, after treatment.

CLINICAL CASE

Male patient, 53 years old, farmer, from the city of Nova Palma, RS, sought specialized care in Otorhinolaryngology in 2017 due to long-standing nasal obstruction. He had previously undergone two endoscopic sinonasal surgeries, without effective improvement in his condition. He presented hypo/anosmia, hypogeusia, intermittent purulent rhinorrhea, intense nasal congestion and facial pain/pressure, in addition to nasal polyposis, which improved after the use of systemic corticosteroids, associated or not with antibiotics, in order to close the diagnosis for CRSwNP. The patient also had a diagnosis of relatively controlled asthma, using a bronchodilator during attacks and had worsening of sinonasal symptoms and asthma with the use of AAS or other NSAIDs, thus characterizing DREA.

Due to his clinical condition and the failure of previous surgical treatments, he underwent desensitization therapy with AAS. He began using a dose of 1.2g of the medication daily, with regular control of his condition. However, she developed peptic ulcer disease and had to interrupt desensitization, consequently, the clinical condition worsened again. The patient did not want to restart therapy due to

the resulting adverse gastrointestinal effects.

On May 18, 2017, the patient underwent a new Lothrop-type endoscopic sinonasal surgery, which consists of removing the high nasal septum and the interfrontal septum with the union of the frontal sinuses and their consequent wide communication with the nasal cavities. In the following months, he maintained control of his symptoms, performing daily nasal lavage with high volume saline solution (250 ml) with Budesonide (0.5 mg).

Furthermore, he required the use of 3 cycles of antibiotics and systemic corticosteroids, until in the 7th month post-operatively, there was already polypoid degeneration occupying practically both frontal sinuses, in addition to most of the ethmoid sinuses.

The patient began to experience worsening of the condition 3 to 4 times a year, always maintaining hypo/anosmia, hypogeusia and nasal congestion, only reporting an improvement in the pain reported before the 3rd surgery. During this period, he was evaluated by a pulmonologist regarding the possibility of using Omalizumab, however, based on the clinical and laboratory profile, he did not meet the criteria to receive the prescription.

The patient began using corticosteroids in 10-day cycles to control symptoms, when in February 2021 he was offered the possibility of using dupilumab. On December 9, 2021, before starting to use the drug, the patient presented a CT scan of the paranasal sinuses with a total score of 22 on the Lund-Mackay score. He then started treatment with a dose of 300 mg in December 2021, with the medicine provided by the state of Rio Grande do Sul through a judicial measure.

As of December 2021, the patient began receiving biweekly doses of 300 mg dupilumab. He showed clinical improvement and improvement in the SNOT-22, applied in May 2022. A new CT scan of the paranasal sinuses in May 2022 also showed an improvement in the Lund-Mackay score, with a total score of 18

During the months of May and June, the patient's supply of dupilumab was interrupted by the State and his clinical case worsened, requiring two courses of oral Prednisolone during this period. In July 2022, the applications were regularized and the patient showed clinical improvement again in November 2022. He is currently undergoing outpatient follow-up with clinical and endoscopic improvement of the disease. He feels more energetic, with less rhinorrhea and without the need to use medication to control his asthma.

DISCUSSION

In Brazil, in June 2020, ANVISA approved the use of dupilumab for CRSwNP in adults who have failed previous treatments, with intolerance or contraindication to the use of systemic corticosteroids and/or surgery. The Guideline for the use of immunobiologicals in CRSwNP, published in 2021 by the Brazilian Association of Otorhinolaryngology and Cervico-Facial Surgery (ABORL-CCF) determines that dupilumab can be indicated as a complementary treatment for CRSwNP in all adults who have failed previous treatments, or who are intolerant or have any contraindication to the use of oral corticosteroids and/or surgery. It also defines that the drug must not be used in the treatment of patients with acute bronchospasm, status asthmaticus, or helminth infections - requiring the treatment of these 3 conditions prior to starting therapy with dupilumab, if any (ANSELMO-LIMA et al, 2022).

The latest edition of the EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps), from 2020, specifically defines the following criteria for the indication of

immunobiologicals in CRSwNP: patients with bilateral polyps, who have undergone sinonasal surgery or who were unfit for surgery and that presented at least three of the following characteristics:

1. Type 2 sinonasal inflammation, evidenced by the presence of eosinophils in tissues ≥ 10/HPF, by the presence of eosinophils in the blood ≥ 250 mm³ or by total IgE ≥ 100 IU/ml;
2. Need for at least two courses of systemic corticosteroids per year, long-term use, for more than 3 months, at a low dose or contraindication to the use of this drug;
3. Significantly impaired quality of life, evidenced through the SNOT-22 questionnaire, with a total score ≥ 40;
4. Anosmia evidenced by smell test;
5. Diagnosis of asthma requiring regular inhaled corticosteroids.

The SNOT-22 is a specific questionnaire for patients with rhinosinusitis and addresses 22 questions related to nasal and paranasal symptoms, general state, psychological state and sleep-related symptoms, with each question scoring from 0 to 5; 0 meaning absence of the problem and 5 the worst possible problem. There are two smell tests: UPSIT and Connecticut. The first was developed by the University of Pennsylvania and comprises 40 different odors distributed across 4 cards, with 1 different odor on each page. The patient must select the option that best describes each odor. At the end, there is a score that classifies the patient into: normal smell, hyposmia (mild, moderate or severe) and anosmia (FORNAZIERI et al, 2010). While the second was created by the Connecticut Chemosensory Clinical Research Center and is composed of 2 phases: the first phase consists of the quantitative assessment of smell through the perception of butyric alcohol in different concentrations in 8 different bottles and the second phase with the qualitative assessment of smell, where the patient must discriminate 8 bottles containing different common, everyday odoriferous substances; During the entire test, the patient must be wearing an eye mask. Before carrying out the test, the patient must also answer a questionnaire and at the end, the examiner makes an average score of the two parts of the test, which varies from 0 to 7 points, with a result above 6 being considered normal (ANITELI et al, 2022).

The dosage of dupilumab for CRSwNP is 300 mg, subcutaneously, once every 2 weeks, generally administered for the first time in an office or clinic/hospital, and can be administered by the patient at home. The most common adverse events observed were: nasopharyngitis, worsening of nasal polyps and asthma, headache, epistaxis and erythema at the injection site (Anvisa leaflet, 2020).

The patient subject of this report presented the following criteria to indicate the use of dupilumab: presence of bilateral polyps, having already undergone sinonasal surgery, need for at least two courses of systemic corticosteroids per year, type 2 sinonasal inflammation evidenced by eosinophilia in laboratory examination (350 mm³ of eosinophils in the blood), significantly impaired quality of life proven by the SNOT-22 questionnaire (score of 103/110) and diagnosis of asthma requiring regular use of inhaled corticosteroids.

Smell tests were not performed due to their unavailability by the attending physician.

It is important to realize, however, that treatment with dupilumab has a relevant limitation: the difficulty of access in Brazil. Despite being approved for use in the disease by ANVISA since July 2020, it is not yet included in the list of medicines of the ANS (National Supplementary Health Agency) and is not offered by the SUS (Unified Health System). Furthermore, due to the onerous cost, purchasing the medicine becomes unfeasible for the majority of the Brazilian

population. A box containing 2 syringes of 300mg each has a PMC (maximum consumer price) in Brazil of R$11,734.77, according to the latest update from CMED (Chamber of Medicines Market Regulation). Considering that 1 box of medication is needed for treatment every 4 weeks, the maximum total cost for a patient who needs this therapy is around R$140,817.24 per year (CMED, 2022), a value well above the average salary in the country, of around R$2,569.00 per month (IBGE, 1st quarter of 2022). Therefore, the most viable way to obtain access to this medication in Brazil today would be through the State through judicialization, since the right to health constitutes a fundamental social human right, and the State's duty is to ensure universal and equal access to health, in accordance with the SUS comprehensiveness guideline (CF, art. 6, 196 and 198, II).

Furthermore, the long-term effects of dupilumab are not yet well known, as the drug began to be used on a larger scale only in 2020 in the USA and Europe and in 2021 in Brazil. Therefore, its long-term benefits or harms are not yet known.

Besides, in the SINUS-52 study, greater treatment efficacy was observed in patients who received a dose of 300 mg every 2 weeks compared to those who spaced the dosage to every 4 weeks after the 24th week. Therefore, despite reducing costs, the dosage of 300 mg every 4 weeks did not prove to be as beneficial as that indicated in the leaflet (BACHERT et al, 2019).

The patient subject of this study, after starting the immunobiological treatment, had a CT scan of the paranasal sinuses on May 4, 2022, with a score of 18 on the Lund-Mackay score, showing clear radiological improvement. More recently, after a longer period of treatment, he presented a score of 12/110 on the SNOT-22 questionnaire, also demonstrating a significant improvement in quality of life, feeling more energetic, with less rhinorrhea, and better quality of sleep., less nasal obstruction and without the need to use medication to control asthma.

These results have also been achieved in some recent publications, such as in a retrospective observational study carried out in Munich, Germany, where a review of the medical records of all patients (75 in total) treated in a tertiary reference center for CRSwNP was carried out. with dupilumab. The study demonstrated that the treatment improved key aspects of the disease endoscopic findings, smell tests and symptoms and suggested that there was no important difference in the outcome of treatment between patients with or without DREA, histological eosinophilia, high levels of eosinophils or total IgE in the blood (BERTLICH et al, 2022).

Another retrospective observational study carried out in Milan and Rome, Italy, verified the medical records of 80 patients followed over a period of 1 year in a specific outpatient clinic for the treatment of CRSwNP with dupilumab. After evaluating the clinical response of patients according to the EPOS guidelines, it was seen that after 12 months of treatment with dupilumab, 4 patients (5%) showed no clinical response, 2 showed a "poor" response, 19 (23, 75%) presented a "moderate" response and 55 (68.75%) presented an "excellent" response. Treatment with the drug showed a reduction in the volume of nasal polyps, restoration of nasal obstruction, improvement in quality of life measured mainly through SNOT-22 and improvement in smell measured through UPSIT. Dupilumab was also well tolerated by all patients in the study (TORRETA et al, 2022).

FINAL CONSIDERATIONS

The use of dupilumab resulted in a significant improvement in the clinical picture and quality of life of the patient with AERD who is the subject of this study, with an improvement in both CRSwNP and bronchial asthma. Despite the high costs, the use of this drug proved to be beneficial and effective in significantly improving the endoscopic, radiological and clinical parameters of patients with severe CRSwNP, in addition to reducing the need for surgery and the use of systemic corticosteroids as rescue treatment. Furthermore, interrupting treatment has been shown to result in loss of its beneficial effects and the dosage of 300 mg every 2 weeks has been shown to be superior to that of every 4 weeks. Dupilumab is, therefore, an effective therapeutic alternative in patients with severe CRSwNP.

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