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Review Article

The role of dupilumab in diverse allergic pathologies

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ABSTRACT

Allergic responses represent a significant health problem due to the ineffectiveness of current treatments, as they attempt to decrease the immune response triggered but are unable to create immune memory that reduces the intensity of such response, so the intensity of the response will always be the same as the first time. An allergic response is characterized by the exacerbated and prolonged release of immunoglobulin E (IgE) that triggers innate immune responses due to the activation of T lymphocytes towards a Th2 phenotype, responsible for the release of interleukins 3 and 4 (IL-3 and IL-4), and the activation of B lymphocytes towards IgE-producing plasma cells.

Currently, monoclonal antibodies (mAbs) are used as treatment for various allergic pathologies as they can be used to inhibit the signaling pathways of various interleukins, inactivating the differentiation of T lymphocytes, B lymphocytes, and the production of IgE. One of the most versatile mAbs in the treatment of various allergic responses is dupilumab, which is designed to inhibit the signaling chain of IL-3 and IL-4, more specifically, it binds to the α receptor of IL-4 and the cytokine-induced receptor complex IL-13. Dupilumab inhibits IL-4 and IL-13 through receptor 1, stopping the release of IgE and proinflammatory cytokines. This treatment can be used to control the inflammatory response caused by allergens. On the other hand, the use of dupilumab is not patented as the treatment of choice for allergic pathologies. Therefore, in this review, we compile the results of clinical studies of dupilumab and other mAbs in atopic dermatitis (AD), eosinophilic esophagitis (EoE), chronic rhinosinusitis with nasal polyps (CRSwNP), and asthma, with the aim of determining which of the mAbs has provided better results.

Key words: dupilumab, treatment, atopic dermatitis, eosinophilic esophagitis, chronic rhinosinusitis, asthma.

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RESUMEN

Las respuestas alérgicas representan un importante problema de salud debido a que los tratamientos actuales intentan disminuir la respuesta inmunitaria desencadenada, pero son incapaces de crear una memoria inmunológica que reduzca la intensidad de dicha respuesta. Esto significa que la intensidad de respuesta será igual en cada episodio.
Una respuesta alérgica se caracteriza por la liberación exagerada y prolongada de inmunoglobulina E (IgE), lo que desencadena respuestas inmunitarias innatas y la activación de linfocitos T hacia un fenotipo Th2, responsable de la liberación de interleucinas 3 y 4 (IL-3 e IL-4), así como la activación de los linfocitos B hacia células plasmáticas productoras de IgE.
Actualmente, los anticuerpos monoclonales (mAbs) se utilizan como tratamiento para diversas patologías alérgicas. Estos mAbs pueden inhibir las vías de señalización de diversas interleucinas, inactivando la diferenciación de linfocitos T y linfocitos B, así como la producción de IgE. Uno de los mAbs más versátiles para el tratamiento de diversas respuestas alérgicas es dupilumab. Este fármaco está diseñado para inhibir la cadena de señalización de la IL-3 y la IL-4. Específicamente, se une al receptor α de la IL-4 y al complejo de receptores inducidos por las citoquinas IL-13. dupilumab inhibe las IL-4 e IL-13 a través del receptor 1, deteniendo la liberación de IgE y citoquinas proinflamatorias. Este tratamiento puede utilizarse para controlar la respuesta inflamatoria provocada por los alérgenos.
Es importante destacar que el uso de dupilumab aún no está patentado como tratamiento de elección para las patologías alérgicas. Por este motivo, en esta revisión se recopilan los resultados de los estudios clínicos de dupilumab y otros mAbs en dermatitis atópica (DA), esofagitis eosinofílica (EoE), rinosinusitis crónica con pólipos nasales (RSC) y asma, con el objetivo de determinar cuál de los mAbs ha proporcionado mejores resultados.

Palabras clave: dupilumab; tratamiento; dermatitis atópica; esofagitis eosinofílica; rinosinusitis crónica; asma.

INTRODUCTION

One of the most pressing public health issues of our time is the ongoing epidemic of allergic diseases, including EoE, AD, CRS, and asthma. While these conditions affect different target tissues, they all involve fundamental mechanisms of allergic inflammation. In this article, we will focus on four of these conditions, EoE, AD, chronic rhinitis with nasal polyps, and asthma; and the promising monoclonal antibody dupilumab. With its demonstrated effectiveness and recommendations, dupilumab has shown significant promise in treating these conditions.

Allergies, also known as hypersensibility reactions type 1, are defined as an immunological response that arises from the interaction of antibodies of IgE with a trigger agent. In normal individuals, the IgE is the less common type of immunoglobulin in the blood serum and the IgE is uniquely produced when the system is threatened by parasitic infections. However, when individuals have a genetic susceptibility to allergies, IgE is produced against normal environmental agents, which in turn produces unnecessary immune responses, known as allergies.[1]

Subsequently, atopic diseases (reaction that generates an exaggerated response of the immune system) condition a Th2 response causing allergic diseases, mainly asthma, which promote the creation of cytokines (IL-4, IL-5 and IL-13) to induce the creation of antibodies for the elimination of extracellular microorganisms.[2]

Immunological and genetic studies have helped to identify the common allergic-inflammatory pathways that underlie many disorders, including those driven by the IL-4R pathway.[3] This pathway is driven by the fundamental role of IL-4 and IL-13 ligands, which activate the IL-4/IL-13/IL-4R axis and trigger Th2 cells to mediate the pro-allergic adaptive immune response. Understanding these pathways is critical for developing effective treatments for allergic and inflammatory conditions.[4] More precisely, IL-4 acts as a regulator of lymphocyte functions promoting the differentiation of naive T-cells; this differentiation is started by activating a naive T cell through antigen presentation done by the dendritic cells in T-cell zones of secondary lymphoid organs where IL-4 is scarce. This antigen/allergen presentation stimulates the T cell antigen receptor (TCR) which crosslinks in the presence of exogenous IL-4. The corresponding IL-4 receptor (expressed in naive T cells) is also stimulated by IL-4; these signals are transduced by STAT6 (Signal transducer and activator of transcription 6), which together with NFAT (nuclear factor of activated T cells), AP-1 (Activator protein 1), NF-KB (Nuclear factor kappa B), and other TCR

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induced signals activate the transcription of IL-4 and GATA3 (gene encoding transcription factor) which regulates the Th2 lineage commitment. Furthermore, due to the positive autocrine feedback loop generated by this mechanism, the differentiation of naive T cells is promoted to favour Th2 differentiation.[5] Afterwards, the Th2 cells stimulate the production of B cells, which undergo a change of class of the heavy chain of IgE and start to differentiate into 2 cell types: memory B cells and Plasmatic cells that produce IgE. These IgE molecules interact with the receptors FCER1 in mast cells and basophils which are, in turn, stimulated and degranulated, causing the symptoms of an allergic reaction.[6] For all these reasons, the IL-4R axis became one of the key targets in the fight against the ongoing epidemic of allergic diseases. Precision medicine aims to interrupt the inflammatory allergic response, attenuate or cancel the chronicity, and severity of the disease by attacking this axis through mAbs.

For example, dupilumab is a humanised antibody that belongs to the subclass 4 of immune globulins, it is designed to inhibit the signalling chain for IL-3 and IL-4, and acts through specific binding to the IL-4 receptor α and shared with the complex of receptors induced by IL-13 cytokines. Dupilumab also inhibits IL-4 via receptor pathway 1, whilst using receptor pathway 2 to inhibit both IL-4 and IL-13, thereby stopping the release of chemokines, IgE and pro-inflammatory cytokines.[7] This approach has recently been approved to treat eosinophilic esophagitis, atopic dermatitis, chronic rhinitis with nasal polyps, and asthma.

This review addresses the role of the IL-4R axis in the allergic inflammation process in the previously mentioned diseases and the advances that have been made with regards to the effect of dupilumab at clinical level with the objective of having a complete analysis of the effectiveness of this medicine. Trials that have studied other mAbs that appear during the research will also be included in order to compare their results with those of dupilumab and to see which mAb is the best therapeutic option so far for each particular disease.

METHODOLOGY

An advanced search was carried out from the year 2018 to the current year 2022 through PubMed, Web of Science, and Elsevier using the following keywords: dupilumab, treatment, and atopic dermatitis/ eosinophilic esophagitis/ chronic rhinosinusitis/ asthma (taking a disease at time). Clinical phase studies (randomised clinical trials, meta-analyses, and systematic reviews) were included in each of the metasearch engines, finding a total of 84 articles.

Inclusion and exclusion criteria: All information obtained from randomised and non-randomized preclinical and clinical trials, meta-analyses and systematic reviews conducted in humans and animals in spanish and english published in the last 5 years was searched with the keywords. Articles carried out in both sexes and in a population of all ages were included. Case reports, case series and those studies that will not discuss any mAb and the diseases in question were excluded.

For the inclusion of the articles, it was also considered that the trials had as their main theme the use of dupilumab for the treatment of each disease and in some cases that it was compared with other treatments and the p value was included, taking as statistically significant a p value < 0.05. The duration of treatment and the follow-up were also taken into account, together with that of conventional treatments for the efficiency and efficacy of each one in different groups of age, race and sex.

PATHOPHYSIOLOGY OF ALLERGIC DISEASES

The term allergy given in 1906 defines the hypersensitivity of the organism against exogenous substances (allergens). This process requires a previous sensitization against allergens in which they become antigens. Therefore, these processes have two clearly differentiated phases:

Sensitization phase: When the body produces IgE antibodies in response to substances such as pollens, which are normally harmless to the body, this is known as an allergic reaction. These substances are sometimes referred to as allergens and can include things like pollen, dust mites, or certain foods. The production of IgE in response to these substances is what triggers the body's immune response and leads to symptoms such as itching, swelling, and difficulty breathing. This facility for the production of IgE is the basis of a number of allergic (atopic) diseases, including most allergic conjunctivitis. The atopic trait, characterised by an increased susceptibility to allergic diseases, is largely determined by genetics and tends to run in families with high likelihood of inheritance. Therefore, atopic patients have an increased capacity for the production of IgE. In fact, the serum levels of this immunoglobulin are usually increased compared to the non-atopic population. It has also recently been suggested that the basis for its increased production depends on increased secretion of certain

lymphokines (IL-4), to the detriment of others (IFN). Given that IL-4 is produced by a subpopulation of T lymphocytes (TH2), while IFN- is produced by TH1. Since TH2 and TH1 behave antagonistically in many functions, it is considered that there would be an imbalance of these immunological responses in these patients. Among the TH2 lymphokines, IL-4 has a fundamental role in the production of IgE. Because IL-4 is critical for B cells to switch from producing IgM to IgE. IL-4 is also necessary to stimulate the TH2 response when there is a detriment of TH1. In fact, there is a dichotomy between both subpopulations of helper T lymphocytes, since TH2 lymphokines (IL-4, IL-10) functionally inhibit TH1 lymphocytes and vice versa, TH1 lymphokines (IFN-) suppress TH2 lymphokines.[8]

Effector phase (immediate hypersensitivity reaction): immediate hypersensitivity reactions are IgE-mediated and initiate with mast cell/basophil activation. First, IgE is bound to the membrane of these cells through FcRI receptors. This union (IgE-FcRI) is monovalent and does not induce signals inside the cell. The presence of the antigen against which some of these molecules react, produces their crosslinking and with it the aggregation of the FcRI to which they are attached. Receptor aggregation causes cell activation and release of mediators.[9] Therefore, it is necessary that at least two specific IgE molecules are involved in order for the aggregation to occur. FcRI receptors are coupled to enzyme systems (protein tyrosine kinases) that are activated after their aggregation. Activation of phospholipase C generates DAG (diacylglycerol) and inositol trisphosphate (IP 3) by acting on a membrane phospholipid (PIP 2, phosphatidyl inositol diphosphate). The first (DAG) is involved in the exocytosis of mast cell granules, by activating a protein kinase C that phosphorylates myosin microfilaments. The second (IP 3) mobilizes intracellular calcium, contained in the endoplasmic reticulum, which is required for the activation of calcium-dependent protein kinases involved in myosin phosphorylation and for the activation of phospholipase A2. This phospholipase, acting on another membrane phospholipid (phosphatidylcholine), releases arachidonic acid (leukotriene and prostaglandin precursor) and lysophosphatidylcholine (PAF precursor). The degranulation process occurs a few seconds after cell activation. The movement of the granules through the cytoplasm depends on energy (ATP) and the integrity of the cytoskeleton, being inhibited by increases in cAMP. The presence of membrane regions rich in hydrophobic lipids (lysophospholipids, monoacylglycerols) and deficient, due to consumption, in polar lipids (phospholipids), favours the fusion of the granules with the cell membrane, leaving its content outside in a process of exocytosis. Mediators performed and stored in mast cell granules are called primary mediators; its action is immediate after cell activation. On the contrary, the mediators that have to be synthesised after said activation are called secondary and exert their action more slowly and later. When the mast cells or basophils are already activated, it comes the release of the pharmacological mediators produced by these cells into the extracellular space, giving rise to allergic symptoms.[9,10]

When this response is exaggerated or is produced against a normally innocuous substance, we speak of a hypersensitivity mechanism that may cause immunological damage and/or clinical symptoms, this is due to the excessive production of Th2 lymphocytes because they generate a high amount of cytokines IL-4, IL-5 and IL-13 with the purpose of generating a high amount of cytokines IL-4, IL-5 and IL-13, IL-5 and IL-13 in order to stimulate IgE antibodies and eosinophil ls in the blood and also in the tissues, producing an inflammation that damages the epidermal barrier and this occurs due to damage, infection or continuous inflammation.[10]

It's important to remember that not all T cell epitopes induce tolerance and that peptides must bind directly to MHC II on antigen-presenting cells to induce tolerance. A recent article shown that these antigens processing independent T cell epitopes (apitopes) bind preferentially to steady-state dendritic cells (DC) in lymphoid organs. Steady-state DC express low levels of costimulatory molecules and hence presentation of T cell epitopes by them is tolerogenic. T cells responding to short peptides presented by steady-state DC become anergic and up-regulate expression of inhibitory receptors (CTLA- 4, TIM3, TIGIT and LAG3) and the transcription factors like MAF and NFIL3, that heads IL-10 production. In an IL-10 dependent manner, the resulting Tr1-like cells suppress the expression of costimulatory molecules on adjacent antigen-presenting cells, thus mediating suppression.[11]

Recent research has suggested that the development of tolerogenic Tr1 cells is driven by epigenetic priming of genes that define a regulatory gene signature. It is plausible that the mechanisms underlying the generation of both Foxp3 and Tr1 cells are similar for both allergens and self-antigens.[11]

Allergens

There are allergens in the different allergic diseases, in the case of atopic dermatitis there are two types of allergens these can be environmental, such as mites, fungi, pollens and animal epithelia, weeds, hot water, soaps, detergents,

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climate with extreme temperatures, humidity or excessive dryness, microorganisms (especially S. aureus, which is a common colonizer of the skin of atopic patients) and food allergens, mainly egg, milk, wheat, soy and peanut. We should assess the existence of a food or environmental allergy because children with atopic dermatitis are frequently sensitized to food, mainly egg, while adults are more sensitized to environmental allergens, being dust mites the most frequent.[12] In rhinosinusitis the main allergens are dust mites, anemophilous fungi, animal epithelium and pollen.[13] In asthma, exposure to environmental allergens such as pollen, animal epithelia, fungi, dust mites, etc. is a risk factor for sensitization. It is a risk factor for allergic sensitization and is considered the trigger for inflammatory phenomena. Childhood infection by certain viruses can cause damage to the bronchial mucosa, which may increase the likelihood of developing sensitivity to inhaled allergens later in life. Additionally, in eosinophilic esophagitis, the consumption of milk from certain animals (such as goats, sheep, and cows) can introduce bovine immunoglobulin G (IgG) proteins, lactoferrin, and serum albumin into the body, potentially triggering an allergic reaction.[14, 15]

IL-4 produced by TCD4 lymphocytes and the absence of innate immunity lead to the activation of the transcription factors STAT6 and GATA-3. The latter is the main regulator of the differentiation of this lymphocyte towards a Th2 phenotype, and enhances the expression of genes for IL-4, IL-5 and IL-13, which recognize the same allergen. Preformed mediators (histamine, tryptase, proteoglycans) and lipid mediators (prostaglandins and leukotrienes) cause early phase symptoms such as erythema, pruritus, sneezing, rhinorrhea, cough, bronchospasm and edema mainly caused by toll-like receptors (TLR), which bind viral, bacterial and fungal structures, inducing the production of defensins and cathelicidins (antimicrobial peptides).[10] The late phase is considered 6-24 hrs later and is characterized by the presence of edema and influx of de novo synthesized cytokines (IL-1, IL-3, IL-4, IL-5, IL-6, IL-13) which are released several hours after mast cells and basophils have been activated. Mast cell and basophil activation occurs when IgE antibodies, present on its cell surfaces binds to allergens and release inflammatory mediators by degranulation, the consequence of these is an alteration of innate immune response, with the reduction of antimicrobial peptides, will give way to increased bacterial and viral infections.[10, 16]

EOSINOPHILIC ESOPHAGITIS

Eosinophilic esophagitis (EoE) is a chronic inflammatory condition characterized by an immune response to food allergens in the esophageal mucosa. This inflammation can cause symptoms such as difficulty swallowing and food impaction in adults, and vomiting and abdominal pain in children.[15] The first guidelines for EoE considered as diagnostic criteria the presence of symptoms of esophageal dysfunction, eosinophilic infiltration of the esophagus (defined histologically as > 15 eosinophils per high power field), together with inability to respond to proton pump inhibitors (PPI) or, alternatively, the normal exposure of the esophagus to acid determined by pH-metry. Gastroesophageal reflux disease (GERD) and EoE were then assumed to be mutually exclusive disorders, with GERD being the only esophageal disease capable of responding to PPI treatment. However, this assumption was counterintuitive, since the a priori probability of the coexistence of both diseases was high. The first prospective series that systematically evaluated PPI treatment in patients with esophageal eosinophilia and symptoms suggestive of EoE showed that up to 50% responded to PPIs. Furthermore, clinical, endoscopic, and histological findings were indistinguishable between PPI responders and non-responders, thus there was a wide overlap between GERD (determined by esophageal pH monitoring) and EoE. After this study, subsequent guidelines excluded esophageal pH monitoring as a criterion for the diagnosis of EoE, but continued to consider response to PPIs as sufficient reason to rule out EoE. The definition of a new potential phenotype of the disease in 2011, was called PPI-responsive esophageal eosinophilia; Remitting EoE vs. PPI.[17]

Epidemiology

The prevalence of this condition has increased significantly, currently affecting one in every 2,000 individuals in Europe and North America. Positioning itself as the second cause of chronic esophagitis after GERD and the main cause of dysphagia and food impaction in children and young adults. Despite not being associated with mortality or risk of malignancy, its chronic nature and progressive behavior have a negative impact on the quality of life of patients.[16] EoE accounts for 7% of diagnoses among adult subjects referred for endoscopic examination due to esophageal symptoms, and this percentage increases to 23-50% if only patients with the most characteristic symptoms of the disease (dysphagia and food impaction are considered). In pediatric patients, the disease still seems to be underdiagnosed, so there are no specific figures in this regard. However, it is known that EoE can present at any age, showing incidence peaks between 30 and 50 years, respectively.[8]

The disease has also been shown to occur more frequently in men than in women, both in the pediatric and adult

population, with an odds ratio (OR) of 2.01 (95% CI: 1.63-2.48) in a meta-analysis of population studies.[18] On the other hand, studies of familial cases have shown that the occurrence of EoE within a family is much more strongly associated with environmental components than with genetic causes.[19] Likewise, an association between a single nucleotide polymorphism (SNP) in the thymic stromal lymphopoietin (TSLP) gene and another SNP in its receptor has been described. The latter is encoded in the pseudoautosomal region of the sex chromosomes.

Another risk factor is atopy, since patients with rhinitis, bronchial asthma and eczema, with a frequency significantly higher than that of the general population (however, there is no direct association between atopy and EoE so far).[16] IgE-mediated food allergy and treatment of food-induced anaphylaxis by oral immunotherapy have also been implicated in the development of de novo EoE.

Pathophysiology characteristics

Genetic, environmental and allergenic factors are involved in the pathogenesis of EoE. Understanding EoE as a secondary response to an immune response mediated by Th2 cells and not by IgE. Food allergens induce Th2 cells to produce IL-13, causing overexpression of eotaxin-3 (eosinophil chemoattractant) and periostin, in addition to downregulation of filaggrin and desmoglein 1, which contribute to impaired barrier function. Activated Th2 cells also produce IL-5, which is responsible for the proliferation and maturation of eosinophils, and apart from eosinophils, mast cells, basophils, and invariant natural killer T (iNKT) cells have been shown to contribute to the pathogenesis of EoE, as mast cells promote inflammation and fibrosis through the production of histamine.[16]

The first data on the evolution of the disease in the absence of treatment were provided by a Swiss series of 30 adult patients with a mean follow-up of 7.2 years, which documented the persistence of dysphagia and eosinophilic infiltration over time. In pediatric patients, a chronic character and frequent relapses were also demonstrated when treatment was discontinued.[20] Therefore, adults diagnosed with EoE during childhood continue to have symptoms and need treatment. Without treatment, esophageal fibrous remodeling and stricture is created in 47%, reaching up to 88% when the diagnostic delay goes from 2 to more than 20 years, and doubles with each 10-year increase in patient age at diagnosis.[21] Functional abnormalities detected by high-resolution esophageal manometry also increase as the disease prevails.

Due to its chronic and progressive nature, the disease can also cause anxiety, depression, sleep impairment and school problems in children, while in adults, EoE affects psychosocial functioning (due to the uncertainty about the long-term evolution of the disease, the prolonged use of drugs, restrictive diets and lack of social interaction due to the risk of food impaction), but not physical well-being or mental functioning. In any case, the quality of life worsens due to EoE.[17]

Diagnosis

In pediatric patients, the most common symptoms largely overlap with those of gastroesophageal reflux, and include vomiting, abdominal pain, refusal to feed, and failure to thrive. These symptoms should guide diagnostic suspicion and endoscopy always accompanied by biopsy, since endoscopic findings alone do not reliably establish a diagnosis of EoE. At least 6 biopsies should be obtained from two different locations in the esophagus (due to 100% sensitivity with this number of biopsies), typically in the proximal and distal half of the organ.[17] In them, areas with endoscopic abnormalities will be found, mainly whitish exudates and longitudinal grooves, where the maximum infiltration by eosinophils is seen. Biopsies should be taken regardless of whether the esophagus appears normal endoscopically, as this has been reported in 10% to 32% of adult and pediatric patients with the disease. Biopsies of the gastric and duodenal mucosa should also be obtained at the time of initial diagnosis in order to exclude eosinophilic gastroenteritis, especially in children or in case of other concomitant gastrointestinal symptoms.[22]

The histological criterion of obtaining 15 eosinophils per high-power field (HFP) or more provides uniformity for all patients while allowing EoE and GERD to be distinguished, since GERD is associated with a low eosinophil count, generally due to below 5 per CGA. However, it must be remembered that GERD and EoE are not mutually exclusive disorders and can coexist in the same patient. The cut-off point of 15 eosinophils by CGA has recently shown a sensitivity of 100% and a specificity of 96% in the diagnosis of EoE.[23] However, this threshold can be arbitrary, since the size of an AGC varies between microscope manufacturers and must always be evaluated within the clinical context, especially in those cases with counts compatible with EoE obtained from samples of asymptomatic patients.[17]

Once the diagnosis is established, symptoms and the presence or absence of eosinophilic inflammation in the mucosa of the esophagus in response to therapeutic inter-

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ventions should be monitored. To monitor inflammatory activity, attention should be paid to the development of the EoE activity index (EEsAI) specific to this disease, which quantifies the potential difficulties anticipated by patients when faced with foods with different consistencies, as well as changes in diet or behavior to solve them. It should also be noted that, although this practice is widespread, clinicians should not make assumptions about the biological activity of EoE solely based on symptoms or endoscopic findings, as biopsies are the only samples that have 100% accuracy. Sensitivity and therefore should infer more in diagnostic and therapeutic decisions.[21, 23]

Conventional treatment

To treat EoE, drugs and dietary modifications capable of inducing and maintaining remission of symptoms and of the eosinophilic inflammatory infiltrate of the esophagus are currently used, as well as increasing the caliber of the esophagus in case of stenosis (due to fibrous remodeling of the organ).

Proton-pump inhibitor

Recommended doses of PPIs in adults include omeprazole or equivalent 20-40 mg twice daily and 1-2 mg/kg in children. It is one of the most used treatments today; since PPIs are capable of achieving a histological remission of the disease (defined as a reduction of the eosinophilic infiltrate below 15 by CGA) in 50-57% of adult patients and 47% in the pediatric population.[17] A recent meta-analysis, including 33 studies and 619 patients with EoE, also showed symptomatic improvement in 60.8% (95% CI: 48.38-72.2%) of patients with PPIs; with the finding of having a better response when the total dose is divided into two doses per day.[24] The interruption of pharmacological treatment implies that the symptoms and esophageal eosinophilia recur after 3 to 6 months, therefore, it is suggested to use minimum effective doses to maintain adherence to treatment. With this, it has been shown (in a series of pediatric cases), that up to 78% reach remission after one year of ingesting half the dose used for induction.[24] In adults, clinical and histological remission occurs in up to 75% of patients with the same therapeutic characteristics.

Topical corticosteroids

Topical swallowed corticosteroids for the treatment of EoE seem to show a favorable safety profile (with esophageal candidiasis as the most frequent adverse effect in 5-10%). Viscous, orodispersible or aerosol formulas are encapsulated within them; but viscose is recommended because of a clinical trial that compared the efficacy of 1mg budesonide administered twice as a viscous solution and achieved up to 64% histological remission compared to 27% aerosol.[23] However, suppression of the pituitary-adrenal axis has been documented in small series of pediatric patients when given prolonged treatment with topical corticosteroids.[25] A reduction in plasma cortisol levels has also been documented (without adrenal insufficiency or impact on growth), so monitoring in the pediatric population is recommended.

The drug release system along the esophagus helps to achieve adequate and sustained mucosal coverage of the organ and therefore an adequate histological remission. However, the resolution of symptoms has been less effective, as there are several trials that show no significant difference between topical corticosteroids and placebo. The explanation is believed to be due to the use of inadequately validated scales to assess symptoms, the inclusion of patients with more severe disease, or the lack of standardization of patients' diets.[17]

Dietary treatment

One of the treatments of choice for EoE due to the absence of adverse effects if adequate nutrition is guaranteed. This has shown a potential efficacy comparable or superior to that of some pharmacological options, with a lower cost for health systems. So far there have been proposals with exclusive feeding using an elemental formula and empiric elimination of foods most likely to cause EoE. The targeted elimination of foods that cause allergic events is not recommended because the European Academy of Allergy and Clinical Immunology (EAACI) has recommended not performing these allergen tests to identify the foods responsible for EoE due to their poor diagnostic accuracy.[26] While empiric elimination has achieved histological remission of the disease in up to 74% of pediatric patients.

The elemental diet is the most effective dietary intervention, capable of inducing histological remission in 90.8% (95% CI: 84.7-95.5%) of patients of all ages. However, it turns out to be a difficult treatment since its taste makes the use of a nasogastric tube frequent, there is a lack of adherence and it has harmful social and psychological repercussions on patients.[27]

The sequential reintroduction of excluded foods under endoscopic and histological control makes it possible to perfectly identify the foods responsible for EoE in each patient. However, it requires exorbitant dietary restriction and a large number of endoscopies. This approach could be considered problematic, especially since it is known that the vast

majority of EoE patients have few foods that trigger their symptoms.[28]

Endoscopic dilatation

Dilation with balloons, bougies, or rigid dilators is the only endoscopic treatment available for EoE. Showing symptomatic improvement in up to 95% of patients (95% CI: 90-98%), with infrequent complications. Reported complications are perforation (0.38%), hemorrhage (0.05%) and hospitalization (0.67%), with no mortality.[29] However, esophageal dilation does not control the chronic inflammation that contributes to esophageal remodeling, so it must be accompanied by concomitant anti-inflammatory treatment (PPI, topical corticosteroids, or diet).

Alternative treatments (mAbs)

Patients with EoE respond poorly to traditional therapies. That is why there is currently ongoing research aimed at curing the disease or at least reducing the symptoms in ways that are much better than the current ones. These investigations focus on immunomodulators that claim to reduce EoE symptoms, including biological agents that target IL-5, IgE, IL-13 and IL-4.

Mepolizumab and reslizumab are two mAbs that are aimed at neutralizing IL-5, which is involved in the recruitment of eosinophils in the esophageal mucosa.[30] Local IL-5-producing Th2 cells are increased in active EoE; mepolizumab has shown a consistent decrease in esophageal eosinophilia but limited improvement in symptom scores compared to placebo. A randomized, blinded, non-placebo-controlled phase II trial enrolled 59 children with EoE intolerant or unresponsive to dietary therapy and steroids to receive mepolizumab at doses of 0.55, 25, or 10 mg/kg every 4 weeks for three doses. In it, the esophageal eosinophil count was reduced in all groups, with a reduction in the maximum count of 32.6% and in the mean count of 89.5%.[31]

Another phase II placebo-controlled trial in 11 adults with active EoE who received mepolizumab 750 mg weekly in two doses, followed by 1500 mg weekly in two doses if not in remission; showed that mepolizumab was safe and well tolerated, with limited non-statistically significant improvement in EoE-related symptoms versus placebo.[32]

On the other hand, infliximab, an IgG1, anti-TNF-α antibody, was studied in patients with EoE, without finding any success both clinically and histologically. A prospective study was conducted to determine the efficacy of TNF-α in decreasing esophageal eosinophilic inflammation in three adult patients with severe EoE. Subjects received two infusions of infliximab at 5 mg/kg at weeks 0 and 2. All concomitant treatments were discontinued for 4 weeks prior to infliximab, patients were subsequently followed up and as a result no significant effect of esophageal eosinophil numbers was obtained.[34, 35]

Omalizumab, an anti-IgE mAb, reduces symptoms associated with EoE, with little effect on esophageal eosinophilia on biopsy.[36] Therefore, the article highlighted that omalizumab may be effective in a small subgroup of EoE patients with mild disease and low peripheral eosinophil counts.[37]

IL-13 is also vital for the pathogenesis of EoE, through the induction of eotaxin-3 secretion by esophageal cells.[38] Two anti-IL13 mAbs and one anti-IL4/13 mAb have been tested in patients with EoE, with variable success. QAX576, a human anti-IL13 mAb dosed intravenously every 4 weeks, significantly improved esophageal intraepithelial counts and lowered eotaxin-3 levels compared with placebo in a phase II trial.[39]

Another humanized anti-IL3 mAb, RPC4046; it prevents IL-13 from binding to its two receptors (Rα1 and Rα2). RPC4046 recently met its primary endpoint in a phase II trial. To date, RPC4046 has been shown to improve endoscopic characteristics and mean eosinophil count, compared to placebo.[40] Although not statistically significant, there was a reduction in symptoms, particularly dysphagia, in the treatment groups compared to placebo. Adverse events included headache, arthralgia, and upper respiratory tract infections in the high-dose treatment arm.

Dupilumab, was evaluated in a phase II study of EoE by Hirano et al.[41] In this study, the drug was dosed weekly, and unlike the other mAbs, dupilumab significantly reduced both dysphagia and peak eosinophil count at 10 to 12 weeks of treatment. The study was conducted in adults with active EoE (2 episodes of dysphagia/week with a maximum esophageal eosinophil density of 15 or more eosinophils per high-power field). The participants were randomly assigned to groups receiving weekly subcutaneous injections of dupilumab (300 mg, n 1⁄4 23) or placebo (n 1⁄4 24) for 12 weeks. The primary endpoint was the change from baseline to week 10 in the Straumann Dysphagia Instrument (SDI) patient-reported outcome (PRO) score. Histologic features of EoE (peak esophageal intraepithelial eosinophil count and histologic EoE scores), endoscopically visualized features, esophageal compliance, and safety were also evaluated. The mean SDI PRO score was 6.4 when the study began. In the dupilumab group, SDI PRO scores decreased by a mean value of 3.0 at week 10 compared to a mean decrease of 1.3 in the placebo group. At week 12, dupilumab reduced peak esophageal intraepithelial eosinophil count by a mean

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of 86.8 eosinophils per high-power field (107.1% reduction; P<0.0001 vs. placebo), severity score of histology scoring system (HSS) of EoE in 68.3%. (P<0.0001 vs. placebo), and the endoscopic baseline score by 1.6 (P 1⁄4 0.0006 vs. placebo). Dupilumab also increased esophageal compliance by 18% versus placebo (p<0.0001). Adverse effects included injection site erythema (35% vs. 8% in the placebo group) and nasopharyngitis (17% vs. 4% in the placebo group).[42] Table 1 shows a comparison of results and negative effects of mAbs in eosinophilic esophagitis.

Table 1. Comparison of results and negative effects of mAbs in eosinophilic esophagitis

Drugs	Biological effect	Negative effects	Research results
Mepolizumab	Neutralizes the cytokine IL-5 which in turn reduces the recruitment of eosinophils in the esophageal mucosa.[31]	Even though it reduces the esophageal eosinophilia, it has no significant symptom improvement when compared to placebo.[31]	It was reported that mepolizumab reduced the esophageal eosinophil count significantly in pediatric patients that undertook the treatment.[32] It was demonstrated that mepolizumab was safe and well tolerated by adults; however, no significant improvement of the symptoms was reported.[33]
Reslizumab	Neutralizes the cytokine IL-5 which in turn reduces the recruitment of eosinophils in the esophageal mucosa.[31]	Even though it reduces the esophageal eosinophilia, the symptoms persisted.[31]	It was reported that symptoms of EoE were reduced by the treatment on some level with patients reporting no dysphagia nor abdominal pain on a relatively normal diet.[35]
Omalizumab	This anti-IgE mAb reduces symptoms related to EoE but does not reduce esophageal eosinophilia.[36]	Does not reduce esophageal eosinophilia.	Omalizumab may be effective in a subgroup of patients with mild disease and low peripheral eosinophil counts.[37]
QAX576	Targets IL-13 (involved in the induction of eotaxin-3 secretion) which is vital for the pathogenesis of EoE.[38]	The family of mAbs anti IL-13 and anti IL-4/13 have had variable results.[39]	It has been reported that this treatment has reduced the eotaxin-3 levels and improved esophageal intraepithelial counts.[39]
RPC4046	It targets and prevents IL-13 from binding to its two receptors (Rα1 and Rα2).[40]	The family of mAbs anti IL-13 and anti IL-4/13 have had variable results. Adverse events such as: headache, arthralgia, and upper respiratory tract infections.[40]	It has been shown to improve endoscopic characteristics and mean eosinophil count, compared to placebo. There has been a non statistically significant reduction in symptoms, particularly dysphagia.[40]
Infliximab	It is a chimeric IgG1 monoclonal antibody that inhibits TNF-α.		Does not have the greatest potential for treating EoE biologically due to lack of success in both treating eosinophilia and reducing symptoms.
Dupilumab	Targets the shared alpha subunit of IL-4 and IL-13 receptors.[41]	Injection site erythema and nasopharyngitis.[42]	It has been reported that dupilumab significantly reduced dysphagia and peak eosinophil count at 10 to 12 weeks of treatment. The patient-reported outcome score was reduced from 6.4 to 3.0 at week 10 with dupilumab treatment.[42]

ATOPIC DERMATITIS

Atopic dermatitis (AD) is defined as a chronic skin disorder that presents with itchy rashes, inflammation, continuous redness and scaling. In addition to skin conditions, AD is often a precursor to other conditions, as people with this skin disorder typically develop allergic rhinitis or asthma.[43] Data from the World Health Organization (WHO) indicate that AD is the result of predisposition to abnormal immune reactivity, mediated by IgE against allergens. Due to this, the current treatment of the disease consists of topical ointment applications and the avoidance of soap and other irritants and the skin lesions also often cause anxiety and stigmatization by peers.[44]

Epidemiology

Actually, AD has a predilection for white ethnicity and those populations located in urban areas, with a lower prevalence in rural areas. However, the disease does not have a predilection for women or men.[45]

Actually, the number of cases has increased, showing growth parallel to industrial development. Between 15%-20% of children and 1-3% of adults in the world population suffer from this atopic disease.[5-7] Within the pediatric population, 45% of cases present before 6 months, 60% in the first year of life and 85% before 5 years.[46]

In Latin American countries, especially in the center of Colombia, Cuba, Ecuador, Honduras and Nicaragua; Its prevalence has increased considerably in recent decades, placing Mexico with a prevalence of 20%. Of the 20%, 60% of the cases are diagnosed during the first year of life and 70% of the patients remit before the age of 16.[9]

Pathophysiology

The pathophysiology of AD is related to metabolic deregulation and deterioration of the skin barrier. Basically, there is an imbalance between the profile of Th2 cytokines (IL-4, IL-5) that facilitates the production of IgE and the expression of antigen presenting cells. The latter interact with circulating T lymphocytes, enhancing the inflammatory response. The set of these conditions in the immune response favors bacterial and viral infections in patients with AD.[44, 47, 48]

It is a heterogeneous and multifactorial disease, caused by the interaction of environmental and immunological factors. This type of eczema is related to a genetic variation that alters the skin's ability to provide some protection against bacteria, allergens and irritants. That is why genetically susceptible individuals develop a certain sensitivity to environmental elements and allergic conditions.[49, 50]

Diagnosis

The diagnosis of AD is mainly based on the clinical signs, morphology and distribution of the lesions. Different criteria have been established in order to support the classification. The most widely used for AD was developed in 1980 by Hanifin and Rajka, and approved by the American Academy of Dermatology.[44, 51, 52]

To provide the correct treatment, it is necessary to stage patients according to the severity of the disease. The Severity Scoring Atopic Dermatitis (SCORAD) and Eczema Area and Severity Index (EASI) scales are used to assess the severity of symptoms that occur with atopic dermatitis, which ranges from mild (SCORAD <25, EASI <7), moderate (SCORAD 25-40, EASI 7.1-21), severe (SCORAD >40, EASI 21.1-50) to very severe (EASI 50-72).[21]

These scales are calculated by observing the different affected areas of the body and determining the percentage that is affected, as well as whether it occurs and at what level of severity Erythema, Edema, Excoriation and Lichenification, in SCORAD Dryness and Exudate are added and the subjective symptoms such as itch or loss of sleep.[22]

The EASI and SCORAD scales are the most used and most effective for the diagnosis of the severity of the symptoms presented in patients affected by atopic dermatitis, likewise it can be used for the evaluation of the results that may or may not be presented with the application of a new drug or treatment. The parameters to be used in this investigation will be from the moderate to severe range because they are the ones in which the activity of the antibody present in the drug has been shown to be more effective, which can be observed thanks to the results presented in the two scales to be used.[22]

Conventional treatment

Topical corticosteroids

They are the treatment of choice for the disease, they are responsible for reducing the inflammation and itching of outbreaks caused by AD, with subsequent maintenance

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limited to 20 weeks after the initial treatment to reduce the risk of relapse. These act on a variety of immune cells, including T cells, monocytes, macrophages, and dendritic cells, interfering with antigen processing and suppressing the release of proinflammatory cytokines.[53]

Calcineurin inhibitors

It stimulates binding to proteins in the cytoplasm, forming a complex that inhibits the activity of the enzyme calcineurin phosphatase, which blocks the activation of calcineurin-dependent T cells, through the inhibition of the production of proinflammatory cytokines and of inflammatory mediators in AD. They have also been shown to affect mast cell activation, and tacrolimus in particular decreases both the number and costimulatory capacity of epidermal dendritic cells, so the duration of this treatment should be adapted to the intensity and persistence of the disease.[54, 55]

Currently, there is no completely effective and specific treatment, so AD is a persistent disease that until now has no definitive cure.[45, 56] Conventional therapies, such as corticosteroid therapy or calcineurin inhibitors; they are moderately effective, but they are not recommended in the long term due to the risk of toxicity and the number of side effects they confer. Therefore, the investigation of an effective drug with a low-risk profile is still necessary with the aim of reducing the number of hospitalizations for severe AD by reducing the number and severity of exacerbations of the disease.[52]

Alternative treatments (mAbs)

The monoclonal antibody is capable of effectively inhibiting IL-4 and IL-13 signalling, with a fundamental effect on the TH2-type response, which is one of the most important factors in these diseases due to atopy. Atopy is a predisposition to an immune response against diverse antigens and allergens leading to CD4+ Th2 differentiation and overproduction of IgE. The clinical consequence is an increased propensity to hypersensitivity reactions. Allergic bronchial asthma and allergic rhinitis are the most common manifestations of atopy followed by atopic dermatitis and food allergy. Two or more clinical diseases can coexist in an individual at the same time or at different times.[7] The monoclonal antibodies also contribute directly to maintaining the epithelial barrier that is affected in AD through the differentiation of keratinocytes and barrier proteins, lipids, and the production of antimicrobial peptides.[51-53]

Few anti-monoclonal bodies have been tested for this type of condition, like lebrikizumab, a monoclonal antibody against IL-13. In a phase II CT in 209 adult patients with moderate to severe AD, with an EASI-50 stage, there were non-negligible responses in the placebo group, which could be attributed to the concomitant use of topical corticosteroids.[57]

Dupilumab was first approved internationally in 2017 for the treatment of moderate to severe atopic dermatitis in adult patients.[58] In 2020, the FDA approved its use for atopic dermatitis in pediatric patients. It has multiple phase III studies that apply this drug to patients and analyze its effects compared to conventional treatments. That is why it is important to analyze all the information on the use of IL-4/IL-13 dupilumab in patients aged 1-5 years who suffer from the disease and conclude the therapeutic improvements that have been seen thanks to its administration; This is important since many pediatricians are still unaware of its adverse effects and benefits.[6, 58]

Dupilumab was recently accepted as a treatment for AD in adults, but not for pediatric patients. Research to accept this treatment in children continues in phase III studies (with many already completed to date), which compare the IL-13/IL-4 mAb with the treatment used up to now (corticosteroids). From the search in the meta-analyses, 8 articles were the most relevant to use in this research. Among these, one points out that dupilumab administered for two weeks was more successful than placebo, with p=0.0001. In addition, in the analysis with the exposure for a longer time, a p=0.0001 was seen within one month, with greater relevance than in the one with the duration of two weeks. It was also seen that dupilumab, compared to placebo, improved symptoms in children aged 6 to 11 years and a dose of 300 mg for a period of one month, weighing less than 30 kg.[58-62]

One trial found that treatment with dupilumab and corticosteroids in children with severe atopic dermatitis produced no clinically relevant mean change.[61] However, another trial with statistically significant results indicated that the use of dupilumab combined with corticosteroids in adults with a history of inadequate response or intolerance to cyclosporine does help to improve the symptoms of the disease; obtaining a P< 0.001 against placebo combined with corticosteroids.[63-65]

Also, through the Bieber study, it was concluded that the monoclonal antibody abrocitinib is more effective than dupilumab, with a reduction of up to 48% against 36.6%, respectively. The placebo in this study showed a short 12% reduction.[66]

Regarding administration time, some studies have demonstrated that dupilumab, in combination with topical cortico-

steroids, was more effective when administered every two weeks at a dose of 300mg, compared to weekly administration. Both dosages, however, were found to be more effective than placebo and topical corticosteroids in reducing the EASI score. Giving a reduction of 40% and 43% against 11% respectively.[67] It was also seen that the administration of dupilumab at a dose of 200-300 mg decreased the EASI scale score by more than 10 points compared to the placebo group, and within this result there was no significant difference between giving the dose every 2 weeks or every month.[61] And the dose of 3mg/kg of dupilumab in children from 2 to 6 years old, turned out to lower the suffering of the disease according to the EASI scale than the dose of 6 mg/kg. However, in children aged 6 months to 2 years, the difference between giving 3 mg/kg and 6 mg/kg was minimal.[68] Finally, it was seen that the use of dupilumab 600 mg had a significant improvement, giving a final EASI score of 65 points with dupilumab, against 75 points given the placebo treatment.[69] See Table 2 in which a comparison of results and negative effects of mAbs in atopic dermatitis is enlist.

Table 2. Comparison of results and negative effects of mAbs in atopic dermatitis

Drugs	Biological effect	Negative effects	Research results
Lebrikizumab	Monoclonal antibody against IL-13.[57]	The negative effects are conjunctivitis and headache.[57]	In a phase II CT in 209 adult patients with moderate to severe AD, with an EASI-50 stage, there were non-negligible responses in the placebo group, which could be attributed to the concomitant use of topical corticosteroids.[57]
Dupilumab	Inhibits the signaling chain for IL-3 and IL-4.[59]	It is an effective treatment; however, other monoclonal antibodies have proven to be more effective.[66]	Dupilumab showed to be more effective when it is administered every two weeks. Dupilumab showed to be more effective in adults when it's combined with corticosteroids.[60-63]

ASTHMA

Asthma is a chronic heterogeneous disease that represents a reversible obstruction to airflow, this is based on a hyperreactivity of the airway in terms of inflammation of these in its bronchial sector.[70] Asthma exacerbations are a leading cause of hospitalizations and emergency department visits, and are responsible for over 3,000 deaths per year. Asthma also carries a large financial burden, with a higher cost burden for those with poorly controlled asthma and in low-income countries.[71]

Epidemiology

Asthma is a pathology that affects more than 300 million adults and children worldwide. According to the database drawn by "The International Study of Asthma and Allergies in Childhood" the prevalence of asthma in school children has been estimated at 9.4%; in Latin America from 11.2% and in Mexico from 2.2 to 12.5%.2. An important factor is smoking, as it leads to more hospitalizations and a rapid decline in lung function in asthmatics.[72]

Pathophysiology

Type 2 inflammation with Th2 cytokines, including IL-13 and IL-4, which promote the development of airway goblet cells that result in increased mucous secretion and nitric oxide synthesis, and promote increased airway contractility. Smooth muscle, as well as a greater production of immunoglobulin E creates an increase in bronchial remodeling processes through the differentiation of fibroblasts to myofibroblasts.[71, 73]

Diagnosis

The most frequent respiratory symptoms in asthma are wheezing, dyspnea and cough, these usually worsen at

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night (in patients under treatment it reveals an ineffectiveness of this). It is important to define the severity of asthmatic symptoms, the need to administer steroids, to hospitalize the patient or to administer intensive care treatment. The types of asthmatic triggers in each patient and their recent exposure to them should be determined. During physical examination, it is important to note dyspnea along with tachypnea, use of accessory respiratory muscles, and cyanosis. Wheezing and rales can be found throughout the chest, which are more intense during expiration than inspiration. Localized wheezing may indicate endobronchial injury. When asthma is adequately controlled, the physical examination may be normal.[74] Pulmonary function tests called spirometry have a reversibility of forced expiratory volume in 1 second (FEV1) = 12%, with diurnal variability of peak expiratory flow (PEF).[75]

Conventional treatment

Short-acting β2-adrenergic agonists

They act as fast-acting bronchodilators, they are used for punctual symptomatic relief, regardless of severity, in exacerbations. It is recommended in cases of mild to moderate asthma that require combination with short-acting anticholinergics.[71]

Fast-acting anticholinergic drugs

They are rescue bronchodilators, the most widely used is ipratropium bromide administered by inhaled route, used as an alternative to β2-adrenergic agents in patients with significant side effects.[71]

Systemic glucocorticoids:

They reduce the progression of asthma attacks, the need for urgent care, hospital admissions and mortality. These inhibit bronchial inflammation, increase the number and sensitivity of β2-adrenergic receptors, and inhibit eosinophil function. They are used in moderate or severe cases and should only be used as long-term maintenance treatment, always in the lowest possible dose to avoid the appearance of possible side effects such as adrenal suppression, osteoporosis, high blood pressure, hyperglycemia, etc.[71]

Inhaled glucocorticoids

Administered alone or in combination with other drugs, they are the basis of asthma treatment, reducing symptoms, the degree of bronchial hyperresponsiveness, the frequency and severity of exacerbations and improving lung function. The benefits are observed with relatively low doses, but in some cases and in relation to the phenotype, higher doses are required.[71]

Alternative treatments (mAbs)

Mepolizumab

It is an IgG1k-type monoclonal antibody that targets IL-5 and prevents its interaction with the α-chain of the IL-5 receptor. Intravenous and subcutaneous mepolizumab has been compared with placebo in 576 patients. Mepolizumab significantly reduced the rate of asthma exacerbations; the reduction was 47% intravenously and 53% subcutaneously. Finally, positive effects accompanied by an increase in expiratory volume were obtained, in addition to reducing exacerbations and improving asthma symptoms with the aim of having a better quality of life.[76]

Reslizumab

It is an anti-IL-5 monoclonal antibody that disrupts eosinophil maturation and promotes programmed cell death. Two multicenter, double-blind, parallel-group, randomized, placebo-controlled phase 3 trials were conducted involving patients with uncontrolled asthma aged 12 to 75 years. As a result, reslizumab was found to significantly reduce asthma exacerbations.[76]

Dupilumab

A phase 3, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of dupilumab in patients with severe asthma dependent on oral glucocorticoids. This study concluded that dupilumab reduced oral glucocorticoid use concurrently with severe exacerbations and increased FEV1. Although, there was a greater presence of transient blood eosinophilia in patients treated with the monoclonal antibody compared to placebo. The use of glucocorticoids against placebo was a decrease with $P < 0.001$. 80% vs. 50% of patients had a dose reduction of at least 50%, 69% vs. 33% had a dose reduction to less than 5 mg per day, and 48% vs. 25 % completely discontinued the use of oral glucocorticoids. On the side of severe exacerbations, it was 59% lower than that of the placebo group and resulted in an FEV 1 that was 0.22 liters (95% CI, 0.09 to 0.34) higher.[77]

Evaluating the efficacy of dupilumab, in three pivotal controlled trials versus placebo phase 2b or 3 from 24 to 52

weeks in patients ≥ 12 years, with moderate to severe asthma not controlled on inhaled corticosteroid treatment or severe asthma dependent on oral corticosteroids, a decrease in the rate of severe exacerbations, along with improvement in lung function at p<0.001, their asthma control at p<0.01, and quality of life in each patient at p<0.01. In addition, it reduced doses of oral systemic corticosteroids without affecting control. Currently in patients ≥ 12 years of age who have moderate or severe asthma with type 2 inflammation/eosinophilic phenotype, uncontrolled despite conventional treatments or in those with dependence on oral systemic corticosteroids for control, this type of treatment is used. It significantly reduced with a p<0.001 of some inflammatory biomarkers associated with type 2 response.[78]

Liberty Asthma Quest, a phase 3, randomized, double-blind, placebo-controlled clinical trial using dupilumab at a dosage of 200 mg or 300 mg given every 2 weeks, reported a significant reduction in severe asthma exacerbations compared to a volume-equivalent placebo (1.14 mL or 2.0 mL, respectively, at p<0.001. In addition, baseline total IgE levels were proportionally lower in patients at p<0.0001 as opposed to placebo.[79] To know the comparison of negative effects of mAbs in asthma see Table 3.

Table 3. Comparison of results and negative effects of mAbs in asthma.

Drugs	Biological effect	Negative effects	Research results
Mepolizumab	IgG1k-type monoclonal antibody that targets IL-5 and prevents its interaction with the α-chain of the IL-5 receptor.[76]	Possible adverse effects register were chest tightness, coughing, shortness of breath, fainting and dizziness.[80]	Positive effects are obtained along with an increase in expiratory volume and improvement of asthma symptoms, as well as a significant reduction in the rate of asthma exacerbations, with the aim of having a better quality of life.[76]
Reslizumab	It is an anti-IL-5 monoclonal antibody that disrupts eosinophil maturation and promotes programmed cell death.[76]	The most frequent are asthmatic crises, headache and nasopharyngitis.[81]	As a result, reslizumab was found to significantly reduce asthma exacerbations.[76]
Dupilumab	Inhibits the signaling chain for IL-3 and IL-4.	Dupilumab causes greater presence of transient blood eosinophilia.[77]	Dupilumab reduces oral glucocorticoid use, severe exacerbations by 59% when compared with the placebo group and increases FEV1.[76] Total IgE levels were proportionally lower in patients treated with dupilumab.[77]

CHRONIC RHINOSINUSITIS WITH NASAL POLYPS

Chronic rhinosinusitis (CRS) is an inflammation of the nasal mucosa and paranasal sinuses with four cardinal symptoms: nasal obstruction, drainage, loss of smell, and facial pain, for at least, the last three months. Factors associated with nasal polyposis include bacterial, fungal, viral infections, allergies, and genetic predisposition. It can be classified into two phenotypes according to the presence or absence of nasal polyps, which will apparently differ in the pathophysiological mechanisms and in the response to the different treatment options.[82]

The main bacteria that cause the disease with nasal polyps are Staphylococcus aureus and Haemophilus Influenzae among the aerobes and Prevotella and Peptostreptococcus among the anaerobes. The increased consumption of fermented foods, together with environmental changes, can cause alterations in the bacterial flora of the mouth, nasal cavity and intestine, which has led to an increase in patients.[83]

Epidemiology

In allergic rhinitis, its global prevalence is 12.9%; in children in Latin America it is 14.6% and in our country it varies from 3.6 to 12%.3. The prevalence of CRS is 22-45% of patients with asthma. The prevalence of chronic polypoid rhinosinusitis in the adult population has been estimated. From 2

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to 4%, it is frequently found in the fourth and fifth decades of life, predominating in males with a 2:1 ratio. This condition is rare in childhood and has been related to cystic fibrosis. In addition, Woakes syndrome is described, which is defined as deforming ethmoiditis with widening of the nasal pyramid due to polyposis since childhood.[84]

Pathophysiology

It is based on the deregulation of immune responses driven by thymic stromal lymphopoietin with the activation of mast cells by an innate type 2 response driven by cysteinyl leukotrienes, and IL-33, whose epithelial expression in nasal polyposis and associated with disease exacerbated by aspirin.[4] Furthermore, it is characterized by the inflammation provided by Th2, which increases IL-5, IL-13 and eosinophils in the polyps. In addition, there is no participation of arachidonate 15-Lipoxygenase (ALOX15), which provides 15-lipoxygenase A, losing its function, and there is no protection against nasal polyps or CRS due to metabolites that activate macrophages towards an M2 phenotype.[85]

Diagnosis

The four cardinal symptoms are nasal obstruction, drainage, loss of smell, facial pain or tightness, these last for at least three months.[83] The use of nasal endoscopy is used for the visualization of edema or obstruction of the nasal mucosa, nasal polyps or secretions. In addition, it serves to classify the pathology and focus the medical or surgical treatment.[80] Other symptoms may include bodily pain and consequent emotional change.[86, 87]

Conventional treatment

Steroids

Topical corticosteroids can be used to decrease the size of the nasal polyp, decrease rhinosinus symptoms, and improve the patient's quality of life; while oral corticosteroids can improve symptoms, but with severe systemic side effects.[84]

Antileukotrienes

Montelukast is an example of this, they can be used as adjunctive therapy to intranasal corticosteroids.[82]

Antibiotics

Amoxicillin with clavulanic acid is the first-line drug. Medication alternatives include clindamycin and combinations of metronidazole with a second or third generation cephalosporin, a macrolide or trimethoprim sulfamethoxazole, these are usually given in seven days, but can be prolonged in case of worsening.[82, 83]

Surgery

It is indicated in patients with orbital or intracranial complications of acute rhinosinusitis refractory to drug treatment, chronic rhinosinusitis with persistent sinonasal infection and purulent discharge, cystic fibrosis, ciliary dyskinesia, dacryocystitis due to sinusitis and resistant to medical treatment, fungal rhinosinusitis.[82, 83]

Alternative treatments (mAbs)

An international, multicenter, randomized, placebo-controlled, double-blind, phase III study looked at the effect of dupilumab on intractable chronic rhinosinusitis with nasal polyps in Japan. Patients on a background of mometasone furoate nasal spray, received 300 mg of dupilumab every 2 weeks for 52 weeks (group A) or 300 mg of dupilumab every 2 weeks for 24 weeks, followed by the same 300 mg of dupilumab but every 4 weeks for the next 28 weeks (group B), or placebo. Co-primary endpoints were at week 24 with nasal polyp score (NPS), nasal congestion (NC) score, and sinus Lund–Mackay CT (LMK-CT) scores. The next symptoms were assessed during the 52-week treatment period; sense of smell, health-related quality of life. Of 49 patients enrolled, 45 completed the study and at week 24 the mean improvement versus placebo were as follows: NPS (Group A: $P < .0001$ and group B: $P = .0011$; NC score (Group A: $P < .0001$ and group B, $P < .0001$); and LMK-CT (Group A: $P = .0005$ and group B: $P = .0425$). Also, the most common treatment-emergent adverse event in dupilumab and placebo-treated patients was nasopharyngitis.[88]

Benralizumab targets the IL-% receptor leasing to signal degradation and apoptosis. OSTRO used in the phase III study with chronic rhinosinusitis with polyps and severe symptoms resistant to treatment with intranasal corticosteroids, used to dosage at 30 mg or placebo every 4 weeks for the first 3 doses and every 8 weeks, presented significant results with $p<0.005$ and improvement in nasal obstruction score compared to placebo at week 40. In addition, sense of smell was shown to be $p=0.003$ against placebo at week 40.[89]

In the SINUS-24 and SINUS-52 randomized, multicenter, double-blind, placebo-controlled, parallel-group studies evaluating dupilumab as an add-on treatment to standard of care in adults with severe chronic polyp rhinosinusitis. Dupilumab was associated with greater improvement versus placebo in patients with ≥3 prior sinus surgeries than in patients without prior surgery at $p < 0.05$. The dosage was in the first group subcutaneous dupilumab 300 mg or placebo every 2 weeks for 24 weeks, and in the second group they were given subcutaneous dupilumab 300 mg every 2 weeks for 52 weeks.[90]

In a phase II study in adults randomized, double-blind, placebo-controlled, refractory to intranasal corticosteroids given dupilumab added to mometasone furoate nasal spray, at 16-week, dupilumab reduced the burden of nasal polyps compared with corticosteroids alone, along with improvement in nasal congestion and airflow, sense of smell, quality of life, and other nasal symptoms at $p<0.05$ versus placebo.[91]

DISCUSSION

It has been demonstrated in different studies that dupilumab has been favored in various allergic pathologies and is used as a key factor for the treatment of these, the most important of the use of this drug inEoE, AD, and CRS with nasal polyps and asthma is described below.

The EoE still has areas to investigate; It is not yet known whether it has different phenotypes that can guide a physician in choosing a particular treatment modality. Further studies are also needed to determine exactly how exposure to aeroallergens and environmental allergies (along with associated symptoms) contribute to the treatment of EoE. Well, it is not yet known why the chronic use of antihistamines and nasal corticosteroid sprays affects the control of EoE. What is known so far is that dupilumab turns out to be the mAb drug with the best results for this disease, compared to other mAbs that fail to reduce the symptoms (dysphagia), the histological characteristics of the disease and the abnormal endoscopic characteristics at the same time compared to placebo.[41, 42]

Speaking of AD, the results were statistically significant and varied between articles that administered different doses to different types of population. Among the most relevant results, it was observed that the administration of dupilumab together with topical corticosteroids was more effective when administered every 2 weeks than when given every week.[61] And both administered every week and every 2 weeks, a much lower EASI result was observed than that found with placebo+topical corticosteroids, which indicates that the disease responds much better to mAbs than to the current treatment. It was also demonstrated that the administration of dupilumab decreased the EASI score by more than 10 points compared to the placebo group, with no significant difference found between administering the dose every 2 weeks or every month and having favorable results.[66]

On the other hand, the effective dose in pediatric patients was observed for the first time. Previously, no study had dared to test the dose in children because of the risk involved. But Paller AS., Siegfried E., et al. were the first to administer 3 mg/kg and 6 mg/kg of dupilumab to children between 2 and 6 years of age and managed to see that the disease conditions according to the EASI scale were satisfactory.[68]

In asthma, a significant improvement has been demonstrated with dupilumab, since in the studies conducted, an efficiency of improvement in the prevention of exacerbations was observed, in the quality of life of the patients and in the decrease in the use of medications. Corticosteroids, with mild transient blood eosinophilia as a result of treatment versus placebo in each trial. And a decrease in initial total IgE levels, with significant p values, and an increase in FEV1.[76, 77]

As shown in Table 4, in chronic rhinosinusitis with nasal polyps, an improvement in resistance to conservative and surgical treatment was reported, along with an improvement in patients quality of life, a decrease in inhaled and systemic corticosteroids was demonstrated, improvement in nasal obstruction was observed as an outcome, and a significant p-value was obtained in each of the trials.[87-91]

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Table 4. Comparison of results and negative effects of mAbs in chronic rhinosinusitis

Drugs	Biological effect	Negative effects	Research results
Dupilumab	Inhibits the signaling chain for IL-3 and IL-4.[88]	Side effects of dupilumab treatment include cough, headache, fever, runny nose, and sore throat. [90]	Dupilumab used a significant improvement at week 24 versus the placebo.[87] It showed to be effective in patients who underwent more than 3 sinus surgeries.[89] In addition with mometasone furoate nasal spray showed and improvement of reduction of the burden of nasal polyps, nasal congestion, sense of smell and quality of life.[90]
Benralizumab	Benralizumab targets the IL-5 receptor leading to signaling degradation and apoptosis.[89]	The most frequent adverse effects are: nasopharyngitis and upper respiratory tract infection.[89]	OSTRO conducted a study where 413 patients were randomized (207 in the benralizumab group and 206 in the placebo group). Benralizumab significantly improved NPS and nasal block score compared with placebo at week 40 (P≤ 0.005).[89]

CONCLUSIONS

Monoclonal antibodies have been found to be more effective than other treatments for atopic diseases. In the case of asthma, the use of dupilumab in conjunction with oral corticosteroids has shown significant promise, with some patients able to reduce or even suspend their use of oral corticosteroids entirely and achieve better control over their symptoms. Similarly, in chronic polypoid rhinosinusitis, dupilumab has been found to improve patients' sense of smell and quality of life even after multiple surgeries. However, more studies are necessary to standardize dosages and application methods across different allergic pathologies, and to analyze the long-term effects of these treatments as potential cure options.

Future projections:

Inclusion of clinical trials that are published, in order to enrich the review of as much updated information as possible. In future research, the use of other mAbs and their comparison with dupilumab will also be integrated, to find out the best treatment for the diseases. Until now, the best option for any of these diseases continues to be dupilumab, as it is the drug with the best statistically significant results.

CONFLICT OF INTEREST

There was no affiliation with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), and non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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