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Immunobiological therapy in the treatment of severe asthma

Terapia imunobiológica no tratamento da asma grave

Terapia inmunobiológica en el tratamiento del asma grave

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Abstract
Introduction: Asthma is an inflammatory, chronic and heterogeneous disease that mainly affects the lower airways, which present nonspecific respiratory symptoms. In most cases, asthma has good therapeutic management, but the number of diagnoses of severe asthma is increasing, which require the use of immunobiologicals. The present study aims to provide a detailed analysis from a therapeutic and pharmacological point of view of the main immunobiologicals. Methodology: The narrative review of the literature was carried out from the PUBMED database using the keywords "Severe Asthma", "Treatment" and "Biological Therapy", with the time filter in the last 10 years, which resulted in 56 articles, the rest were discarded because they did not have a title or abstract directly related to the key words or had online access restrictions. Results and Discussion: Due to greater knowledge about the pathophysiology of Asthma, as it presents different pathways of inflammatory activation, notably, the IgE B lymphocyte activation pathways, the Th2 response, the action of IL-5 that recruits neutrophils and others inflammatory cells, among other interleukins. In this context, the use of immunobiologicals, for example, Omalizumab, Mepolizumab, Reslizumab, Dupilumab and Tezepelumab, in cases refractory to conventional therapy stand out as an assertive and physiological alternative given the pathological context developed in severe asthma. Conclusion: Uncontrolled asthma and Severe Asthma are conditions that are refractory to conventional asthma treatment, within the spectrum of potential complications that may arise if advanced therapies are not initiated.
Keywords: Asthma; Anti-asthmatic agents; Biological treatment.

Resumo
Introdução: A asma é uma doença inflamatória, crônica e heterogênea que acomete principalmente as vias aéreas inferiores, as quais apresentam sintomas respiratórios inespecíficos. Em sua maioria dos casos a asma possui bom manejo terapêutico, porém é crescente o número de diagnósticos de asma grave, os quais requerem o uso de imunobiológicos. O presente estudo objetiva uma análise detalhada sob o ponto de vista terapêutico e farmacológico dos principais imunobiológicos. Metodologia: A revisão narrativa da literatura foi realizada a partir da base de dados PUBMED utilizando as palavras chaves de "*Severe Asthma*", "*Treatment*" e "*Biological Therapy*", com o filtro de

tempo nos últimos 10 anos que acarretaram em 56 artigos, os demais foram descartados por não possuir título ou resumo relacionado diretamente às palavras chaves ou possuírem restrições de acesso online. Resultados e Discussão: Em decorrência do maior conhecimento acerca da fisiopatologia da Asma, visto que apresenta diferentes vias de ativação inflamatória, destacadamente, as vias de ativação dos linfócitos B IgE, a resposta Th2, da ação de IL-5 que recruta neutrófilos e demais células inflamatórias, dentre outras interleucinas. Nesse contexto, o uso de imunobiológicos, por exemplo, Omalizumabe, Mepolizumabe, Reslizumabe, Dupilumabe e Tezepelumabe, em casos refratários à terapia convencional se destacam como uma alternativa assertiva e fisiológica diante do contexto patológico desenvolvido na asma grave. Conclusão: A asma não controlada e a Asma Grave são condições de refratariedade ao tratamento convencional da asma, dentro do espectro de potenciais complicações que podem surgir caso não iniciada terapêuticas avançadas.
Palavras-chave: Asma; Antiasmáticos; Tratamento biológico.

Resumen

Introducción: El asma es una enfermedad inflamatoria, crónica y heterogénea que afecta principalmente las vías respiratorias inferiores, las cuales presentan síntomas respiratorios inespecíficos. En la mayoría de los casos el asma tiene un buen manejo terapéutico, pero cada vez son más los diagnósticos de asma grave que requieren el uso de inmunobiológicos. El presente estudio pretende proporcionar un análisis detallado desde el punto de vista terapéutico y farmacológico de los principales inmunobiológicos. Metodología: Se realizó la revisión narrativa de la literatura a partir de la base de datos PUBMED utilizando las palabras clave "Asma Severa", "Tratamiento" y "Terapia Biológica", con el filtro de tiempo en los últimos 10 años, lo que resultó en 56 artículos, el resto fueron descartados por no tener título o resumen directamente relacionado con las palabras clave o por tener restricciones de acceso en línea. Resultados y Discusión: Debido al mayor conocimiento sobre la fisiopatología del Asma, ya que presenta diferentes vías de activación inflamatoria, en particular, las vías de activación de los linfocitos B IgE, la respuesta Th2, la acción de la IL-5 que recluta neutrófilos y otras células inflamatorias, entre otras interleucinas. En este contexto, el uso de inmunobiológicos, por ejemplo, Omalizumab, Mepolizumab, Reslizumab, Dupilumab y Tezepelumab, en casos refractarios a la terapia convencional, se destacan como una alternativa asertiva y fisiológica dado el contexto patológico que se desarrolla en el asma grave. Conclusión: El asma no controlada y el asma grave son afecciones refractarias al tratamiento convencional del asma, dentro del espectro de posibles complicaciones que pueden surgir si no se inician terapias avanzadas.
Palabras clave: Asma; Antiasmáticos; Tratamiento biológico.

1. Introduction

Asthma is an inflammatory, chronic and heterogeneous disease of the respiratory system that presents different types and individual characteristics (phenotypes and endotypes), especially in response to therapy, which is marked by variations in the exacerbation rate, response to treatment and remission rate. (Schoettler & Strek, 2019; Busse, 2019; Pelaia et al, 2017). The symptoms and signs of asthma are nonspecific and include tachypnea, dyspnea, cough, wheezing and chest pain (Papi et al, 2018). In most cases of asthma, it is possible to achieve effective treatment with standard inhaled medications, however, around 5-10% of the more than 334 million people who currently suffer from asthma worldwide have subtypes of inadequately controlled asthma and difficult to treat (severe asthma) (Papi et al, 2018; Pelaia et al, 2020; Dragonieri & Carpagnano, 2021).

Severe asthma is defined by lack of control regardless of adherence to treatment with inhaled corticosteroids and long-acting bronchodilators, ICS-LABA, high dose optimized with the correct inhaler technique and control of contributing factors, such as comorbidities and environmental exposures, or worsening when the dose of ICS-LABA is reduced. In 2023, the use of biological therapies such as Omalizumab, Mepolizumab, Reslizumab, Benralizumab, Dupilumab and Tezepelumab was recommended for treatment (Venkatesan, 2023). Often, asthma may appear resistant to treatment due to modifiable factors, such as inappropriate use of inhalation devices, poor adherence to treatment, smoking or the presence of comorbidities, or even incorrect diagnosis (Pelaia et al, 2020). Therefore, regular reviews of treatment plans are essential. Severe asthma is a subtype of asthma that is difficult to control. Currently, the term "severe asthma" is a retroactive description. It is sometimes referred to as "severe refractory asthma" as it historically resisted high doses of inhaled treatment. However, with the development of biological therapies, the term "refractory" is no longer appropriate. Asthma is not considered serious if there is significant improvement after correction of contributing factors, such as improving inhaler technique and adherence to treatment. , which

are adjusted during therapeutic evaluations. Patients with advanced asthma can currently receive treatment with a variety of monoclonal antibodies targeting the main inflammatory cytokines involved in the pathogenesis of asthma (Venkatesan, 2023).

Asthma activates the immune system, both through innate and adaptive immunity, triggering a condition of bronchial hyperresponsiveness, a condition of exaggerated sensitization of the bronchi. During this process of inflammatory response, mucus is overproduced and the wall thickens, a situation that leads to narrowing, therefore, causes chronic inflammation and forms a cluster of inflammatory cells, such as eosinophils and neutrophils. In allergic asthma, the reaction begins with the contact of the allergen with helper T lymphocytes, which have the function of recognizing the antigen and secreting cytokines responsible for differentiating B lymphocytes into plasma cells, which will secrete immunoglobulin E (IgE) and these will bind to the mast cell membranes. In the second contact, the IgEs, upon binding, will cause degranulation and, thus, release histamine, leukotrienes and prostaglandins, which predisposes to bronchospasms. Th2 lymphocytes, located in the bronchial mucosa, induce the synthesis of IgE by plasma cells, through IL4 and IL3. Thus, they favor the differentiation and activation of eosinophils through IL5 action, which leads to the recruitment of inflammatory cells, for example, eosinophils and neutrophils. Furthermore, in asthma, changes in apoptosis can increase the survival of inflammatory cells in the bronchi, such as lymphocytes and eosinophils. Consequently, in asthmatic inflammation, there is an increase in cytokines such as IL5 and IL13. Furthermore, in neutrophilic asthma, where there is greater activation of innate immunity, as it is a pre-programmed response of the body to infections, it involves pro-inflammatory cytokines, for example, TNF alpha, FNkB, responsible for the increase in IL8 (summons neutrophils) and IL17 (stimulate inflammation by neutrophils in the airways) (Pelaia et al., 2018).

Asthma inflammation mechanisms are divided into T2 type and non-T2 type. Type 2 has a higher prevalence, has allergic asthma as the most common subtype and its main mediator is Immunoglobulin E (IgE), a marker of allergic processes, given that it inhibits the activation of mast cells and basophils (Schoettler & Strek, 2019; Busse, 2019). Therefore, the effectiveness of treating this type of asthma, when severe, with omalizuamb was seen, as it is an Anti-IgE class drug, which is even recommended by the GINA guidelines. Non-type T2, also called non-allergic asthma, is represented by neutrophilic asthma, characterized by the presence of neutrophils and related to smoking and obesity, in addition to having a low response to inhaled corticosteroids. Comorbidities are common in asthma and can considerably worsen symptoms. Rhinitis and rhinosinusitis, with or without nasal polyposis (and rhinoconjunctivitis in children), are the most common comorbidities associated with uncontrolled asthma (Papi et al, 2018). Allergic rhinitis affects more than half of children with asthma and is even more prevalent in adults and children with asthma compared to those without the condition, affecting up to 82% of nonsmoking adults with severe asthma in one study. The correlation between obesity and asthma suggests a relationship between these two conditions, with mutual negative effects. This comorbidity is also related to residual lung volume, worsening dyspnea in asthmatic individuals. Furthermore, there are changes in inflammatory states in the lungs, lung immune cells and adipose tissue in obese individuals (Ntontsi et al, 2020). Gastroesophageal reflux is common and contributes to worsening symptoms in adults and children with asthma. In adults who smoke, the coexistence of asthma and COPD may occur, being described as asthma-COPD overlap syndrome. Obstructive sleep apnea is common in adults with asthma, especially in severe cases. In children, fatigue, irritability and difficulty concentrating are characteristics of poorly controlled asthma. However, obstructive sleep apnea should be considered if these symptoms persist, even with good treatment adherence (Paoletti et al., 2022).

In this broad context of individuals with asthma globally, patients with severe asthma stand out due to the lack of appropriate response to conventional treatment. These individuals can be considered as candidates for complementary biological therapies. Currently, there are six biological medicines authorized for the treatment of severe asthma, which are Omalizumab, Mepolizumab, Reslizumab, Benralizumab, Dupilumab, Tezepelumab (Busse, 2018).

It is also important to note that asthma often coexists with other conditions, including rhinosinusitis, nasal polyps, atopic

dermatitis, obesity, diabetes, gastroesophageal reflux, and depressive and anxiety disorders, which further complicates clinical assessment. Additionally, about 50% of adults with asthma have type 2 airway inflammation with eosinophils, but when corticosteroids are stopped in clinical trials, persistent eosinophilic airway inflammation is often seen. Atopy, a predisposition to allergies, is common in adults and children with asthma, especially severe asthma in children and adults with early onset (Schoettler & Strek, 2019; Peer Ameen Shah & Brightling, 2023; Kroes et al., 2020). Additionally, non-eosinophilic asthma is a less understood variant of the condition where inflammation focuses on neutrophils and involves a complex interplay of immune cells. This response may be related to bacterial colonization of the airways or the effects of corticosteroids, which can influence neutrophil survival and suppress type 2 immunity, resulting in an upregulation of type 1 or type 17 immunity (Krings et al., 2019; Assaf, & Hanania. 2019; Porsbjerg et al., 2020).

Comorbidities are common in asthma and can considerably worsen symptoms. Rhinitis and rhinosinusitis, with or without nasal polyposis (and rhinoconjunctivitis in children), are the most common comorbidities associated with uncontrolled asthma. Allergic rhinitis affects more than half of children with asthma and is even more prevalent in adults and children with asthma compared to those without the condition, affecting up to 82% of nonsmoking adults with severe asthma in one study. The correlation between obesity and asthma suggests a relationship between these two conditions, with mutual negative effects. This comorbidity is also related to residual lung volume, worsening dyspnea in asthmatic individuals. Furthermore, there are changes in inflammatory states in the lungs, lung immune cells, and adipose tissue in obese individuals. Gastroesophageal reflux is common and contributes to worsening symptoms in adults and children with asthma. In adults who smoke, the coexistence of asthma and COPD may occur, being described as asthma-COPD overlap syndrome. Obstructive sleep apnea is common in adults with asthma, especially in severe cases. In children, fatigue, irritability and difficulty concentrating are characteristics of poorly controlled asthma. However, obstructive sleep apnea should be considered if these symptoms persist, even with good treatment adherence. (Papi et al, 2018; Ntontsi et al, 2020; Paoletti et al., 2022).

Uncontrolled asthma is characterized by inadequate control of symptoms and/or recurrent exacerbations (usually two or more per year) (Papi et al, 2018). This form of treatment-resistant asthma is one that does not respond satisfactorily to the prescription of medium- or high-dose inhaled corticosteroids, along with a second controller (usually a LABA) or maintenance oral corticosteroids (Peer Ameen Shah, & Brightling, 2023). This does not imply a “challenging patient”. Often, asthma may appear resistant to treatment due to modifiable factors, such as inappropriate use of inhaler devices, poor adherence to treatment, smoking or the presence of comorbidities, or even incorrect diagnosis (Krings et al., 2019). Therefore, regular reviews of treatment plans are essential. Severe asthma is a subtype of asthma that is difficult to control (Bakakos et al., 2020). Currently, the term “severe asthma” is a retroactive description (Ntontsi et al, 2020). It is sometimes referred to as “severe refractory asthma” as it historically resisted high doses of inhaled treatment. However, with the development of biological therapies, the term “refractory” is no longer appropriate. Asthma is not considered serious if there is significant improvement after correction of contributing factors, such as improving inhaler technique and adherence to treatment, which are adjusted during therapeutic evaluations (Eger & Bel, 2019) Patients with advanced asthma can currently receive treatment with a variety of monoclonal antibodies targeting the main inflammatory cytokines involved in the pathogenesis of asthma (Agache et al., 2020).

The groundbreaking achievement in the treatment of severe asthma was the introduction of its first biological treatment – the anti-IgE monoclonal antibody omalizumab (Busse 2018; Sivan et al., 2022). The following years brought other biological agents targeting different factors, including IL 5, IL-5R, IL-13, IL-4R, and others. Each of these medications blocks a particular immune pathway, triggering and controlling allergic or non-allergic airway inflammation (Porsbjerg et al., 2020; Wan & Woodruff, 2016; Dorscheid et al., 2022). With monoclonal antibodies now available for asthma, doctors can select a medication according to the asthma phenotype (A Prabakaran., 2020; Hilvering, & Pavord, 2015; Rogliani et al., 2019).

The present study aims to elucidate and clarify the main pathophysiological mechanisms of severe asthma, in addition to detailing the immunobiological therapeutic options available for severe asthma within its pharmacokinetic, pharmacodynamic spectrum and therapeutic efficacy. These objectives, currently in the literature, are scarce in a joint and protocolized manner, motivating the description of the current study.

2. Methodology

The narrative review of the literature was carried out (Rother, 2007; Snyder, 2019) from the PUBMED database using the keywords "Severe Asthma", "Treatment" and "Biological Therapy", with the time filter in the last 10 years (2014-2023) which resulted in 662 articles, of which only 56 were used, the remaining 606 were discarded because they did not have a title or abstract directly related to the keywords or had online access restrictions.

3. Results and Discussion

3.1 Mepolizumab

Mepolizumab is a monoclonal antibody that acts against IL-5, and its mechanism of action is through binding to human IL-5, in order to prevent the interaction of this interleukin with its receptor complex, expressed on the cell surface of eosinophils. (Dragonieri & Carpagnano, 2021; Pelaia et al, 2020). Mepolizumab was approved in 2015 by the Food and Drugs Administration, being the first anti-IL-5 used to treat severe asthma.

The immunobiological is indicated for individuals over 6 years of age with severe refractory eosinophilic asthma, who remain decompensated, despite optimized therapy (Dragonieri & Carpagnano, 2021). Several studies have demonstrated the effectiveness of mepolizumab in reducing blood eosinophils and the frequency of exacerbations, with a reduction of up to 50% (Papi, 2018). Among them, one investigated the efficacy of mepolizumab through a systematic review, in which the first two large clinical trials evaluating the efficacy of the immunobiological were described (Menzella, 2016).

We highlight a randomized clinical trial with 61 patients with refractory eosinophilic asthma and a history of recurrent exacerbations. The individuals received monthly infusions of mepolizumab or placebo for one year, so that at the end of the study, a smaller number of severe exacerbations was found in the patients using mepolizumab in relation to the group that received placebo, in addition to a decrease in eosinophils in sputum and blood (Haldar, 2009).

In another randomized clinical trial, carried out with patients with persistent sputum eosinophilia and symptoms despite corticosteroid treatment, nine patients received 5 monthly infusions of mepolizumab 750mg and 11 patients received placebo. As a result, 12 asthma exacerbations were recorded in 10 patients who received placebo, and only one exacerbation in one patient using mepolizumab (Nair, 2009).

Subsequently, a study called MENSA selected 576 asthmatic patients with frequent exacerbations and evidence of eosinophilic inflammation despite high doses of inhaled corticosteroids, and these individuals were divided into three groups, one assigned to receive treatment with mepolizumab at an intravenous dose of 75 mg to every four weeks for 32 weeks, another to receive a subcutaneous dose of 100mg at the same time interval and, finally, a group to receive a placebo. As a primary outcome, a reduction in the rate of exacerbations of 47% was observed in the group that received intravenous mepolizumab and 53% in the group that received subcutaneous mepolizumab compared to the placebo group. Also in this study, at the end of treatment, an increase in pre-bronchodilator FEV1 of 100ml in the intravenous mepolizumab group and 98ml in the subcutaneous mepolizumab group was demonstrated as a secondary outcome compared to the placebo group, and when the post-bronchodilator FEV1 was observed, this increase was 146ml and 138ml, respectively. Thus, it was possible to associate mepolizumab with improved lung function (ORTEGA, 2014).

Regarding the use of inhaled corticosteroids, the SIRIUS study was a double-blind randomized clinical trial involving 135 patients with severe refractory eosinophilic asthma that sought to evaluate the role of mepolizumab in reducing IC doses. In the study, one group of patients was assigned to receive mepolizumab at a dose of 100mg subcutaneously once every four weeks for 20 weeks, and another group received a placebo. As a result, the mepolizumab group showed a reduction in ICS dose 2.39 times greater than the placebo group. Furthermore, this group also had a 32% relative reduction in the rate of exacerbations (Bel, 2014)

When it comes to adverse reactions, in the MENSA and SIRIUS studies, around 2% of patients abandoned the clinical trial due to such events. The most common reactions were headache, reactions at the injection site, back pain and fatigue, with these events being reported mainly between the days of administration of the immunobiological (Miyokawa, 2020).

3.2 Reslizumab

Reslizumab is an immunobiological used for severe asthma, which has two divisions, the T2 type and the non-T2 type. The use of this medication is most recommended for type 2, as it is a severe uncontrolled eosinophilic asthma and its mechanism of action acts to reduce the production and maturation of eosinophils. Furthermore, type T2 operates through an immunological response through Th2 cells or innate lymphoid cells, having a moment of sensitization to allergens, causing a cascade of events to occur, as B lymphocytes will be activated and begin to secrete IgE, these will bind to their receptors on basophils and mast cells, which at the same time release several cytokines, which attract eosinophils to the respiratory tract (Agondi, 2010).

It is a humanized monoclonal antibody (IgG4 subtype) that focuses on IL-5 (interleukin 5, which is a fundamental stimulant for the growth and release of eosinophils, in addition to performing functions throughout their lifespan) acting in opposition to it (Matera, 2017). It behaves like an antagonist, as it directly binds to IL-5, neutralizing it and preventing its attachment to eosinophils, thus reducing activity and survival (Brom et al, 2015).

Furthermore, its use is strictly intravenous, with a dose of 3mg/kg slowly (Lim & Nair, 2015). Its effectiveness has been proven by studies using the drug and placebo, in which the results demonstrate a considerable reduction in the frequency of exacerbations (gradual increase in symptoms) by approximately 6% per year, in addition to improving lung function and reducing the need for of other medications, such as bronchodilators, salbutamol and terbutaline (Charles et al, 2022). In fact, studies also indicate that its side effects are similar to placebo, for example cough and headache (Lim & Nair., 2015).

3.3 Omalizumab

Omalizumab was the first immunobiological developed and licensed for severe asthma in 2003 by the Food and Drugs Administration (Dragonieri & Carpagnano, 2021). It is a recombinant monoclonal antibody focused on immunoglobulin E (IgE), responsible for controlling allergic reactions and active immunity against parasites (Pelaia et al, 2020).

Omalizumab binds to IgE, inhibiting its binding to high-affinity IgE receptors on the cell membrane of mast cells and basophils. In this way, by inhibiting all IgE-dependent molecular and cellular events involved in the immune and inflammatory cascades of allergic asthma, a reduction in the allergic response is seen and, consequently, prevention of asthma exacerbations (Dragonieri & Carpagnano, 2021).

Omalizumab was used for patients aged 6 years and over with uncontrolled allergic asthma even with high doses of corticosteroids. Its dosage is based on serum IgE levels and the patient's weight, and is administered subcutaneously every 2 to 4 weeks (Dragonieri & Carpagnano, 2021). The efficacy and safety of omalizumab is well-known due to several studies that have shown it to be a generally well-tolerated immunobiological drug with relevant data on symptom control, improved quality of life, decreased corticosteroid doses and less loss of working days, in addition, it does not have major adverse effects, and it is

common to experience diffuse rash, fever, nosebleeds, headache, and gastric problems after using the medication (Varricchi et al., 2022; Schoettler et al. 2019)

From this perspective, it is possible that patients taking omalizumab who have a high level of eosinophils in their blood are more likely to suffer from asthma exacerbations if the medication is discontinued (Dragonieri & Carpagnano, 2021). Given this, other studies reported that in adults with severe asthma using high doses of corticosteroids and long-acting beta-agonists there was a 25% reduction in the incidence of exacerbations when compared with the group that started omalizumab and placebo (Schoettler et al. 2019).

In a pediatric study with 34 patients, treatment with omalizumab was associated with improvement in symptoms, FEV1 and culminated in a reduction in the dose of oral corticosteroids (Schoettler et al. 2019). In a study by Inner-city children, it was reported that omalizumab reduced the number of seasonal exacerbations, however without changing data on infections due to airway pathogens (Castillo et al., 2017).

3.4 Benralizumab

Benralizumab is a selective biological drug that acts on the interleukin5 (IL-5) receptor, which is the most important cytokine in allergic and non-allergic eosinophilic bronchial inflammation as it helps in its induction, maintenance and amplification, with it and its receptor being the targets of this drug (Agache et al., 2020; Pelaia et al., 2018).

As it is a monoclonal antibody produced in the laboratory, that is, a protein that remains in the blood helping to recognize and fight invaders, which has a specificity mechanism that acts in the region of the target antigen, which occurs through recognition and consequent binding to the specific location (Pelaia et al., 2018).

Furthermore, this process contributes to the reduction of eosinophils in the blood, which contribute to severe asthma, as they cause inflammation in the lung, blocking IL-5 receptors, and is therefore indicated for eosinophilic asthma (many eosinophils in the lung and/or blood) in adults (Agache et al., 2020; Pelaia et al., 2018; Charles et al., 2022; Matera et al., 2017)

It is an injectable drug into the subcutaneous tissue, 30 mg per dose, in the first three applications spaced 28 days apart and then only every 56 days (McGregor et al., 2019; Matera et al., 2017). However, it is not recommended to stop treatment unless on medical orders, as symptoms may return. Therefore, compared to others, such as mepolizumab and reslizumab, it has less frequent doses and has greater potential to reduce exacerbations (McGregor et al., 2019).

Furthermore, its efficacy and safety have been proven through studies using GRADE, which takes advantage of frequency, past and current severity of crises, spirometry and even peak expiratory flow, having 4 levels, corroborating the improvement of exacerbation rates. severe eosinophilic asthma, with a reduction index of 0.53, in addition to a reduction in the daily dose of oral corticosteroids (steroid hormones), as this in itself already has a high impact on reducing the exacerbation of severe asthma (Agache et al., 2020; Pelaia et al., 2018).

Furthermore, it was proven that there was a reduction in the use of oral corticosteroids, an increase of 0.21L in forced expiratory volume in 1 second (FEV1) and a decrease in fractional exhaled nitric oxide (FeNO), which are biomarkers of eosinophilia, in addition to its exacerbation rate. annual rate was -3.79, proving the effectiveness of anti-IL5, including benralizamab (Charles et al., 2022).

These studies are extremely important, as treatment options were previously limited to medications such as oral and/or inhaled corticosteroids, which have adverse reactions that generally affect the user, such as the appearance of bruises, poor healing, loss of calcium, arterial hypertension and cataracts, and from the use of immunobiologicals it was noted a reduction in asthma exacerbations, improvement in lung function and a reduction in the use of corticosteroids, improving quality of life, even with side effects after the injection such as headache, pharyngitis, and local reactions (Agache et al., 2020).

3.5 Dupilumab

Dupilumab is a monoclonal antibody approved in 2018 that binds to the alpha subunit of the IL-4 receptor, mutually to the IL-13 receptors, in a way that inhibits the IL-4 and IL-13 pathways (Dragonieri & Carpagnano, 2021). The immunobiological is used as complementary maintenance therapy in patients with severe eosinophilic asthma at T2 level or who depend on corticosteroids that fit the GINA stage 4 or 5 profile from 12 years of age onwards.

Dupilumab is administered subcutaneously in an initial dose of two injections of 200 mg each, followed by a 200 mg injection every 14 days, or in an initial dose of two injections of 300 mg each followed by a 300 mg dose every 14 days. In addition to asthma, dupilumab is indicated for the treatment of atopic dermatitis and nasal polyposis (Dragonieri & Carpagnano, 2021).

Regarding the effectiveness of the immunobiological, research was carried out with 769 patients with uncontrolled persistent asthma, who were randomized in a double-blind study to receive dupilumab in doses of 200 or 300mg every two or four weeks or placebo for 24 weeks. The primary outcome of this trial was the difference in FEV1 from week 12 of treatment in patients with a blood eosinophil count of 300/µl, so that regardless of the dose of dupilumab administered, significant improvements in lung function and decreased rates were reported. of exacerbations per year compared to the placebo group. This study, however, was insufficient to establish the ideal dose and frequency of the immunobiological (Wenzel et al., 2016; Ragnoli et al., 2022).

In the LIBERTY-ASTHMA QUEST study, the most effective dose of dupilumab, safety and efficacy, was investigated. The study was carried out with 1902 patients by administering doses of 200 or 300 mg subcutaneously or placebo every two weeks for 52 weeks in patients aged 12 years and over with uncontrolled severe asthma, regardless of blood eosinophil count. As a primary outcome, it was possible to observe that dupilumab, in the two doses administered, was effective in attenuating the annual rates of exacerbations and hospitalizations for asthma and was also shown to improve FEV1(Castro et al., 2018; Ragnoli et al., 2022)

In the VENTURE study, in turn, the possibility of reducing the use of oral corticosteroids (OC) was evaluated using dupilumab at a dose of 300mg every two weeks for 24 weeks. During the trial, corticosteroids were reduced from week 4 to week 20, and then continued until the end of the study. As a result, it was found that there was a reduction in the dose of corticosteroids of 70.1% in patients who received the immunobiological, while this reduction in the placebo group was 41.9%. Furthermore, the percentage of patients who had their OC doses reduced to less than 5mg/day was 69% in the dupilumab group and 33% in the placebo group. Furthermore, it was observed that there was a 59% drop in exacerbation rates in the group that used dupilumab compared to the placebo group (Ragnoli et al., 2022; Rabe et al., 2018).

Regarding adverse events, the most common were reactions at the injection site, upper airway infections and conjunctivitis. Temporary eosinophilia also occurred, which did not affect study outcomes (Dragonieri & Carpagnano, 2021).

3.6 Tezepelumab

Tezepelumab is a human monoclonal antibody that binds to thymic stromal lymphopoietin (TSLP), which is a cytokine from the alarmin group, derived from epithelial cells of keratinocytes, respiratory tract and gastrointestinal tract. This cytokine is released upon inflammatory stimuli, playing an important role in regulating type 2 immunity.

Tezepelumab then acts by preventing the binding of TSLP with its receptor complex, inhibiting its action (Pelaia et al, 2020; Ragnoli et al., 2022; Dragonieri & Carpagnano, 2021). The monoclonal antibody in question is the most recent, being approved by the FDA in 2021 for the treatment of severe non-mediated and immune-mediated type 2 asthma (Nopsopon et al., 2022).

It is administered subcutaneously at a dose of 210mg every four weeks (Menzies-Gow et al., 2021; Corren, et al., 2017). In the PATHWAY study, which included 584 patients, in which doses of 70mg every 4 weeks, 210mg every 4 weeks and 280mg every 2 weeks were compared versus placebo over a period of 52 weeks. Among the primary outcomes, it was observed that the annual rate of asthma exacerbations decreased by 62%, 71% and 66%, respectively, compared to placebo (Corren et al., 2017).

Furthermore, it was observed that the rate of exacerbations in people using medium-dose inhaled corticosteroids (ICS) was 48% lower in the tezepelumab groups than in the placebo group and in patients using high-dose ICS at doses of 70, 210 and 280 mg of the monoclonal antibody resulted in annual asthma exacerbation rates at week 52 of 0.35, 0.26, and 0.27, respectively, while placebo had a 1.12 rate (Corren et al., 2017).

In the ongoing phase 3 NAVIGATOR study, 528 patients were assigned to receive tezepelumab 210 mg every 4 weeks and 531 patients received placebo. As a result, it was seen that the annual exacerbation rate in the tezepelumab group was 0.93, while that in the placebo group was 2.10, demonstrating a 56% reduction in these episodes in asthmatic patients (Menzies-Gow et al., 2021; Corren et al., 2017).

Furthermore, at the end of week 52, there was a change in FEV1 baseline of 0.23 liters in patients using tezepelumab and 0.09 liters in patients in the placebo group, and it is also worth highlighting that the The time for the first exacerbation to occur was longer in the immunobiological group than in the placebo group, attesting to a longer period of stability in the medicated group (Menzies-Gow, A. et al., 2021). As for adverse events, in the two studies the most prevalent were bronchitis, upper airway infections and headache (Menzies-Gow et al., 2021; Corren et al., 2017).

4. Conclusion

Uncontrolled asthma and Severe Asthma are conditions that are refractory to conventional asthma treatment, within the spectrum of potential complications that may arise if advanced therapies are not initiated. Therefore, the use of immunobiologicals has a positive impact when used assertively in the treatment of individuals with severe asthma, as they reverse the refractory condition with considerable clinical repercussions. Therefore, the present study reinforces the importance of deepening the analysis and clinical comparisons of the different immunobiologicals within the pharmacological field for inflammatory airway diseases.

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