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Original research

Comparison of efficacy between face-to-face and online consultation against overweight and obesity

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ABSTRACT

Introduction: Overweight and obesity have progressively increased in recent years. Online consultation has become a useful tool for healthcare professionals and patients that cannot be assisted through face-to-face consultation. **Objectives**: Our study aimed to compare the efficacy between online and face-to-face consultation as a strategy in the management of overweight and obesity. **Material and Methods:** An experimental, cross-sectional study was carried out in 88 patients between 25-30 years old. Patients were classified into two groups of 44 individuals: online and face-to-face consultation. Nutritional evaluations were conducted in each consultation, which comprised of anthropometric, dietetic, and physical assessments. The therapy consisted of individually designed menus made by a specialist and other recommendations based on the World Health Association (WHO) guidelines. **Results:** Most patients in both groups achieved normal anthropometric measurements after the intervention (41/44 face-to-face group; 39/44 online group). Intragroup analysis (before and after intervention) of body mass index (BMI), weight, and fat percentage in both groups revealed a significant improvement after the intervention ($p<0.0001$). Intergroup analysis of BMI ($p<0.4031$), weight ($p<0.2265$), and fat percentage ($p<0.3872$) showed no significant difference. The analysis of efficacy revealed an efficacy of up to 95% in the online consultation group when compared to the face-to-face consultation one. **Conclusions:** No significant difference was found between online and face-to-face groups. The efficacy of online consultation was 95%. These results allow us to conclude that online and face-to-face consultation have a similar efficacy.

Key words: obesity; overweight; online consultation; face-to-face consultation.

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RESUMEN

Introducción: El sobrepeso y obesidad han aumentado progresivamente en los últimos años. La consulta virtual es una herramienta útil para el personal de salud y pacientes que no pueden asistir de manera presencial. **Objetivo:** Comparar la eficacia de la consulta presencial contra la virtual, como estrategia para el tratamiento del sobrepeso y obesidad. **Material y métodos:** Se realizó un estudio experimental transversal en 88 pacientes de 25-30 años. Se asignaron dos grupos de 44 individuos: consulta virtual y presencial. La valoración nutricional se realizó en cada consulta, y consistía en analizar datos antropométricos, dietéticos y físicos. El tratamiento consistió en menús individuales diseñados por un especialista y otras recomendaciones de guías de la Organización Mundial de la Salud (OMS). **Resultados:** La mayoría de los pacientes de ambos grupos lograron mediciones antropométricas normales después de la intervención (41/44 presencial y 39/44 virtual). El análisis intragrupal (antes y después de la intervención) del índice de masa corporal (IMC), peso y porcentaje de grasa reveló mejoría significativa ($p<0.0001$). El análisis intergrupal del IMC ($p<0.4031$), peso ($p<0.2265$) y porcentaje de grasa ($p<0.3872$) no mostró diferencias significativas. La fórmula de eficacia mostró una eficacia del 95% de la consulta virtual. **Conclusiones:** No se encontraron diferencias significativas entre ambos grupos. Se encontró un 95% de eficacia de la consulta virtual. Con esto, podemos concluir que la consulta virtual tiene una eficacia similar a la presencial.

Palabras clave: obesidad; sobrepeso; consulta virtual; consulta presencial.

INTRODUCTION

The prevalence of overweight and obesity has increased in recent decades, reaching up to 24.9% in Latin America. It is estimated that by 2030, 39% of the population in Mexico will be obese.[1] Both obesity and overweight are highly associated with metabolic and cardiovascular diseases, such as systemic arterial hypertension (SAH), hypercholesterolemia, type-2 diabetes mellitus (T2DM), and metabolic syndrome. Every year, over 3.4 million people die because of the previously mentioned diseases. The cost of treatment for obesity and associated diseases was 880 million dollars in Mexico in 2013.[2-4]

Several factors are involved in the etiology of obesity, including nutritional and psychological disturbances, sedentarism, genetics, and metabolic/endocrine dysfunction.[5-9] Regardless of the etiology, obesity requires immediate and adequate treatment to prevent the development of cardiovascular complications.

The benefits of weight loss are very clear. For instance, it decreases serum triglycerides, total cholesterol, and low-density lipoproteins (LDL). In patients with T2DM, it is associated with a reduction in glycosylated hemoglobin (HbA1c) and glycemia. In patients with SAH, it is associated with a reduction of blood pressure. In addition, weight loss decreases the prevalence of cardiovascular diseases.[10-13]

The treatment of obese patients must include nutritional assessments and lifestyle modifications. Other options such as medications, surgery or psychological assessments can also be considered. Nonetheless, the most effective therapy is a combination of nutritional assessments and lifestyle modifications.[14-19]

The current pandemic has delayed medical care for several diseases due to confinement, which has caused an increase in the incidence of health problems, such as obesity and its related complications.[20] This situation has prompted healthcare professionals to seek new ways to provide medical care that is safe and effective. The use of information technologies and telemedicine has emerged as an excellent tool for healthcare professionals in providing medical care through digital platforms.[21,22] Due to the pandemic, many healthcare professionals suspended face-to-face consultations and began to use telemedicine.[23-24] Telemedicine includes a large category of healthcare interventions applied via digital platforms.[25] Online consultation -a type of telemedicine service- is superior to telephone consultation and can be particularly useful as an alternative method to face-to-face consultation.[26]

In this study, we compared the efficacy of online versus face-to-face consultation as a strategy in the management of obesity and overweight.

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MATERIALS AND METHODS

Study design

An exploratory clinical trial was carried out to assess the efficacy of online consultation as a treatment strategy against overweight and obesity. All study participants met the following inclusion criteria: individuals between 25-30 years old, with a body mass index (BMI) >25 kg/m^2 who accepted to participate in the study and signed an informed consent. Patients that did not signed the informed consent, did not attend consultations, or had comorbidities such as T2DM, SAH, cardiopathies, oncological diseases among others, were excluded. Patients that did not attend at least 12 consultations or did not complete the treatment were eliminated from the study. Eighty-eight patients from three states of Mexico (Tlaxcala, Puebla, and Mexico City) were randomly classified into two study groups: 1) Face-to-face (n=44); 2) Online consultation (n=44). The face-to-face group included 31 women and 13 men, while the online group included 27 women and 17 men. Table 1 shows the characteristics of the participants at baseline. Group one attended consultations at Hospital Francisco de Asís, Tlaxcala, Mexico, every fifteen days during a six-month period. To perform the nutritional and anthropometric evaluations before and after the therapeutic intervention (dietary recommendations, physical activity, and nutritional advice), individuals in group two attended a face-to-face consultation only on the first and last sessions. The rest of the sessions in this group were online.

Table 1. Characteristics of the participants at baseline

Characteristic	Face-to-face group (n=44)		Online group (n=44)	
Sex	Males	Females	Males	Females
	13	31	27	17
Body weight (kg, mean ± SD)	30.26 ± 3.57		29.95 ± 2.57	
BMI (kg/m^2, mean ± SD)	80.67 ± 11.65		80.41 ± 11.13	
Arm circumference (cm, mean ± SD)	29.51 ± 3.75		30.24 ± 3.27	
Waist circumference (cm, mean ± SD)	91.11 ± 9.9		90.87 ± 9.7	
Tricipital skinfold thickness (mm, mean ± SD)	21.72 ± 6.52		20.72 ± 6.97	
Mean fat percentage (%)	33.38		33.48	

*BMI: Body Mass Index

This study was carried out in three phases: Phase 1) Recruitment and selection: two groups of 44 patients each were randomly assigned. For group assignment, the names of the eighty-eight individuals were placed in a tombola. Afterwards, each name was randomly selected from the tombola and sequentially allocated to one of the two groups until reaching 44 individuals per group. Phase 2) Online and face-to-face consultation: face-to-face consultations lasted a maximum of 45 minutes, while online consultations lasted a maximum of 30 minutes. A six-month program with consultations every fifteen days was designed for both groups. The consultation methodology was the same in both groups, a nutritional assessment was performed through clinical indicators and anthropometric measures. In the face-to-face consultation group, the healthcare professional was responsible for performing the anthropometric measurements at each consultation. In the online consultation group however, the healthcare professional only performed the first (before intervention) and last (after intervention) anthropometric measurements. Patients in the online consultation group were trained to take their basic anthropometric measurements for the rest of the consultations. A software called "Nutrimind" was used in both groups, and it allowed patients to have a photographic record of their personalized treatment and anthropometric measurements. This software was used to register medical records, treatment (physical activity and diet), and anthropometric measurements (weight, height, body mass index and fat percentage) recommended by The International Society for the Advancement of Kinathro-

pometry (ISAK).[27,28] Healthcare professionals and patients were able to access the records throughout the intervention. Phase 3) Results comparison: the results obtained from both groups during the six-month period were further analyzed to assess the efficacy of the online consultation and compare it with the face-to-face consultation. Efficacy was measured through the efficacy formula designed by Quito Polytechnic University, which measures the percentage over which a goal is achieved. The result obtained through the efficacy formula is classified in 5 groups (number 1 to 5), where a result > 91% indicates that the process is highly efficient, between 61% and 80% that it is efficient, and < 30% that it is inefficient.[29]

Sample size

As this research was an exploratory study, the sample size was determined by the feasibility of recruitment. A sample of 44 individuals per group was established considering that the number of patients per group in consultation -with the criteria required for the study- fluctuated between 44 and 50 individuals. This sample size allows the detection of an effect size of 0.1 or larger. To reach the established sample, we recruited 44 individuals per group according to the inclusion criteria.

Ethical considerations

This investigation was carried out under the guidelines of the Declaration of Helsinki, the regulations of the General Health Law on Health Research Matters, and the Official Mexican Standard NOM-012-SSA3-2012. A letter of informed consent was obtained from the patients. Patient records were always kept anonymous. All procedures were approved by the Committee of Research of the Faculty of Health Sciences of the Universidad Anáhuac México (No. 201869).

Online consultation

The online consultations were scheduled on a biweekly basis and the time for each one lasted 30 minutes. The initial and final consultations were done face-to-face so that the researcher was able to perform anthropometrical assessments. The subsequent consultations were provided through the application "Zoom" in a videoconference where the patient reported their measurements (weight, waist, hip and relaxed arm perimeter) with the support of a guide made by the researcher under the ISAK guidelines (2019), using a floor scale at home and an anthropometric tape to measure perimeters. The data registered by the patient was reported to the researcher before starting the videoconference.

Nutritional assessment

The nutritional assessment was performed before, during, and after the intervention by a clinical nutritionist with ISAK anthropometry accreditation level 1,2,3. The nutritional assessment consisted of dietetic, clinical, and anthropometric indicators. We measured the following anthropometric indicators in both groups: BMI, weight, height, and fat percentage estimation. Both groups had an average BMI of 30 kg/m^2, a weight of over 80 kg, and a fat percentage > 33% (obesity) before the intervention. These indicators were evaluated in every consultation in the face-to-face consultation group. Patients in the online consultation group were trained to take their basic anthropometric measurements, except fat percentage estimation. Body fat percentage was calculated through the Siri formula, the most accepted equation to determine fat percentage in young adults. Siri formula is approved by ISAK.

Implemented treatment

A nutrition specialist designed a nutritional treatment, which contained 1 to 5 different menus to be chosen by the patient. The menus were modified every fifteen days. The distribution of macronutrients was as follows: 60% of complex carbohydrates, 15% of high biological value proteins (proteins that can be completely absorbed by the gastrointestinal system), and 25% of monounsaturated and polyunsaturated fats. Both groups had similar objectives namely the reduction in fat percentage, the maintenance of muscle mass or conversely, the increase in muscle growth according to the patient's requirements, decreases in body weight, and better quality of life. Patients were recommended to perform at least 20 minutes of daily aerobic physical activity, according to the recommendations of the WHO.[30]

Statistical analysis

The results of the study were analyzed using the Statistical program "Prisma GraphPad". The intragroup analysis was

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performed using paired Student T and Wilcoxon Test. In this study we first analyzed in the same group the effects of the nutritional treatment on anthropometric measurements. Afterwards, intergroup comparisons of the efficacy of the treatment were performed using Mann-Whitney U and unpaired Student T Test. Finally, in order to know the efficacy of online consultation, the efficacy formula designed by Quito Polytechnic University, which measures the percentage over which a goal is achieved, was used. In this way, the efficacy was measured by comparing the results obtained in the face-to-face consultation against the results of the online group. The following formula was used: *Efficacy = (Achieved (online group) Result / Expected (face-to-face group) result).*[29] Statistical significance was established at $p < 0.05$.

RESULTS

At the beginning of the study, the mean BMI of the face-to-face group was 30.26 kg/m^2, ± 3.57 (mean ± SD), while in the online group was 29.95 kg/m^2 ± 2.57. Mean BMI decreased to 24.03 kg/m^2 ± 2.58 in the face-to-face group ($p < 0.0001$; Paired Student T Test) and 23.86 kg/m^2 ± 1.48 in the online group ($p < 0.0001$; Paired Student T Test) after the intervention. Intergroup analysis of BMI showed no significant differences ($p = 0.4031$ before the intervention and $p = 0.1032$ after the intervention; Mann-Whiney U Test; Figure 1). The initial mean weight in the face-to-face group was 80.6 kg ± 11.65, while in the online group was 80.4 kg ± 11.13. After the intervention, the face-to-face group mean of percentage of weight loss was 19.92% ± 7.14 (64.47 kg ± 8.71) ($p < 0.0001$; Students T Test) and 19.57% ± 6.09 (64.26 kg ± 8.58) in the online group ($p < 0.0001$; Students T Test). Intergroup analysis of weight showed no significant differences ($p = 0.2265$ before the intervention and $p = 0.1576$ after the intervention; unpaired Student T Test; Figure 2). When evaluating fat percentage in both groups, similar results were found. Before the intervention, the face-to-face group had a mean fat percentage of 33.38% (obesity). On the other hand, the mean fat percentage in the online group before the intervention was 33.48%. After the intervention, the mean fat percentage decreased to 22.99% in the face-to-face group (acceptable; $p < 0.0001$; Students T Test) and 23.05% in the online group ($p < 0.0001$; Students T Test). Intergroup analysis of fat percentage showed no significant differences ($p = 0.3872$ before the intervention and $p = 0.3450$ after the intervention; unpaired Student T Test; Figure 3). When comparing the fat percentage in women before and after the intervention, it decreased from 35% to 20% ($p < 0.0001$; Wilcoxon test). Similarly, the fat percentage in men decreased from 32% to 21% ($p = 0.0001$; Wilcoxon test). Both genders achieved acceptable fat percentage levels according to different consensus.[30] No significant difference was found when comparing the results of the online and face-to-face groups after the intervention in both women ($p = 0.9511$; unpaired T test) and men ($p = 0.5861$; unpaired T test).

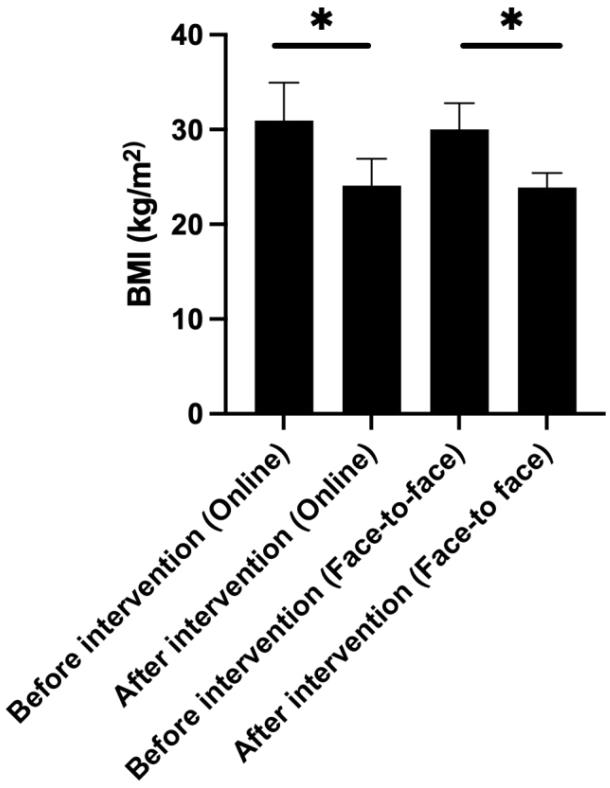

Figure 1. BMI in the online and face-to-face groups. A significant decrease in BMI can be observed in both groups after the intervention. Bars represent the BMI mean ± standard deviation per group (44 individuals each one). *$p < 0.0001$. BMI: Body Mass Index.

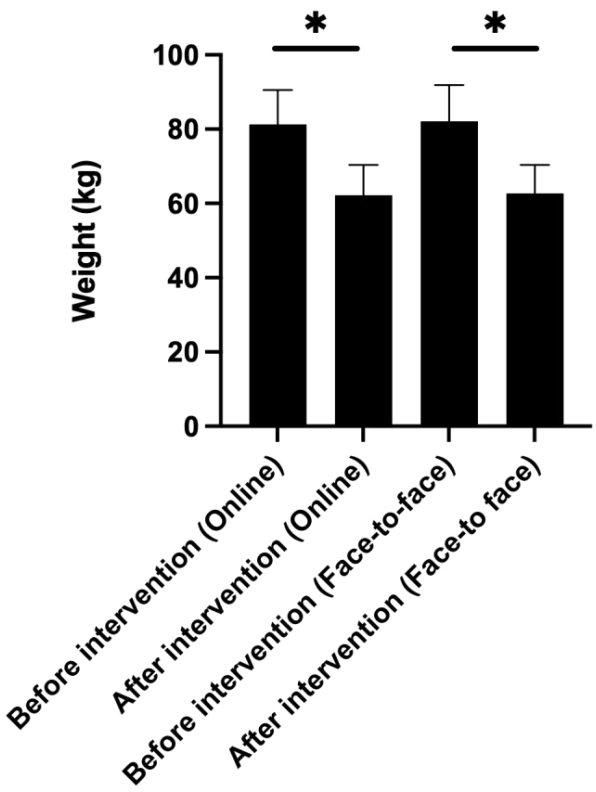

Figure 2. Weight in the online and face-to-face groups. A significant decrease in weight can be observed in both groups after the intervention. Bars represent the weight mean ± standard deviation per group (44 individuals each one). *p < 0.0001.

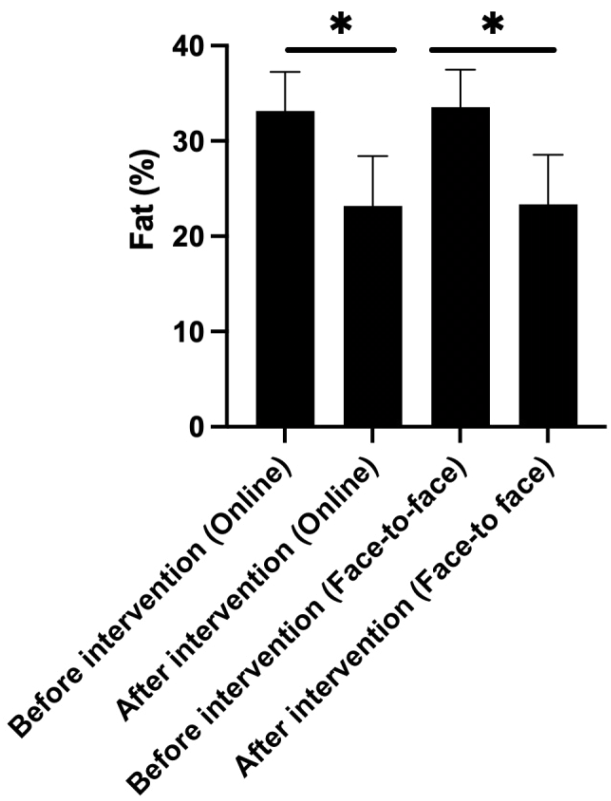

Figure 3. Fat percentage in the online and face-to-face groups. A significant decrease in fat percentage can be observed in both groups after the intervention. Bars represent the fat percentage mean ± standard deviation per group (44 individuals each one). *p < 0.0001.

Finally, among the 44 patients who attended the face-to-face consultation, 41 (93%) achieved a normal BMI. Conversely, of the 44 patients who attended the online consultation, 39 (88%) achieved a normal BMI. The efficacy formula revealed an efficacy of up to 95% of the online consultation (Efficacy = achieved result in the online group / achieved result in the face-to-face group = 39 / 41 = 0.95 X 100 = 95%). This result is interpreted as very efficient according to the efficacy formula.[29]

DISCUSSION

In the present study we aimed to compare the efficacy of online versus face-to-face consultation. A significant decrease in overweight and obesity was found in both groups. Interestingly, no significant difference in BMI, weight, and fat percentage was found when comparing both groups. Therefore, it is possible to conclude that online and face-to-face consultation have a similar efficacy. In fact, when applying the efficacy formula, we found that online consultations had an efficacy of 95%. However, we must consider that the therapeutic adherence played a vital role in these results. If the nutritionist was unable to convince the patient to comply with the nutritional intervention through the online consultation, then the efficacy could have decreased.

Other studies using online consultation have shown similar results. A study performed in the United States by Serdar et al. which aimed to compare face-to-face and online programs to control eating disorders, found that both programs have similar outcomes (decrease in psychiatric symptoms), demonstrating that online and face-to-face interventions have similar effects.[31] A systematic review and meta-analysis that evaluated the implications of telemedicine in overweight and obesity reported a significant improvement in

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at least 1 dietary or physical outcome measure in 4 of the 8 studies evaluated. Furthermore, this same study also established that maintaining therapeutic adherence could be challenging only through eHealth, an online consultation program, thus recommending a combination of both strategies.[32]

Online consultation comes to be a practical, secure, and economic option for patients. This type of medical care allows patients to have professional attention without spending money and time on transport, and without the risk of becoming infected with COVID-19 due to the current pandemic. A recent systematic review of the barriers and facilitators of online consultation showed that patients of different age groups and with different health conditions benefited from receiving an online treatment.[33] Additionally, this modality also has benefits for healthcare professionals as it decreases the general costs of consultation, allows them to see more patients per day, and makes it easier for time management purposes.[22,34] Moreover, online consultation could play an important role in big cities where transportation costs are high and has an impact on the ability to assist to a nutritional consultation.

With the current situation in the world, online consultation is a more than viable option for nutritionists as it ensures the safety of both parties without losing efficacy. However, it is worth mentioning that online consultation has some limitations, such as communication barriers, inadequate infrastructure (absence of adequate digital platforms), poor patient training to perform anthropometric measurements at home, and difficulties in giving instructions for proper treatment.

Communication, as in the face-to-face consultation, plays an important role in online consultation, not only to establish a treatment based on clinical and nutritional assessments, but also to ensure that patients have no doubts about their disease or treatment. Is in this regard that, a systematic review presented the lack of appropriate training and confidence by a healthcare professional as an obstacle to implementing telemedicine.[35]

For further inquiries about this topic, we suggest a longer follow-up of at least one year and more precise tools for the evaluation of corporal composition, such as phase angle to assess nutritional state and electric bioimpedance to assess fat percentage. In addition, future studies should also evaluate atherogenic risks and metabolic comorbidities in obese and overweight patients when comparing online and face-to-face consultation.

CONCLUSIONS

In the present study, we found no significant differences between patients who received face-to-face nutritional consultation against those who received online nutritional consultation. Nonetheless, these results can only be conclusive for groups of patients similar to the one evaluated in this trial and cannot be generalized to all obese patients.

Online consultation is an excellent tool for both the nutritionist and the patient, since it provides an efficacy similar to that of a face-to-face consultation, but with greater comfort, privacy, and efficient use of time. In addition, online consultation offers a great alternative to face-to-face consultation due to the current pandemic.

ETHICAL DISCLOSURES

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflict Disclosure. The authors declare no competing interests. The contents of this publication are solely the responsibility of the authors.

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Review Article

Viral hepatitis, hallmarks and molecular features

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ABSTRACT

Hepatitis is a liver inflammation which has different etiologies, it can be caused pharmacologically or can be associated with fatty liver or alcohol consumption. However, viral infection is the most important cause. Recently, the World Health Organization (WHO) has published reports of outbreaks of hepatitis of unknown etiology in several countries in children less than 16 years old. In this review we describe the general aspects of viral hepatitis, the molecular description of the hepatotropic viruses, laboratory findings, molecular diagnosis, and prevention strategies. In addition, the main characteristics of some viruses that are not hepatotropic but have been previously reported to be related to some types of hepatitis are mentioned. Finally, a brief description of new cases of hepatitis of unknown origin is presented and the adverse effects of SARS-CoV-2 vaccines are briefly discussed.

Key words: hepatitis; virus; liver; unknown etiology.

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RESUMEN

La hepatitis es una inflamación del hígado la cual tiene distintas etiologías, ya sea farmacológica, asociada con hígado graso o el consumo de alcohol, siendo la más notable la infección viral. Recientemente la Organización Mundial de la Salud (OMS) ha publicado reportes de brotes de hepatitis de etiología desconocida en varios países en niños menores de 16 años. En esta revisión se describen los aspectos generales de la hepatitis viral, la descripción molecular de los virus hepatotrópicos, los hallazgos de laboratorio, el diagnóstico molecular y las estrategias de prevención; además se hace mención a las características principales de algunos virus que no son hepatrópicos pero en los que previamente se ha reportado su relación con algunos tipos de hepatitis. Por último, se realiza una descripción breve de los casos nuevos de hepatitis de origen desconocido y se abordan brevemente los efectos adversos de las vacunas del SARS-CoV-2.

Palabras clave: hepatitis; virus; hígado; etiología desconocida.

INTRODUCTION

The liver is an organ located in the upper right section of the abdominal cavity, beneath the diaphragm, and above the stomach, the right kidney, and intestines. It weighs about three pounds, and it is cone shaped. Its main functions include bile secretion, bilirubin metabolism, coagulation factors synthesis, nutrient metabolism, mineral and vitamin storage, and xenobiotics metabolism.[1-5]

Liver disease can be acute or chronic; mild or severe; and reversible or irreversible. Hepatitis means liver inflammation, which has different etiologies. Its cause can be associated with fatty liver, alcohol consumption, pharmacological causes or due to a virus. The latter has showed to be the main cause that can damage this organ. There are several different types of hepatitis, which depending on what triggers it, and the duration of the inflammation, are divided into acute (sudden) or chronic (long-lasting) hepatitis. Acute hepatitis (AH) is an inflammatory process causing liver cell death either by necrosis or by triggering apoptosis; lasts for less than six months, and it is characterized by normalization of the liver function tests. It is mainly caused by a viral infection; however, it can also be the result of exposure to drugs (acetaminophen) or ethanol consumption. On the other hand, chronic hepatitis (CH) is defined as an inflammation of the liver that continues for a period of at least 6 months, caused by various pathogenic agents, which leads to inflammatory processes and cellular necrosis of the liver tissue. It is a disease that can progress to cirrhosis, liver cell carcinoma, liver failure and eventually death.[6-12]

Recently the WHO has published reports of outbreaks of hepatitis of unknown etiology in several European and American countries. At least 169 cases, as of April 21st, 2022, all of them in children under 16 years of age. It is important to highlight that the common viruses associated with acute viral hepatitis (hepatitis viruses A to E) have not been detected in any of these cases, so it's important to review the general aspects of this disease.[13]

In this review, we focus on viral hepatitis, we will describe its main characteristics, and review the data available to date on new hepatitis of unknown etiology.

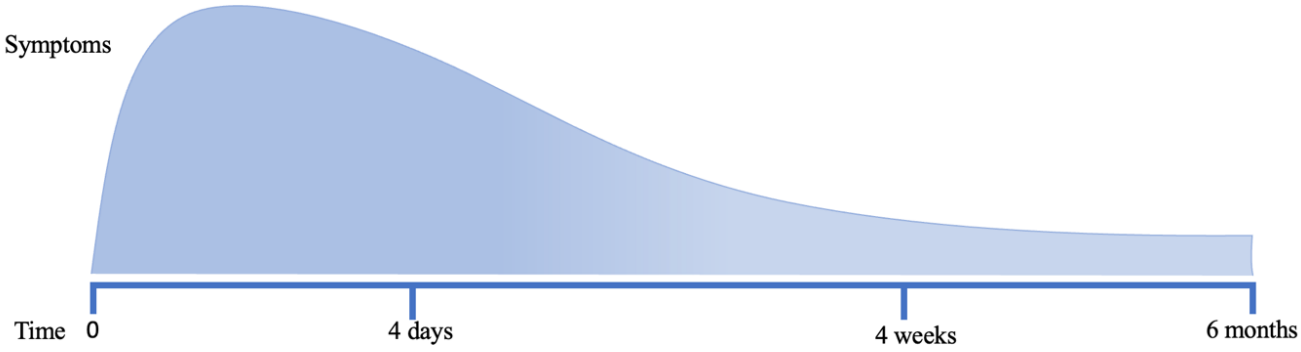
GENERAL ASPECTS OF VIRAL HEPATITIS

ACUTE HEPATITIS

AH may be asyntomatic, nevertheless; it could be frequently accompanied with fever, jaundice, dark urine, lethargy, fatigue, nausea, and gastrointestinal symptoms such as abdominal pain, diarrhea, and vomiting. Viral infections are the most common cause of acute hepatitis, being Hepatitis A virus (HAV) infection the main cause. The transmission occurs from person to person, during fecal-oral route or through the consumption of contaminated food and water. Several other viral infections, for example, Hepatitis E (HEV) and Hepatitis B virus (HBV), are also associated with acute hepatitis, but with a lower prevalence. HEV is transmitted through the same route as HAV, while HBV is transmitted by sexual contact, blood transfusion, and other infected fluids.[11, 14-15]

Viral hepatitis infection is classified into three stages, all presenting different signs, symptoms, and temporality. First, is the prodrome stage, which lasts 3-4 days beginning with the manifestation of general non-specific signs and symptoms of an illness, corresponding to mild fever, fatigue, and general malaise. Afterwards, these evolve into gastrointestinal manifestations such as anorexia, loss of appetite, nausea, discomfort in the right upper quadrant of the abdomen, and alterations of taste and smell. Ultimate-

ly, when cephalalgia, photophobia, cough, coryza, myalgia, cutaneous exanthema, urticaria or arthritis as extrahepatic phenomena appear, patients are highly contagious during this period.[16-17] Subsequently, the stage of emerging jaundice due to increased serum bilirubin causes yellowing of the skin and sclera of the eyes, darkening of the urine, and pale stools. This period lasts 1-4 weeks when symptoms are diminished. Patients may lose weight and pruritus might occur if cholestasis is severe. It is important to mention that patients will present abdominal pain due to the enlargement and hypersensitivity of the liver or as a consequence of splenomegaly.[16] At last comes the convalescence phase, in which the general symptoms disappear, but abnormalities in liver function tests still persist. Generally, AH has a good prognosis with a self-limiting course and resolution lasting less than six months until the patient liver functions' return to its normal state, as in the case of infection with Hepatitis A. Occasionally, acute hepatitis can evolve into liver failure with a critical prognosis as shown in Figure 1.[18]



Prodrome stage

Non-specific signs and symptoms of an illness: mild fever, fatigue, and general malaise.
Gastrointestinal manifestations: anorexia, loss of appetite, nausea, discomfort in the right upper quadrant of the abdomen and alterations of taste and smell.
Finally: cephalalgia, photophobia, cough, coryza, myalgia, cutaneous exanthema, urticaria or arthritis as extrahepatic phenomena.
The patients are highly contagious during this period.

Jaundice stage

Yellowing of the skin and sclera of the eyes, darkening of the urine, and pale stools, lose weight, pruritus.
The patients will present abdominal pain due to the enlargement and hypersensitivity of the liver or as consequence of splenomegaly.

Convalescence stage

The general symptoms disappear.
Abnormalities in liver function tests persist and resolution lasting less than six months until patients liver functions return to its normal state.
Nevertheless, occasionally acute hepatitis can evolve into liver failure with a critical prognosis.

Figure 1. Viral infection stages with signs, symptoms and temporality.

CHRONIC HEPATITIS

CH is defined as an inflammation of the liver that continues for a period of at least 6 months, leading to inflammatory processes and cellular necrosis of the liver tissue. It can be developed by fatty liver, alcohol-related liver disease and the use of certain drugs, when these are taken over a long period of time, such as amiodarone, isoniazid, methyldopa, and acetaminophen. CH could also be associated with viral infections; Hepatitis C virus infection is associated in 80% of cases and is characterized by viral persistence in the host hepatocyte. Less cases are related to Hepatitis B with or without Hepatitis D virus. CH is often asymptomatic for decades until chronic complications start to show up as a consequence of advanced liver damage stages when specific symptoms occur. These include, cirrhosis development, which may include liver and spleen enlargement, spider angiomas, telangiectasis, palmar erythema (redness of the

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palms), ascites, coagulopathy, and hepatic encephalopathy. Unlike AH, it is not uncommon for CH to progress to fibrosis. Due to repair with connective tissue, the excessive hepatic necrosis accompanied by an excessive decomposition of the extracellular matrix (ECM) developing cirrhosis -which is the final stage of the fibrotic process characterized by permanent hepatocyte damage, nodular regeneration, aberrant architecture and mostly accompanied by scar tissue formation that impairs hepatocyte function and impaired portal blood flow- CH can progress into liver cancer or death.[19-23]

HEPATOTROPIC VIRUSES

Although there are multiple hepatitis etiological factors, viral hepatitis is the global leading cause of the inflammation of the liver tissue. Hepatitis A and B viruses were discovered in 1960. It was not until 1990 that other hepatitis viruses were no longer classified as non-A, non-B, and up to date there has been four more hepatitis viruses recognized; Hepatitis C, D, E and G, as seen in Table 1.[24-25]

Table 1. Canonical Hepatotropic and Non-canonical Hepatotropic viruses

DISEASE	VIRUS	VIRUS CHARACTERISTICS	TRANSMISSION	SIGNS AND SYMPTOMS	DIAGNOSIS
HEPATOTROPIC VIRUSES					
HEPATITIS	HAV (Hepatitis A Virus)	Family: Picornaviridae Viral symmetry: non-enveloped, Icosahedral capsid Nucleic acid: Single strand (ss) positive (+) RNA (acts directly as a messenger) Genome size: approximately 7.500 kilobase (kb)	Oral-fecal route and it is mainly associated with the lack of access to potable water.	Weakness, fatigue, nausea, vomiting, abdominal pain, arthralgias, myalgias, diarrhea and anorexia.	Molecular biology techniques (RT-PCR); serological tests (surface antigen) or antibody detection (IgM, IgG)
	HBV (Hepatitis B Virus)	Family: Hepadnaviridae Viral symmetry: enveloped, Icosahedral capsid Nucleic acid: Incomplete double-stranded (ds) circular DNA genome virus Genome size: 3.2 kb Others: Eight genotypes (A-H)	From mother to child at birth, body fluids and through sexual contact; sharing needles, syringes, or other drug-injection equipment.	Fatigue, nausea, vomiting and right upper quadrant pain before or during jaundice onset.	
	HCV (Hepatitis C Virus)	Family: Flaviviridae Viral symmetry: enveloped, Icosahedral capsid Nucleic acid: Single-stranded (ss) positive (+) RNA viruses linear double-stranded DNA. Genome size: 9.6 kb Others: It is classified into eight genotypes	Primarily by parental routes including blood transfusions, intravenous drugs injections or by high-risk sexual practice.	Nonspecific, they can include fatigue, sleep disturbances, nausea, diarrhea, abdominal pain, anorexia, myalgia, arthralgia, weakness, depression, anxiety and weight loss.	
	HDV (Hepatitis D Virus)	Family: Kolmioviridae Viral symmetry: enveloped, capsid of unknown symmetry Nucleic acid: circular single strand (ss) negative (-) RNA Genome size: 1.7 kb Others: The only member of the Deltavirus genus, It is classified into eight genotypes, It's enveloped by HBV surface antigens	It only affects patients with this co-infection of the B and D viruses. It is spread by perinatal transmission and through contact with infected body fluids.	The infection may be asymptomatic, and usually progresses to mild self-limited disease or severe acute hepatitis with spontaneous resolution.	

	HEV (Hepatitis E Virus)	Family: Hepesviridae Viral symmetry: non-enveloped, icosahedral capsid Nucleic acid: single-stranded (ss) positive (+) RNA Genome size: 7.2 kb	By the fecal-oral route, it is also associated with lack of access to drinking water and animals can act as a reservoir of the virus.	Almost all patients with HEV are asymptomatic or may develop a mild HAV-like illness.	
	HGV (Hepatitis G Virus)	Family: Flaviviridae Viral symmetry: Enveloped, capsid of unknown symmetry Nucleic acid: single-stranded (ss) positive (+) RNA Genome size: 9.4 kb Others: Lymphotropic human virus	Through percutaneous injuries, contaminated blood, sexual contact, and vertical mother-to-child transmission.	Typically considered nonpathogenic.	
OTHER NON-CANONICAL HEPATOTROPIC VIRUSES					
Erythema infectiosum	Parvovirus B19	Family: Parvoviridae Viral symmetry: non-enveloped, icosahedral capsid Nucleic acid: linear single-stranded DNA Genome size: 5.6 kb Others: it is the only parvovirus pathogenic for humans, may develop acute hepatitis	Mainly through respiratory droplets, and in some cases by blood transfusions and the placental route.	This infection may be asymptomatic or associated with headache, erythema infectiosum and anemia in children and multiple joint pains and inflammation and general malaise in adults.	Serological tests
Infectious mononucleosis	Epstein-Barr	Family: Herpesviridae Viral symmetry: Enveloped, icosahedral capsid Nucleic acid: Linear double-stranded DNA Genome size: 170 kb Others: Human herpesvirus type 4, infection can affect liver	Body fluids, especially saliva.	Liver involvement, leading to elevation of liver enzymes, cholestatic hepatitis, characterized by obstruction of bile flow.	Serological Testing and Molecular Assays
Infectious mononucleosis	Cytomegalovirus	Family: Hepesviridae Viral symmetry: enveloped icosahedral capsid Nucleic acid: Double-stranded DNA virus Genome size: 236 kb Others: the largest genome of any known human virus, Human herpesvirus 5, it is associated with hepatitis and pancreatitis in immunocompetent patients	Body secretions such as saliva, urine, tears, blood or genital secretions.	Typically cause mononucleosis syndrome or usually presents as asymptomatic infection.	Serological Testing and Molecular Assays
Chickenpox	Varicella -zoster virus	Family: herpesviridae Viral symmetry: enveloped, icosahedral capsid Nucleic acid: Linear double-stranded DNA virus Genome size: 125 kb Others: Human herpesvirus 3, Neurotropic virus, can develop complications, related to the liver	airborne, with viruses coming from the vesicles that form on the skin, as this is where they are found in high viral concentrations.	Persistent radicular pain, this viral infection can develop other complications, related to the liver.	symptoms and signs analysis, RT-PCR from blister

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Yellow Fever	Yellow fever virus	Family: Flaviviridae Viral symmetry: enveloped, icosahedral capsid Nucleic acid: Single-stranded, positive-polarity RNA genome Genome size: 11 kb Others: some reports related with hepatitis	By mosquitoes of the Aedes and Haemagogus species.	High fever, skin hemorrhages and the death of liver and kidney cells are common.	Serological Testing and Molecular Assays
Rubella	Rubella virus	Family: Matonaviridae Viral symmetry: enveloped, icosahedral capsid Nucleic acid: Positive-stranded RNA Genome size: 9.7kb Others: may be playing a role in liver injury	Airborne transmission, mother-to-child transmission.	During pregnancy, miscarriage or stillbirth, serious birth defects such as deafness, eye and heart abnormalities; in adults was associated with elevations of serum aminotransferases, globular degeneration, and focal necrosis of liver cells.	Serological Testing and Molecular Assays
Acute respiratory infection	HADV Human adenovirus	Family: Adenoviridae Viral symmetry: non-enveloped, icosahedral Nucleic acid: Doubled-stranded DNA Genome size: 36kb Others: recently reported in cases of severe acute hepatitis in children	Inhalation of aerosolized droplets, fecal-oral spread, or conjunctival inoculation.	Pharyngitis, coryza or pneumonia, and in children serotypes 40 and 41 have been associated with gastrointestinal symptoms such as diarrhea, abdominal pain and vomiting.	Antigen detection, polymerase chain reaction (PCR), virus isolation, and serology

Hepatitis A Virus (HAV)

HAV belongs to the Picornaviridae family and Hepatoviral genus, which are non-enveloped icosahedral single strand positive RNA non-enveloped small viruses. It is approximately 7,500 nucleotides in length and its RNA acts directly as a messenger. So far, the mechanism of the virus entering the host cell is not very clear. Previously, it was suggested that the virus enters the cell using its phosphatidyl serine residues allowing it to bind to HAV cellular receptor 1 protein (HAVCR1). Recently it has been shown that this receptor is not essential for virus entering into the cell, nonetheless studies to characterize the related molecules are still lacking. Still the process after virus entry into the cell is better understood. Once the virus enters by endocytosis, RNA is directly translated by a cap-independent mechanism using the IRES structures present. Then, by intermediate steps the virus is assembled and released from the cell. It is worth mentioning that HAV replication does not have a cytopathic effect on hepatocytes.[26-28]

According to the World Health Organization (WHO), there are nearly 1.4 million new cases of HAV globally every year, causing just about 7,000 deaths. Hepatitis A is an acute infection that appears in non-vaccinated population or among people that have not been infected before. It is transmitted through an oral-fecal route, and it is mainly associated with the lack of access to potable water as shown in Figure 2.

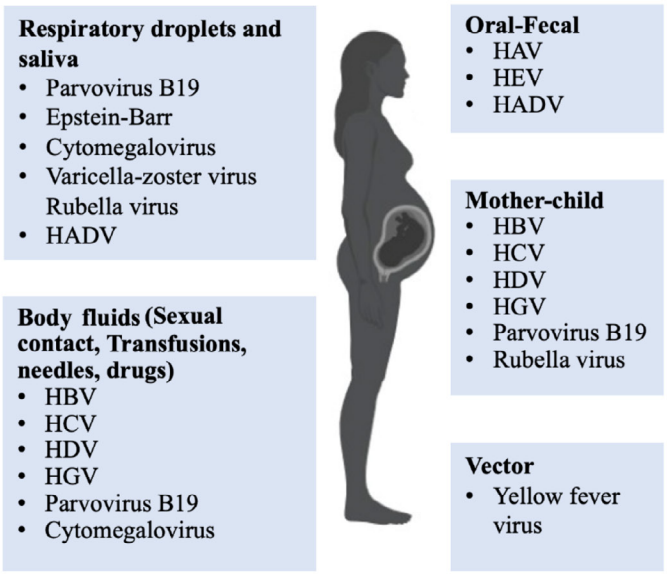

Figure 2. Transmission routes.

HAV has regularly an incubation period of 2-4 weeks, usually causing fever, malaise, and jaundice, being the most common symptoms. Weakness, fatigue, nausea, vomiting, abdominal pain, arthralgias, myalgias, diarrhea and anorexia can also be related with this infection.[24-25, 29]

Hepatitis B Virus (HBV)

The HBV a member of the Hepadnaviridae family, is enveloped and has an icosahedral symmetry. It is an incomplete double-stranded circular DNA with a genome virus of 3.2 kb in length, with a lipopeptide layer and an internal nucleocapsid. At least 8 different genotypes (A-H) have been identified. Once the virus is in the perisinusoidal space, it utilizes its surface antigens binding to the sodium taurocholate co-transporting polypeptide (NTCP) receptor on the hepatocytes membrane and enters via endocytosis. Since the virus is without cover, the nucleocapsid is maintained until the viral DNA reaches the nucleus. Once in the nucleus, the double helix is completed and covalently locked. Thus, it can remain in the nucleus for a long time. Nevertheless, it can also integrate into the genome of the infected cell. Genome integration is a mechanism by which HBV causes neoplastic transformation and the development of cancer.[30-32]

This virus can be transmitted either from mother to child at birth. Figure 2 shows that the incubation period is variable between 28-180 days, producing an acute or chronic hepatitis infection. Acute HBV infection can be presented as a subclinical disease, which is the most common way, to an icteric hepatitis. Patients could experience fatigue, nausea, vomiting and right upper quadrant abdominal pain before or during jaundice onset. During the acute phase, there is an elevation of the HBV viral load and total bilirubin. Although a great portion of acute HBV infections can resolve with liver enzyme normalization, a chronic HBV phase will begin if the ALT remains elevated after six months from its initial presentation.

Chronic HBV may be developed in younger patients with genetic predisposition or in those who did not develop symptoms when acute HBV infection occurred. Regularly, these patients are asymptomatic for years until there is an HBV exacerbation or complication. The worse disease progression of HBV infection can be related to several host factors, such as male gender, alcohol intake and obesity. Patients with chronic HBV could develop liver cirrhosis or hepatocellular carcinoma (HCC), as a complication due to the parenchymal inflammation and fibrosis of a long-term infection.[12, 21, 25, 29, 32]

Hepatitis C Virus (HCV)

This is an enveloped virus belonging to the Flaviviridae family. It is classified into eight genotypes, positive-sense single-stranded (ss) RNA viruses with an Icosahedral capsid. Its genome is approximately 9.6 kb in length. HCV is transmitted primarily by parental routes including blood transfusions, intravenous drugs injections or by high-risk sexual practice.

As Figure 2 shows, HCV is estimated to infect more than 1% of the global population, and nearly 80% develop a slowly evolving, asymptomatic chronic liver disease which is characterized by cell damage, inflammation and fibrosis that can later develop into cirrhosis or Hepatic carcinoma after a few decades. Chronic HCV infections can occur in nearly all patients with an HCV infection, while 15%-45% of patients may present spontaneous clearance of the virus or an acute HCV infection. Nearly all cases of acute HCV infections are asymptomatic. Some patients present similar symptoms as other acute hepatitis, like jaundice, nausea, dark urine, and others. Such symptoms may appear or develop from 2-26 weeks after exposure, and they usually last two to twelve weeks. Although symptoms of an HCV infection are nonspecific, they can include fatigue, sleep disturbances, nausea, diarrhea, abdominal pain, anorexia, myalgia, arthralgia, weakness, depression, anxiety, and weight loss. It is also important to note that patients who develop cirrhosis may also develop ascites and other stigmata of cirrhosis.[23-24, 28-29, 33]

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Hepatitis D Virus (HDV)

This virus belongs to the Kolmioviridae family and is the only member of the Delta virus genus. It is distinct from other types of hepatitis viruses because requires of HBV for its replication and is therefore, referred to as HBV satellite virus. It's a single-stranded negative-sense RNA virus, it's the only animal virus having a circular RNA and it's enveloped by the HBV surface antigens. Its genome is very small (~1700 nucleotides) and has a capsid of unknown symmetry. HDV does not encode for an RNA-dependent RNA polymerase (RdRp) like other RNA viruses but relies on host DNA-dependent RNA polymerases (DdRp) for RNA synthesis and replication of its genome in the cell nucleus. Therefore, it only affects patients with this co-infection of the B and D viruses. HDV is spread by perinatal transmission and through contact with infected body fluids. The infection may be asymptomatic, and usually progresses to mild self-limited disease or severe acute hepatitis with spontaneous resolution. On the other hand, HDV superinfection in chronic HBV carriers often results in a prolonged clinical course.[25, 29, 34-35]

Hepatitis E Virus (HEV)

HEV is a non-enveloped virus, from the Hepeviridae family, classified into four genotypes. Positive-sense single-stranded (ss) RNA viruses, with an icosahedral capsid and a genome 7.2 kb in length, currently HEV life cycle and pathogenesis remain unknown. HEV infection is one of the biggest struggles for the global public health system as it is a causative agent of endemic and epidemic hepatitis worldwide. According to WHO, there are nearly 20 million international new infections annually, with an estimate of nearly 3.3 million acutely symptomatic patients and more than 4,400 deaths during 2015. HEV is usually transmitted by the fecal-oral route.

It is also associated with lack of access to drinking water, and animals can act as a reservoir of the virus. Almost all patients with HEV are asymptomatic or may develop a mild HAV-like illness. Genotypes one and two have an incubation period of 2-10 weeks, and genotypes three and four become a chronic infection which is unique to the immunocompromised population. It is worth to mention that those patients with liver disease who are pregnant or malnourished are more likely to present a progression from acute infection to liver failure due to their immunosuppressive condition.[23-25, 29, 36]

Hepatitis G Virus (HGV)

It is a single-stranded RNA virus with positive polarity, which is related to HCV, also known as human pegivirus 1. Its genome is approximately 9.4 kb in length, it is enveloped, and it has capsid of unknown symmetry. In contrast to other hepatitis viruses it is found primarily in lymphocytes and not hepatocyte. Therefore, it is considered a lymphotropic human virus. It is transmitted through percutaneous injuries, contaminated blood, sexual contact, and vertical mother-to-child transmission. Surprisingly, co-infection of human lymphocytes with HGV and HIV inhibits HIV replication, as a consequence this virus is typically considered nonpathogenic.[37-41]

OTHER NON-CANONICAL HEPATOTROPIC VIRUSES

Parvovirus B19

Parvovirus 19 is a non-enveloped linear single-stranded DNA virus that belongs to the Parvoviridae family, with 5.6 kb genome in length, it is the only parvovirus pathogenic for humans. This infection may be asymptomatic or associated with headache, erythema infectiosum and anemia in children, and multiple joint pains and inflammation and general malaise in adults. Aplastic anemia is mentioned as a complication of this infection in young adults. The infection may develop acute hepatitis, manifested by yellowing of the skin (jaundice) and hepatosplenomegaly or maintained even for years in immunocompetent individuals. Parvoviruses are transmitted mainly through respiratory droplets, although they can also be spread through blood transfusions and the placental route.[42-45]

Epstein-Barr Virus

The Epstein-Barr virus genome is linear double-stranded DNA, it's enveloped with icosahedral capsid and a genome size of around 170 kb. This virus is a member of the Herpesviridae family, it is transmitted mainly by body fluids, especially saliva. It is one of the most common viruses in humans, it's the main cause of infectious mononucleosis and it's also linked to the development of several human cancers. EBV infection can cause liver involvement, leading to elevation of liver enzymes, but it usually resolves on its own. However, in some less common cases, cholestatic hepatitis, which is a rare form of acute hepatitis characterized by obstruction of bile flow, may occur sporadically.[46-50]

Cytomegalovirus

Cytomegalovirus (CMV) is a double-stranded DNA virus, has an icosahedral capsid and it is enveloped, it has the largest genome of any known human virus, and it is a member of the Herpesviridae family. Like EBV, to which it is related, it is transmitted through bodily secretions such as saliva, urine, tears, blood, or genital secretions. Typically causes mononucleosis syndrome or is usually present as an asymptomatic infection. Chang et al. and other authors have previously reported cases of CMV associated with hepatitis and pancreatitis in immunocompetent patients, in which elevated lipase levels, elevated aminotransferases and epigastric pain after an acute viral prodrome are present.[48, 51-52]

Varicella-Zoster Virus

Varicella-zoster virus belongs to the Herpesviridae family, it is an enveloped linear double-stranded DNA virus with an icosahedral capsid and a genome of 125 kb in length. It is the etiologic agent of chickenpox and herpes zoster. It is very easily transmitted by airborne, with viruses coming from the vesicles that form on the skin, as this is where they are found in high viral concentrations. Although it is a neurotropic virus, which can cause persistent radicular pain, this viral infection can develop other complications, related to other organs such as the liver.[53-55]

Yellow Fever Virus

Yellow fever virus has a single-stranded positive-polarity RNA genome, with 11kb of length, is enveloped and has an icosahedral capsid, belongs to the Flaviviridae family and is an arbovirus transmitted by mosquitoes of the Aedes and Haemogogus species. High fever, skin hemorrhages and the death of liver and kidney cells are common in this viral infection and has a high case fatality rate. Evidence of the relationship of this virus with the development of hepatitis is pointed out in some reports such as the one published by Rezende et al. in which they present a patient who showed hyporexia, asthenia, adynamia and jaundice two months after the onset of acute yellow fever; accompanied by an increase in transaminases and direct bilirubin levels. It is also accompanied by weakness and fatigue that may last for several weeks, while slightly abnormal liver function may persist for 60 days or more.[56-58]

Rubella Virus

Rubella virus is an enveloped positive-stranded RNA virus with icosahedral capsid that belongs to the Matonaviridae family, it is highly contagious and transmitted through airborne transmission. It is well documented that infection during pregnancy can cause miscarriage or stillbirth, and can cause serious birth defects such as deafness, eye and heart abnormalities. Several years ago, two independent reports on a 24-year-old and a 28-year-old man with rubella infection were associated with elevations of serum aminotransferases, globular degeneration, and focal necrosis of liver cells, and it was suggested that cytotoxic T cells may be playing a role in liver injury in acute rubella infections in adults.[59-62]

Human Adenovirus (HAdV)

HAdV are doubled-stranded DNA non-enveloped viruses from the Adenoviridae family, with a incosahedral capsid, and a genome of 36 kb in length. The typical route of transmission is through inhalation of aerosolized droplets, fecal-oral spread, or conjunctival inoculation. These viruses usually cause self-limited infections in the non-immunocompromised population and after an incubation period of 2 to 14 days, symptoms of this respiratory tract infection may be observed including pharyngitis, coryza or pneumonia, and in children serotypes 40 and 41 have been associated with gastrointestinal symptoms such as diarrhea, abdominal pain and vomiting.[63-64] Its relationship to the development of hepatitis is discussed further on.

DIAGNOSIS

The diagnosis of acute hepatitis is based on laboratory findings as elevated levels of Aspartate Transaminase (AST), Alanine Aminotransferase (ALT) above 500 IU/L, total bilirubin elevated levels, serological markers like virus surface antigens and serum antibodies detection. In the case of chronic hepatitis, the serological detection is persistent for more than six months; after this period the virus should have been cleared of serum. On the other hand, hepatitis viruses could be detected by molecular techniques as real-time polymerase chain reaction (RT-PCR), for viral nucleic acid present in relatively small amounts in body fluids of infected patients. Diagnosis for CH includes blood tests followed by a liver biopsy to confirm or reject the diagnosis of hepatitis. The blood test as in AH, measures the levels of liver

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enzymes (transaminases) and other substances produced by the liver, which will appear elevated, helping the medical practitioner to identify the main cause and determine the severity of liver damage. As mentioned before, a liver biopsy will be also necessary to confirm the diagnosis, as it determines how severe the inflammation is, if any fibrosis has been developed on the tissue, and allowing to specify the stage of necroinflammatory activity (mild, moderate, severe, and very severe), helping to identify the cause of hepatitis. Depending on the results, the medical practitioner may ask for complementary tests like markers (in case of fibrosis), abdominal ultrasound to verify if the liver is enlarged, if it has nodular appearance, and when performing with doppler it can even show signs of portal hypertension. An endoscopy will evaluate the presence of gastroesophageal varices due to portal hypertension that is associated with liver cirrhosis. Finally, the progression of the initial fibrosis to advanced cirrhosis can culminate in hepatic cellular carcinoma. Quantification of alpha-fetoprotein (AFP) is commonly used as a biomarker for early detection and follow-up of hepatic cell carcinoma.[8, 21, 65-68]

PREVENTION STRATEGIES

Viral Hepatitis remains as a problem for the global public health system due to the high non-vaccinated population. According to WHO, in its latest update of June 2022, in 2019 chronic HBV infection had an estimated prevalence of 296 million infected people which represents an increase of 15.18% (compared to the 2017 report). Furthermore, the annual incidence has been estimated at 1.5 million new cases and 820,000 deaths associated with HBV infection, mainly due to cirrhosis and hepatocellular carcinoma. The biggest risk factor for chronic HBV is perinatal transmission, which can be prevented with a birth and three-dose vaccination, administration of Hepatitis B immunoglobulin (HBIG) to infants, and antiviral treatment of high-viral-load mothers. However, it should be noted that HBV vaccination has resulted in a decrease in the incidence of HBV infection; also important is the screening of blood bank donors with HBV serologic markers, which has virtually eliminated post-transfusion Hepatitis B. The protective effect of the Hepatitis B vaccine is related to the formation of antibodies against HBs Ag induced by the vaccine. Currently due to the vaccine introduction in childhood, young adults are now becoming more susceptible to HAV infections, therefore one of the greatest challenges for HAV is to increase vaccination coverage globally, still implementing the single-dose schedule, to decrease the new infections, and, in the long term, to achieve its eradication. Although vaccines are particularly effective in pre-exposure situations, administration of Hepatitis A vaccine to those who live with a child who develops Hepatitis A has been shown to be effective in preventing secondary cases, and also induces a permanent immunity that protects against further contact with the virus. On the other hand, there is still no vaccine available against Hepatitis C, so its prevention requires the application of health measures.[12, 24, 29, 69-70]

UNKNOWN ETIOLOGY HEPATITIS

In general, despite the great variety of viruses that exist and that can cause liver infection, the reality is that the vast majority of viral hepatitis is due to one of the hepatitis viruses discussed above. Recently alerts have been activated due to outbreaks of acute hepatitis in children where the liver damage has not been attributable to one of these hepatitis viruses (Hepatitis A-G). This outbreak has been observed in children under 16 years of age in more than 40 countries in which serum transaminases were seen to rise above 500 IU/L and causing acute liver failure in approximately 10% of the cases, and which, as of early April of this year had already resulted in at least 21 deaths and 38 liver transplants. In these reports, the patients had no history of travel to any hepatitis epidemic area or hepatitis due to drugs or any other non-infectious cause was ruled out. The most common symptoms have been gastrointestinal or systemic, and commonly associated with hepatitis such as yellowing of the eyes or skin, dark urine. Interestingly, respiratory symptoms were also reported in the weeks prior to hospital admissions. It is worth mentioning that most of the patients had no history of vaccination against COVID-19 due to their age range. Previously it has been noted the association of rubella virus with liver damage, this due to the activation of the immune system, specifically the cytotoxic T cells, widely involved in containing viral infection. Important to remember as well is the fact that in front of the SARS-CoV-2 infection the deregulation of the immune system has been reported; leaving aside the protection against infectious agents causes an adverse effect when overactivated.[60, 71]

Since these outbreaks are not related to infection with classical hepatitis viruses, as has been demonstrated and confirmed by various molecular tests, it is worthwhile analyzing the timeline of the development of these cases. So far, the sequence of these events have been as follows: from October 2021 to February 2022, nine cases of hepatitis of unknown origin were reported in Alabama, United States; all were positive for Adenovirus 41, however they also presented coinfection with other viruses such as EBV, only 2

patients required liver transplantation.[72] In early April, 10 cases of severe acute hepatitis of unknown origin were reported in children in central Scotland. On April 21st, 2022, the WHO published at least 169 case reports of outbreaks of hepatitis of unknown etiology in several European and American countries.[13] On May, reports already included 15 countries worldwide, most of them in Europe, reaching 191 cases, where at least 50% were positive for adenovirus -of which 10% reported a co-infection with SARS-CoV-2- 17 liver transplants were required and one death was reported.[63] At the end of May, the number of cases reached 600 patients.[73] By early June, these outbreaks had already affected more than 800 children and had spread to 40 countries.[71] More recently, on July, the WHO reported 1010 cases of this type of hepatitis and 22 deaths.[74]

DISCUSSION AND CONCLUSION

It is important to highlight that currently 12.8 billion doses of the different presentations of the vaccine against COVID-19 have been administered, nearly 3.65 million doses per day- which represents almost 70% of the world's population.[75] We should keep in mind that these vaccines have a safety profile and quality control, no drug therapy is exempt from adverse effects. In the case of COVID-19 vaccines, some distinct adverse effects have been reported, with malaise, fatigue and headache being the most common.[76] In addition, there have been reports of adverse effects related to liver damage by COVID-19 vaccines. Mann et al. have reported a case of hepatoxicity caused by the Pfizer vaccine, a messenger RNA vaccine, which presented jaundice data, abdominal pain that appeared 9 days after the second dose of the vaccine, increased values of various metabolites such as ALP, bilirubin and aspartate transaminase, as well as a considerable increase in white blood cells.[77] Likewise, Ghorbani et al. report a case with hepatitis data after the Sinopharm vaccine, an attenuated virus vaccine.[78] However, as we have mentioned, most of these cases of hepatitis have been in patients that, because of their age range at the time of the development of the disease, had not yet been administered a dose of COVID-19 vaccine, so it is very unlikely that they are part of the adverse effects due to vaccination. Nevertheless, it should not be underestimated that we could be facing cases of hepatitis due to the sequelae of a previous infection with SARS-CoV-2, remembering that during the development of this disease a series of disorders occur at different levels as in the case of the cytokine storm.

In conclusion, there is not enough information about the etiology of these types of hepatitis of unknown origin, and more studies and reports are needed to reinforce the analysis of the relationship of viral infections, such as adenovirus or EBV. We must recall that the approach of the study considers the analysis of the risks of developing hepatitis against viral coinfections by SARS-CoV-2 co-infections. It should also be considered necessary that the analysis of other etiologic factors that may trigger the disease, such as those due to the use of drugs or those of autoimmune component, could involve the production of super antigens and the relationship with other pathologies. Finally, it is necessary to be aware of the different side effects that the COVID-19 vaccine could cause in patients under 16 years of age, because they are still in the early stages of vaccination, keeping in mind that vaccination is a successful and safe strategy that prevents complications due to SARS-CoV-2 infection.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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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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