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New treatment for migraines: Use of monoclonal antibodies – Review

Novo tratamento de enxaquecas: Utilização de anticorpos monoclonais - Revisão

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ABSTRACT

Migraine is one of the most prevalent diseases in the population and, in addition, it is one of the main disabling diseases, having a negative impact on the quality of life of the sufferer. Migraine will mainly affect individuals of economically active age, reducing productivity and impacting the entire labor market. In the field of migraine therapies, monoclonal antibodies that inhibit Calcitonin Gene-Related Peptide (CGRP) stand out, which has a strong correlation with the pathophysiology of migraine attacks. Thus, the present study aims to investigate the literature to review the treatment of migraines with the use of monoclonal antibodies, analyzing the prognosis and improvement of the patients submitted. A systematic review of the literature was carried out, produced between September 2021 and April 2022 by two independent researchers. A total of 1,105 articles were identified, of which 33 were included in the inclusion criteria, and were then analyzed. The use of monoclonal antibodies, Erenumab, Eptinezumab, Fremanezumab and Galcanezumab showed better results in all parameters analyzed when compared to the placebo groups. They demonstrated a reduction in the average number of migraine days per month, a decrease in the number of days with a migraine, a reduction in the use of acute medication, and an improvement in quality of life scores. It is concluded that monoclonal antibodies are an innovative therapy for migraine and emerge as preventive options with good tolerability in terms of adverse effects and efficacy. Further research is needed to further evaluate long-term efficacy and safety due to the recent introduction of this therapy.

Keywords: Migraine, Monoclonal antibodies, Efficacy.

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INTRODUÇÃO

Migraine or migraine is a neurological disease characterized by a type of primary headache. It has a high prevalence in the world population, being characterized as disabling to its patients due to its throbbing or pulsatile pain that has a variable duration, from a few hours or even a day (1). In addition, accompanied by this pain, neurological symptoms such as vertigo and dizziness and more systemic symptoms such as nausea and gastrointestinal symptoms can be associated (2). It was estimated in 2016 that approximately 3 billion individuals in the world suffered from this pathology and, in Brazil, this prevalence was between 14 and 15,000 cases per 100,000 inhabitants. In addition to this considerable presence among the population, this disease is more prevalent in females and mainly affects people between 35 and 45 years of age, which is of economically active age (3,4).

Migraine has a complex pathophysiology that is not fully elucidated, resulting in a treatment that is difficult to approach (2). Conventional migraine therapy is based on two approaches, symptomatic and prophylactic, both of which are not ideal for the permanent solution of pain crises (5,6,7). Symptomatic treatment of severe acute seizure is usually addressed with the use of triptans. Its prophylactic approach is based on the administration of tricyclic antidepressants, anticonvulsants, beta-adrenergic blockers, and calcium channel blockers (5, 6, 8). New treatments emerge as the pathophysiology of migraine becomes more elucidated, including Monoclonal Antibodies (7). Antibodies were discovered in 1890 by Emil von Behring and Shibasaburo Kitasat (9). However, it was only later discovered that the antibodies were glycoproteins, secreted by B lymphocytes, which acted specifically against antigens that could infect the organism of their carrier (10). A specific antigen is capable of triggering a polyclonal immune response, that is, an antigen can have several epitopes, and each antibody is capable of binding to a single epitope, which characterizes these immunoglobulins as highly specific (10). Immune responses composed of only a single type of antibody (monoclonal) are rare due to the need for a highly specific antigen for a single type of antibody. However, if they do occur, they are extremely accurate, performing an action only on their specific target (9).

Monoclonal antibodies were first described in 1975 by Georges Köhler and César Milstein (11). This type of antibody got its name because of its production method. In this case, the cloning process of a single B lymphocyte was carried out and, from the clones of this lymphocyte, several morphologically identical antibodies would be secreted, which would act on the same specific antigens (10,12).

These new drugs have demonstrated enormous therapeutic potential for several pathologies because they have a highly specific mechanism of action and have few side effects. Among the pathologies in which these drugs can act are migraine, breast cancer, psoriasis, some rheumatologic diseases and inflammatory bowel disease (10,13). The number of possibilities for treatment with monoclonal antibodies is still uncertain, but it is estimated that the potential of this type of drug in therapy is enormous(9,10).

In the field of migraine therapies, monoclonal antibodies that inhibit Calcitonin Gene-Related Peptide (CGRP) stand out, which has been shown to be strongly related to the pathophysiology behind migraine attacks (14). In view of this correlation, monoclonal antibodies that act on the CGRP pathways have been developed and are now being investigated in order to gain a better understanding of their use in therapeutics, including Erenumab, Eptinezumab, Fremanezumab and Galcanezumab (14,15,16).

OBJECTIVES

The present study aims to review and elucidate the treatment of migraines with the use of Monoclonal Antibodies, analyzing the prognosis and improvement rate of patients who undergo this treatment.

METHODOLOGY

The present study was based on a systematic review of the literature, carried out between September 2021 and April 2022, compiling results of primary studies, through an impartial and comprehensive review of the literature. It was elaborated according to the steps established for the realization of a systematic review, which include the elaboration of a research question, formulation of a research strategy, literature search, selection of articles, data extraction, evaluation of methodological quality, synthesis of data, evaluation of the quality of evidence and, finally, the writing of the systematic review

The research question elaborated and answered in the present study was "What is the prognosis and rate of improvement of migraine patients treated with Monoclonal Antibodies?", which was elaborated by the acronym PICO (population to be studied, intervention, comparison and outcome).

The search for articles was carried out from the selection of terms located in DeCS (Descriptors in Health Sciences) and MeSH (Medical Subject Headings) and used in the Scielo, Pubmed, Scopus-elsevier, Lilacs-bvsalud and, finally, Web of Science databases.

The terms used were "Migraine", "CGRP", "monoclonal antibodies", "Erenumab", "Fremanezumab", "Galcazenumab", "Eptinezumab", and their respective synonyms, associated with Boolean operators according to the search strategy of each database.

Among the inclusion criteria were primary studies that matched the research question, clinical trials with comparison with control groups (placebo), research conducted in humans or animal models, published between 2010 and 2021, and consistent with the Portuguese, English, and Spanish languages. The exclusion criteria adopted were those articles that did not fit the research question, theses, dissertations and case reports, and studies in languages other than those mentioned in the inclusion criteria.

It resulted in a total of 33 articles, which were included in all the criteria presented, and were then submitted to the stage of data extraction and evidence quality.

THEORETICAL BACKGROUND

PATHOPHYSIOLOGY OF MIGRAINE AND THE ROLE OF CGRP

Migraine or migraine does not yet have a fully elucidated pathophysiology, however, it has been evolving in recent decades. In the past, it was considered that the vascular alteration present in the pathology generated the pain sensation, however, today it is known that vasodilation is a consequence of neurogenic activation, not a cause of pain itself. (17) In this sense, the pathophysiology of migraine cannot be defined as a single pathway, but rather as a complex disorder of the cerebral pathway that involves cortical and subcortical areas, as well as regions of the brainstem. (18)

Among the pathways that play a role in migraine expression, we have the trigeminovascular system. It consists of axons derived from the trigeminal ganglion that extend to the meninges and intracranial arteries. These structures converge in the trigeminocervical complex, located in the caudal nucleus of the trigeminal cortex, along the dorsal horn of C1 and C2 of the spinal cord. This complex also projects ascending pathways to brainstem nuclei, neural ganglia, cerebellum, and the brain. (17, 18).

In the midst of afferent activation of the trigeminal by pro-pain stimuli, there is the release of neuropeptides, such as bradykinin, somatostatin, neuropeptide Y and, among them, the calcitonin gene-related peptide (CGRP) (17, 18). This neuropeptide is characterized by a potent vasodilator, found in the trigeminal spinal nucleus, more comprehensively, in the cell bodies and dendrites of second-order neurons and in the axon terminals of first-order neurons. (17).

Its release results in potent cerebral arteriolar vasodilation. In addition to this important action, its role in second- and third-order neurons was observed, generating a modulation of the central mechanisms of pain, and making evident its role in cranial nociception. (17, 18) Regarding this neural modulation, studies have revealed that the increase in CGRP in migraine patients is related to a reduction in descending pain inhibitory mechanisms, generating susceptibility and sensitization to migraine. (18)

In addition, the release of CGRP after stimulation of the trigeminal ganglion generates neurogenic inflammation with dilation of meningeal vessels, increased vascular permeability, plasma extravasation and release of pro-inflammatory mediators by mast cells (17). These changes cause an increase in peripheral and central pain sensitization signals, as well as a reduction in the activation threshold of neurons in the central nervous system, resulting in allodynia and central pain. In addition, due to the mechanisms mentioned above, this neuropeptide is also associated with the possibility of migraine chronification (17, 19).

With this activation of the trigeminovascular complex and all the changes caused, including those resulting from the action of the CGRP, there is the formation of a cascade that culminates in the stimulation of important brain regions. Among these are the brainstem, the periaqueductal gray matter, the dorsolateral pons, and the cortical region, resulting in pain sensation. (18)

Therefore, the CGRP, as presented above, plays an important role in the pathophysiology of the pathway of nociceptive mechanisms of the trigeminal vascular system, having an important repercussion on the pathophysiology of the disease itself. However, it is important to emphasize that the pain reaction caused does not occur through direct action on nociceptors, but through interaction with neurons, glial cells and blood vessels of the meninges (20)

CALCITONIN GENE-RELATED PEPTIDE - CGRP

CGRP is a neuropeptide composed of 37 amino acids, expressed in both peripheral and central neurons. It was initially related to the pathophysiology of migraine in 1985, and this theory came to be supported when the increase in its concentration during acute migraine attacks, and its respective reduction with symptomatic relief, was analyzed. Since this discovery, the important role of CGRP in the pathophysiology of migraine has been further studied and recognized (21).

Characterized by the neuropeptide most commonly found in the trigeminal nerve, CGRP can be identified in sensory neurons, myelinated and unmyelinated fibers (related to pain

transmission), thalamus, hypothalamus, and cerebellum, and is also present in regions that make up the trigeminovascular pathway (17, 18, 21). In addition to these regions, it can be found in places that do not participate in the pathophysiology of migraine such as the kidneys, adrenal glands, and pancreas. (7)

CGRP has two isoforms, αCGRP and βCGRP. The former is expressed primarily in the nervous system and the latter in the sensory enteric system. In both regions, this neuropeptide acts on vasomotor activity, being characterized as the most potent vasodilator of the calcitonin family, however, they differ in potency and regulation, according to their locations in the body (17, 22). The CGRP receptor, to which these molecules bind, is bound to the G protein, and has three subunits, these being the calcitonin-like receptor (CLR), the activity-modifying protein 1 (RAMP 1) and the receptor component protein (RCP). CGRP, when it binds to its receptor, has a high affinity for RAMP1 and a lower affinity for CLR, binding facilitated by CPR, stimulating stimulatory G protein (Gs) and causing activation of its signaling pathway. At the end of this promoted cascade, the alterations promoted by the CGRP are evidenced, such as pain modulation, vascular dilation and neurogenic inflammation. (17, 21)

The CGRP, therefore, has an important function of vasodilation and modulation of the pain reaction during migraine, being a causative mechanism, and, consequently, a means of approach for the treatment and respective prevention of migraine. (20)

MONOCLONAL ANTIBODIES

Monoclonal antibodies that act on the CGRP neuropeptide pathway have been studied since the beginning of the twenty-first century and had their first patents registered in 2006 (19). CGRP was closely related to pain attacks in migraine patients, so monoclonal antibodies developed specifically to act on this pathway are a viable pharmaceutical option with few related adverse effects (21).

In addition to the low profile of adverse effects present in this therapy, monoclonal antibodies have advantages over other drugs tested when compared in terms of half-life, hepatotoxicity and permeability of the blood-brain barrier (17, 20).

The reports of small occurrences of side effects are explained by the functional conformation of the antibodies themselves. It is known that antibodies are composed of two regions, one of which is the constant region, which is responsible for the effector functions of immunoglobulins or, in other words, for mediating the different physiological interactions of the antibody, and a variable region, which is responsible for interacting with specific epitopes of

antigens (11,9). The characteristic super specificity of antibodies is determined by their variable region. It will be able to recognize the 3-dimensional conformation of the specific epitope of an antigen, but it will be able to recognize only a single conformational arrangement, i.e., a single epitope (9,12). Thanks to this high specificity, monoclonal antibodies developed to act on the CGRP pathway, both on the neuropeptide itself and on its receptor, demonstrated a potent affinity for binding to their specific targets and a low affinity for binding to other epitopes not belonging to their targets. Thus, it provides a well-defined targeted therapy with no adverse effects in exuberance (17).

Furthermore, antibodies have a long half-life when they are located in the systemic circulation (20-45 days), because of their nature as IgG immunoglobulins and because they have a high affinity for neonatal Fc receptors (17, 19). This long half-life is one of the main characteristics of monoclonal antibodies that make them suitable for a prophylactic treatment against migraine attacks, requiring only 1 application monthly, or sometimes at even lower frequencies (17, 19).

Since immunoglobulins are proteins, they cannot be administered orally, requiring parenteral, subcutaneous or intravenous application (17, 19). Subcutaneous applications are more convenient for drug administration, but these have been shown to have lower bioavailability (40-80%) and slower drug absorption (17). This difference occurs because the intravenous administration will ensure that the entire content of the injection reaches the systemic circulation of the patient, while the subcutaneous route will require lymphatic transport to the left subclavian vein, through which the drug will reach the systemic circulation, and this transport process has obstacles for the drug molecules, which ends up being, in part, lost (17).

Another advantage of using monoclonal antibodies is that they are metabolized primarily through the reticuloendothelial system rather than through the cytochrome p450 pathway in the liver (17, 19). In this way, the chances of hepatotoxic adverse effects decrease, because the liver is not overloaded with the metabolization of this drug (17, 19). In the case of monoclonal antibodies, the main route of metabolization will be by protein degradation in reticuloendothelial cells present in the skin, muscles, liver and intestine, where 33, 24, 16 and 12% of the metabolization of monoclonal antibodies are carried out, respectively.

Another factor considered for the low number of adverse effects in this therapy is the low permeability of the blood-brain barrier to monoclonal antibodies, unlike oral prophylactic drugs for conventional migraines (17, 19). The blood-brain barrier in healthy conditions is impervious to monoclonal antibodies, but low doses of these antibodies can be seen in the brain parenchyma

(0.35% of the drug) and even lower doses in the cerebrospinal fluid (less than 0.1%) (17). And, even at low doses, neonatal Fc receptors will act on the choroid plexus so that the IgG molecules present in the cerebrospinal fluid are quickly returned to the vascular circulation (17).

Among the monoclonal antibodies that act on the CGRP for the treatment of migraine, we have as representatives Erenumab, Eptinezumab, Fremanezumab and Galcanezumab (14,15,16).

Erenumab

Unlike other monoclonal antibodies, Erenumab is the only drug in this class that acts on the CGRP pathway that is fully human and that, instead of acting directly on the CGRP peptide, acts on its canonical receptor (14 19). More specifically, Erenumab will be an IgG2-type immunoglobulin that will act by blocking the production of cyclic AMP induced by CGRP, by competitively and reversibly binding to the receptor of this neuropeptide (14 , 19). Erenumab's affinity for the CGRP receptor is up to 5000 times higher than its affinity for the other receptors in this family (amylin, calcitonin, and adrenomedullin receptors), giving this drug its low adverse event profile (14, 19). What's more, this drug had a half-life rate of approximately 28 days, making it ideal for ongoing prophylactic treatments with a low dropout rate among patients (17).

Eptinezumab

Eptinezumab is a humanized monoclonal antibody that acts directly on the CGRP neuropeptide, both in its alpha and beta subunits (17). This antibody is of the IgG1 class and, unlike the other monoclonal antibodies mentioned in this text, it is developed from yeast cells, unlike ovarian cells of hamsters, as is the case with the others (19). Another important difference between Eptinezumab and the other antibodies for prophylactic treatment of migraines is its route of administration. The application of these monoclonal antibodies should always be parenteral, as they are composed of proteins, but Eptinezumab will be the only drug among these that will be injected intravenously, while the others will be injected subcutaneously (17, 19). This difference in the route of application ensured that Eptinezumab had the highest maximum serum concentration result among the drugs discussed here, reaching its maximum value in only 4.8 hours after injection and maintaining a half-life of an average of 31 days (17, 19).

Fremanezumab

Like Eptinezumab, Fremanezumab is a humanized monoclonal antibody that acts directly on CGRP in a potent way, both in its alpha and beta isoforms (15). However, this drug belongs

to the class of IgG2a immunoglobulins and will be administered subcutaneously. An interesting factor was observed in their studies, in which patients with lower BMI had higher peak serum concentrations of this drug than those with higher BMI scores (15, 19). Another factor observed in their studies was that the minimum dose for this drug to become efficient in the treatment was injections of at least 225 mg (19). Regarding its half-life, divergences were found between 2 studies. In the first, this time was indicated as 31 days, while the other reported a time of 39-48 days for metabolization of half of the drug (17, 19).

Galcanezumab

The third humanized monoclonal antibody that will act directly on CGRP is Galcanezumab. It will be able to bind to both the alpha and beta forms of this neuropeptide, preventing it from performing its vasodilation function (16, 17). Belonging to the IgG4 class, this drug will be administered subcutaneously and has a half-life of 25-30 days with a time to maximum serum concentration between the 7th and 14th day after administration (17, 19). An important finding was that capsaicin-induced dermal blood flow was interrupted for a long time when capsaicin-induced dermal blood flow was interrupted for about 42 days (19, 23).

RESULTS AND DISCUSSION

EVALUATION OF THE QUALITY OF THE ARTICLES

33 articles were evaluated for methodological quality. The risk of bias was low 6.06% n:2, moderate bias 84.8% n:28, and high bias 9.09% n: 3.

As for the domains, random sequence generation, allocation concealment, and participant and team concealment were present in 90.9% (n: 30) of the studies, and were not applied in 3 studies (Tepper, S.J. et al, 2020; Kudrow, D. et al, 2021; Ashina, M. et al, 2019).

The detection bias, which analyzes the concealment of outcome evaluation, was unsatisfactory in most studies 84.8% n:28, because these studies did not describe whether the outcome evaluator was blinded. 6% n:2 were satisfactory in this regard and 9% n:3 described that the evaluator was not blind.

Regarding attrition bias (incomplete outcome data), reporting bias (selective reports) and other sources of bias, all studies (100% n:30) were satisfactory, meeting the requirements.

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Table 1: Quality assessment (Cochrane)

AUTOR/ANO	VIÉS DE SELEÇÃO	VIÉS DE SELEÇÃO	VIÉS DE DESEMPENHO	VIÉS DE DETECÇÃO	VIÉS DE ATRITO	VIÉS DE RELATO	OUTRAS FONTES DE VIÉS
CRITÉRIO DE VIÉS	1	2	3	4	5	6	7
Goadsby et al, 2017	S	S	S	I	S	S	S
Sakai, Fumihiko et al, 2019	S	S	S	I	S	S	S
Dodick et al, 2018	S	S	S	S	S	S	S
Skljarevski, Oakes et al, 2018	S	S	S	I	S	S	S
Lanteri-Minet et al, 2021	S	S	S	I	S	S	S
Dodick , Silbertein et al, 2018	S	S	S	I	S	S	S
Lipton e Cohen et al, 2020	S	S	S	I	S	S	S
Lipton e Goadsby et al, 2020	S	S	S	S	S	S	S
Sakai, Igarashi et al, 2021	S	S	S	I	S	S	S
Sakai, Tatsuoka et al, 2021	S	S	S	I	S	S	S
Ashina et al, 2021	S	S	S	I	S	S	S
Skljarevski, Matharu et al, 2018	S	S	S	I	S	S	S
Reuter et al, 2018	S	S	S	I	S	S	S
Okonkwo et al, 2021	S	S	S	I	S	S	S
Diener et al, 2020	S	S	S	I	S	S	S
Dodick et al, 2019	S	S	S	I	S	S	S
Silberstein et al, 2020	S	S	S	I	S	S	S
Smith, T. R. et al, 2020	S	S	S	I	S	S	S
Ashina, M. et al, 2020	S	S	S	I	S	S	S
Lipton, R. B. et al, 2019	S	S	S	I	S	S	S
Takeshima, T. et al, 2021	S	S	S	I	S	S	S
Silberstein, S.D. et al, 2017	S	S	S	I	S	S	S
Ferrari, M.D. et al, 2019	S	S	S	I	S	S	S
Tepper, S.J. et al, 2020	N	N	N	N	S	S	S
Kudrow, D. et al, 2021	N	N	N	N	S	S	S
Ashina, M. et al, 2019	N	N	N	N	S	S	S
Goadsby, P.J. et al, 2020	S	S	S	I	S	S	S
Dodick, D.W. et al, 2020	S	S	S	I	S	S	S
Wang, S.-J. et al, 2021	S	S	S	I	S	S	S
Dodick, D.W., Stephen, et al, 2014	S	S	S	I	S	S	S
Sun, H. et al, 2016	S	S	S	I	S	S	S
Tepper, S. et al, 2017	S	S	S	I	S	S	S
Dodick, D. W, Egilius. et al, 2014	S	S	S	I	S	S	S

CHARACTERISTICS OF THE STUDIES

Among the 33 articles selected to support the study, the oldest are dated in 2014: (54) and (57). And the most recent ones were published in the year 2021: (33, 34, 35, 38, 49, 53)

Most of the studies deal with international multicenter studies analyzing patients from various areas of the world n=23 (70%), however it is possible to highlight the main regions of the world where patients were analyzed: North America (n=19, 58%) and Europe (n=14, 42%) were the places most used by the researchers. Some other research sites used were: Japan (n=6, 18%), Australia (n=2.6%) and Latin America (n=2.6%).

The methodologies of each study are important because they bring methodological quality to the article and, consequently, a higher level of evidence and confidence in the research carried out. Among the studies analyzed were phase 3 studies (n=15, 45%), phase 2 studies (n=7, 21%), randomized studies (n=29, 88%), non-randomized studies (n=4, 12%), placebo-controlled

studies (n= 30, 91%), studies that did not use placebo (n=3, 9%), studies that applied the double-blind methodology (n=28, 85%), and studies in which both researchers and patients knew the drugs and doses they were being administered (n=5, 15%).

In addition, all studies were conducted in human patients with continuous follow-up ranging from 12 weeks of analysis to up to 3 years. The studies relied on different samples of patients to conduct the research, with the study with the largest sample evaluating 1121 patients conducted by Lipton, RB et al, 2020, initially, and the study with the smallest sample had 128 patients conducted by Kudrow, D et al, 2021, a mean age range of 18-65 years was the most common among the studies, and some included patients up to 75 years of age.

ADVERSE EFFECTS PRESENTED

During the studies conducted, the side effects associated with the drugs were reported in order to understand the repercussions that they could have on the health of the patients. Most studies used control groups that received only placebo doses to be able to adequately compare drug-related adverse effects. In most of these studies, it was observed that there was no significant discrepancy in the incidence of side effects between the placebo groups and the groups receiving the monoclonal antibodies. Moreover, the studies also showed that the vast majority of all side effects recorded were mild to moderate in intensity without presenting a significant risk to the subjects of the research.

Studies conducted with the erenumab antibody showed a mean incidence rate of medication-related adverse effects of 38.3%, compared with 34.2% in the placebo group. Within this group, 1.18% were adverse effects considered severe, and in the placebo group this rate was 0.86%. The most prevalent adverse reactions observed in the study and their respective incidence rates compared to the placebo groups were: nasopharyngitis (11.83%; 14.8%), upper airway infection (4.69%; 1.7%), pain at the application site (5%; 1%), constipation (4.27%; 1.175%), and nausea (2.5%; 1.5%). In addition to these, there were other adverse effects at a lower incidence, namely: erythema at the site of application, sinusitis, dizziness, fatigue and back pain. (25, 26, 27, 29, 37, 44, 45, 48, 50, 51, 53, 55, 56) The eptinezumab antibody studies had a mean incidence rate of study-related side effects of 22.83% and the placebo group had 26.5%. This is the lowest incidence rate of adverse effects observed among the studies of the four drugs, although it is close to the incidence rate observed in the placebo group. The following are the most prevalent adverse effects throughout the studies and their respective incidence rates in the eptinezumab and placebo control groups: nasopharyngitis (5.91%;

10.91%), upper airway infections (5.9%; 5%), urinary tract infections (2.87%; 3.9%), nausea (2%; 1.43%), and fatigue (1.95%; 0.7%). Other adverse effects observed during the studies were dizziness, sinusitis, and drug site reactions. (32, 39, 40, 41, 42, 43, 49, 54)

The monoclonal antibody Fremanezumab had a mean incidence of study-related adverse reactions of 38% and a mean of 35.5% in the placebo group. The mean incidence of severe adverse effects in patients using fremanezumab over the course of the studies was 1%, whereas in the placebo group this mean was 1.5%. Among the adverse effects observed throughout the studies that stood out for their higher incidence, we can mention, along with their respective incidence rates and comparison with the placebo group, reactions at the injection site (27.65%; 21.4%), the main reactions being pain at the injection site (14.8%; 12.33%) and erythema at the injection site (13%; 10.5%), nasopharyngitis (4.8%; 4.5%) and upper airway infection (3.25%; 2.5%). Other adverse effects have been reported, but to a lesser extent, namely: nausea, dizziness, fatigue, back pain, cough and headache. (46, 47, 30, 31, 33, 34, 35)

Finally, the monoclonal antibody Galcanezumab had a mean incidence of side effects related to the studies of 71.9%, and the placebo group had a mean of 64.75%. Thus, it is possible to observe that Galcanezumab had the highest incidence rate among the monoclonal antibodies analyzed, but it is not more dangerous than the others because it has an incidence rate relatively close to that of the placebo group. The adverse effects considered severe in the group that received the drug had a mean incidence of 1.85% and in the placebo group 3.25%. The mean incidence rate of the most common adverse effects is presented below with comparison with the placebo group: nasopharyngitis (10.3%; 12.5%), application site pain (11.1%; 9.2%), application site erythema (5.9%; 0.4%), upper airway infection (7%; 9%), and dizziness (4.65%; 3.6%). Other adverse effects observed on a smaller scale were nausea, fatigue, back pain, and headache. In the study conducted by Skljarevski V et al, 2018, a significant discrepancy was observed between the galcanezumab group and the placebo group regarding application site reactions, so the incidence in patients receiving galcanezumab was higher. (28, 36, 38, 52, 57)

ANTIBODIES USED BY ARTICLES

In the articles analyzed, 4 different monoclonal antibodies were used: Erenumab, Eptinezumab, Fremanezumab and Galcanezumab.

O fármaco mais utilizado foi o Erenumab (39,39% n= 13) sendo eles: Goadsby et al, 2017; Sakai, Fumihiko et al, 2019; Dodick et al, 2018; Lanteri-Minet et al, 2021; Reuter et al, 2018; Lipton, R. B. et al, 2019; Takeshima, T. et al, 2021; Tepper, S.J. et al, 2020; Ashina, M. et

al, 2019; Goadsby, P.J. et al, 2020; Wang, S.-J. et al, 2021; Sun, H. et al, 2016; Tepper, S. et al, 2017 (25, 26, 27, 37, 44, 45, 53, 56). Em seguida, Eptinezumabe (24,24% n= 8) (Lipton e Cohen et al, 2020; Diener et al, 2020; Dodick et al, 2019; Silberstein et al, 2020; Smith, T. R. et al, 2020; Ashina, M. et al, 2020; Kudrow, D. et al, 2021; Dodick, D.W., Stephen, et al, 2014)(32, 39, 40, 41, 42, 43, 49). Fremanezumabe veio em seguida, correspondendo a 21,21% n= 7 (Dodick , Silbertein et al, 2018; Lipton e Cohen et al, 2020; Sakai, Igarashi et al, 2021; Sakai, Tatsuoka et al, 2021; Ashina et al, 2021; Silberstein, S.D. et al, 2017; Ferrari, M.D. et al, 2019)(30, 33, 34, 35, 46, 47). Por fim, Galcanezumabe (15,15% n=5) (Skljarevski et al, 2018; Skljarevski et al, 2018; Okonkwo et al, 2021; Dodick, D.W. et al, 2020; Dodick, D. W., Egilius et al, 2014)(28, 36, 38, 52 e 57).

IMPROVEMENT RATES

By analyzing the improvement rates of the monoclonal antibodies used, different parameters were evaluated.

Erenumabe

Regarding the efficacy of treatment with the monoclonal antibody Erenumab, it was observed that there was a better performance of the groups submitted to the drug when compared to the placebo groups in the following aspects: decrease in the average number of migraines per month, percentage of patients with improvement equal to or greater than 50%, 75% and, in some cases, even patients with 100% improvement, reduction in the number of days per month in which specific medications for immediate relief for migraine are needed, HIT-6 score (Headache Impact Test), which is composed of 6 items that assess periodicity, disability and psychological distress related to migraine pain crises, and the MIDAS score (Migraine Disability Assessment Scale) that evaluates, basically, the number of productive days lost in the last 3 months due to migraine episodes.

Regarding the decrease in the number of days with migraine attacks per month, it was observed that, in most studies, patients receiving erenumab had a higher rate of decrease, regardless of the dose used; 7mg, 21mg, 28mg, 70mg or 140mg. (25, 26, 27, 37, 44, 45, 53, 56)

Regarding the percentage of patients who achieved a reduction in the number of migraines greater than or equal to 50%, the groups receiving erenumab also stood out in relation to patients in the placebo group with a higher number of patients exceeding this milestone. (25, 26, 27, 37, 45, 53, 56) A smaller number of studies evaluated the number of

patients who achieved 75% or more response to treatment or 100%, but in those that evaluated these marks, it was seen that patients treated with erenumab achieved these marks in greater quantities when compared with patients in the placebo group. (37, 53) Another value analyzed was the reduction in the use of specific drugs for the acute treatment of migraine attacks, and the number of days in which patients treated with erenumab needed these drugs for acute treatment were lower than in patients treated with placebo. (26, 37, 56)

The scores to assess the impact of migraine on the lives of patients are useful to ascertain an improvement in the quality of life of these patients before and after treatment, in the HIT-6 score patients treated with erenumab had a more significant decrease in the score compared to patients in the placebo group, Lipton RB et al, 2019 showed significant differences in the percentage of patients achieving a decrease greater than or equal to 5 points in the HIT-6 score, where 49.4% of patients undergoing erenumab treatment showed such a decrease, while 30.5% of patients in the placebo group achieved the desired result. (26, 29, 44) Evaluating the MIDAS score, Lipton RB et al, 2019, also demonstrated that a greater number of patients in the placebo group had scores corresponding to the denomination severe or very severe compared to the group medicated with erenumab. (44)

Eptinezumabe

The preventive effect on seizures was superior in all groups that underwent the drug, regardless of dose (300mg, 100mg, 30mg 10mg), when compared to the placebo groups. (32, 39, 40, 41, 42, 43, 49)

The ability to show improvement ≥ 50% or 75% was higher in all groups submitted to treatment that evaluated this item (32, 39, 40, 41, 43). When analyzed individually, eptinezumab showed different numbers regarding the percentage of subjects who achieved the improvement ≥ 50% and ≥ 70%, when compared to placebo in the studies. More than half of the patients showed an improvement ≥ 50%, which was represented by Silberstein et al, 2020, with an improvement of 61-64% depending on the dose to be administered (100mg or 300mg, respectively)(32, 39, 40, 41, 43). Regarding the improvement ≥ 70%, the numbers reduce subtly, being represented by 33.3-26.8% by Dodick et al, 2019 and 43.1-39.3% by Siberstein et al, 2020 (40,43).

The average daily percentage of migraines per month was reduced most significantly in patients who underwent treatment (32, 39, 41, 42, 43). Lipton and Goadsby et al, 2020 and Diener et al, 2020 obtained similar results, showing between 8.2 and 8.8 days of reduction, as

well as Smith, T. R. et al, 2020 and Ashina, M. et al, 2019, with a reduction between 4.1 and 5.3 days (32, 39, 41, 42, 43)

Furthermore, according to Lipton and Goadsby et al, 2020, the use of acute medication for pain control was considerably reduced when compared to placebo. (32)

It was also possible to observe an improvement in the scores applied to the groups that underwent the use of monoclonal antibodies. Evaluating the HIT-6 score, all studies that presented this evaluation and that had patients undergoing treatment with the monoclonal antibody showed a reduction in their scores. According to Dodick et al, 2019 and Kudrow, D. et al, 2021 there was a reduction of up to 10 points in this score, in addition, a reduction in the percentage of patients who had severe life impact from chronic migraine was observed from 91.1% to 38.5% by the end of the study period (32, 40, 41, 49). In the evaluation of the MIDAS score, there was a reduction in the score from 56.8 (baseline) to 22 in the patients who received the treatment. In addition, there was a reduction from 84.4% to 26.8% in patients with severe dysfunction due to seizures and an increase in the percentage of patients with mild or no dysfunction from 5.5% to 59.4%. (49)

Fremanezumabe

The average daily percentage of migraines per month was reduced when compared to the placebo group (30, 33, 34, 35, 46, 47). The mean reduction in the frequency of days of pain per month in the group submitted to treatment was 4.1 +- 0.4 in the 225 mg dose and 4.4 +- 0.4 in the 675 mg dosage, and in all studies, the reduction was more significant in the group that received the drug monthly (225 mg) (30, 33, 34, 35, 46, 47). In addition, Ferrari, M.D et al, 2019 showed a 36.8% reduction in the mean percentage of the number of migraine days in the monthly group (225mg) and 34.9% in the quarterly group (675mg) (47).

The ability ≥ show 50% improvement on monthly days was higher among the group that received the treatment when compared to placebo. The monthly dosage of fremanezumab improved between 47.7 and 29%, with a mean of 37.8%. On the other hand, the quarterly dosage of fremanezumab improved by 45.3-29.1%, with a mean of 38.1% (30, 33, 34, 35, 46, 47). Ashina et al, 2021 also analyzed the reduction capacity≥ 75% in the average monthly number of days, showing a reduction of 12% for the monthly drug and 8% for the quarterly drug. (35)

The use of acute medication was reduced in all studies that analyzed this condition. The mean reduction in the number of days in which medication for acute treatment was required was 3.6 +- 0.4 for the monthly and quarterly groups (30, 33, 35).

The scores evaluated by the studies showed significant improvements in the groups submitted to the treatment. HIT-6 showed a reduction in the treatment groups, with a mean reduction of 7.36 days on the monthly drug and 6.92 days on the quarterly drug compared to that reported at the beginning of the studies (33, 35, 46, 47). The MIDAS score also showed a reduction in all studies in which it was applied, showing a reduction between 24.6-26.3 in the individuals who received the monthly dose and between 20-23 in those who received the quarterly dose (30, 35, 47). The MSQOL scale, used by Lipton, R. B. et al, 2019 and Ferrari, M. D. et al, 2019, which assesses quality of life by analyzing restrictive and emotional function, showed a significant increase in its numbers (31, 47). These authors also used the EQ-5D scale, which measures general health status, which also showed improvement in the group that received Fremanezumab when compared to the placebo group.

Galcanezumabe

The studies conducted with the galcanezumab antibody evaluated the efficacy of this drug with respect to the following dose options: 5mg, 50mg, 120mg, 150mg, 240mg and 300mg. Regarding the decrease in the mean number of migraine episodes in the month, more expressive results were observed in the galcanezumab groups compared to the placebo groups, where there was a decrease in migraine days regardless of the dose used. (28, 36, 38, 52 and 57) Okonkwo R et al, 2021 further looked at the difference in efficacy of galcanezumab in patients with episodic and chronic migraine, where patients diagnosed with episodic migraine had a decrease in mean migraine days of 2.9 when treated with galcanezumab and patients in the placebo group a decrease of 0.3. Patients diagnosed with chronic migraine had a decrease of 5.9 days in the galcanezumab group compared to 2.2 days in the placebo group. (38)

Regarding a 50% or greater response to treatment, patients treated with galcanezumab also demonstrated a superior rate of response compared to the placebo group regardless of the dose administered. (36, 52, 57) Skljarevski V et al, 2018 obtained results about the response to treatment of 75% or higher and 100% response, where they observed that patients medicated with galcanezumab 240mg obtained significantly higher results than those presented by the placebo group.

Regarding symptomatic relief drugs in acute treatment, it was possible to notice a more pronounced decrease in their use in patients treated with galcanezumab compared to the placebo group, so that regardless of the dose administered, the results in the galcanezumab group continued to be superior in terms of efficacy. (36, 38).

Only one study evaluated the efficacy of galcanezumab in relation to the HIT-6 score, and found that this drug at a dose of 120mg was effective in prophylactic treatment and in improving quality of life, with a decrease in the frequency of migraine-related pain crises, compared to the placebo group, however, it also observed that the drug with 300mg of dosage did not demonstrate such significant efficacy when compared to the placebo group. (28)

GENERAL CONCLUSIONS

Analyzing the studies presented, it was possible to observe that erenumab proved to be a good option for prophylactic therapy for migraine, being able to achieve the efficacy goals in the vast majority of the studies that evaluated it and demonstrating superiority in relation to the control group in all parameters evaluated in the present study. Regardless of the dosage analyzed, there were good results within the study, demonstrating that it is an effective and safe drug when judged by the data it presents.

Eptinezumab showed improvement in all aspects when compared to placebo, obtaining better responses at 300 mg or 100 mg dosages. In addition to being the monoclonal antibody with the lowest incidence rate of adverse effects, which makes it stand out among the other drugs of this class analyzed in the present study

Fremanezumab also showed improvement in all items evaluated when compared to the placebo groups. However, its monthly administration, through the dosage of 225 mg, presented better results in relation to the reduction of the daily average of migraines per month when compared to the group with quarterly administration, of 675 mg.

Galcanezumab, on the other hand, showed good results in terms of its efficacy compared to the placebo groups used as control in the studies, but it also had the highest rate of adverse effects, even though it was close to the incidence of adverse effects presented by the placebo groups analyzed in their studies. In any case, analyzing the results presented, this drug still seems to be safe for use by patients with a satisfactory efficacy in the response to treatment.

FINAL THOUGHTS

Based on the data presented, it is possible to observe the potential that monoclonal antibodies have in the prophylactic treatment of migraines, both chronic and episodic. This class of drugs showed positive results in the studies, with all four drugs showing a significant decrease in the number of migraine episodes compared to the control group and a relatively low rate of adverse effects when compared to the control group. However, even though it presents results

that speak in favor of their therapeutic potential, there is still much to understand about these drugs.

Thus, further studies are needed in relation to these drugs, in order to analyze the long-term safety and efficacy related to chronic use, which doses offer the greatest therapeutic advantage with the lowest risk of life, and which of the drugs of this class, analyzed in the present study, have the best prophylactic action.

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