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Original

Evaluation of the use of CGRP monoclonal antibodies (mAbs) in migraine prophylaxis in a private clinic

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Abstract

Introduction
Migraine is considered the second most prevalent neurological disorder in the population and highly disabling.
Objective
The aim of this study is to evaluate the use of calcitonin gene-related peptide (CGRP) monoclonal antibodies in migraine prophylaxis, with emphasis on therapeutic response, adverse effects, and impacts on quality of life.
Methods
A quantitative, retrospective, and descriptive study was carried out, through the analysis of medical records and telephone interviews with patients *seen at the Serviço de Neurologia e Neurocirurgia*, in the city of Passo Fundo, RS, Brazil, currently or previously having used at least one dose of the medication.
Results
44 patients participated in the study, and 79% of the sample was using erenumab, 14% frenezumab and 7% galcanezumab. After treatment, approximately 14% of respondents had a resolution of 100% of the monthly pain days and 61% reported headache up to 5 days a month, considered to be excellent in 66% of the sample. Therefore, medications reduced, on average, 15 days/month of headache attacks, corresponding to a decrease of approximately 67% of pain days. Approximately 80% of participants noted reduction in pain intensity and 77% improvement in work capacity. In addition, 93.2% of patients reported no adverse effects and 72.7% said they intended to continue therapy.
Conclusion
Thus, it is understood that CGRP monoclonal antibodies are able to reduce monthly headache days, reduce pain intensity and promote improvement in work capacity. Therefore, they can be considered effective, safe and well-adhered medications for migraine prophylaxis.

Keywords:
Calcitonin Gene-Related Peptide
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Introduction

For many years, neurology has sought to understand the most diverse pathologies that affect the brain. Unveiling and recognizing them helps not only to improve the quality of life of the population, but also to promote an increase in life expectancy. Obtaining adequate therapeutic measures can prevent the evolution or offer support to live with diseases that are, many times, incapacitating.[1] In this context, migraine emerges. For over 400 years, migraine was described as the result of a hereditary discharge of nervous origin that affects the central nervous system.[2]

According to the International Classification of Headache Disorders[3], migraine is described as a "recurrent headache disorder manifesting in episodes lasting 4 to 72 hours. Typical features of the headache are unilateral location, pulsatility, moderate or severe intensity, worsening by routine physical activity, and association with nausea and/or photophobia and phonophobia". It is the second most prevalent neurological disorder in the population, affecting about 15% of people, especially women before the age of 35.[4]

In the meantime, the great social effect caused by the disease is estimated. The study ''My migraine voice'', which analyzed the impact of migraine in patients who suffer more than four days of attacks per month, estimated social harm in 87% of the patients interviewed, with 85% having negative repercussions in living with the disease, 83% having sleep disorders, and 38% having already sought emergency medical care within a year.[5]

Today we are convinced that migraine is related to neural and vascular mechanisms that trigger headache attacks through the activation and sensitization of the trigeminovascular pathways, the brainstem, and the diencephalic nuclei. Premonitory symptoms can precede the headache by up to 72 hours, with symptoms such as mood swings, nausea, fatigue, phonophobia, and torticollis. Also, migraine with aura is characterized by a wave of cortical neuronal depolarization (cortical spreading depression), which causes a series of symptoms, mainly visual, sensory, or aphasia.[6]

Pain processing is complex and mediated by hypothalamic dysfunction, peripheral sensitization, and activation of the trigemino-vascular system. Thus, an increase in parasympathetic afferents to the superior salivatory nucleus in the brainstem activates the sphenopalatine ganglion, which generates vasodilation and release of inflammatory mediators in the dura mater, mostly the calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase activating polypeptide 38 (PACAP-38), which, through trigemino-vascular signaling, cause arterial vasodilation, mast cell degranulation, and plasma leakage. This stimulus propagation similarly involves the thalamus and cortical areas, which explains the broad symptomatology of migraine.[7]

Early intervention in the treatment of migraine has as a principle to stop pain at its onset and prevent its progression. However, the most used prophylactic medications, such as antiepileptics, antihypertensives, and antidepressants, have been shown to have little effect in combating the disease.4 One study showed that the adherence rates of patients to prophylaxis with antidepressants, antihypertensives, and anticonvulsants are extremely low, due to lack of specificity of the medications and side effects, and only 30% of the patients maintain the use of the medications after six months.[8]

Thus, the development and improvement of new medications that support the needs of patients unmet by current therapies is critical.4 Anti-CGRP antibodies are pioneering prophylactics for the treatment of the disease and act directly on blocking the main pain-related neuropeptide. Monoclonal antibodies (*i.e.*, erenumab, frenezumab, galcanezumab, and eptinezumab) have shown promise in the prophylactic treatment of migraine. An experimental study by Raffaelli et al.[9], applies this theory in practice and proves the efficacy of the four medications, with a significant portion of patients achieving a reduction of monthly days of pain by more than 50% and about 36% of patients achieving 100% remission of monthly days of headache.[9]

Thus, this study aims to evaluate the therapeutic response of patients using anti-CGRP antibodies in a private clinic in the city of Passo Fundo, located in the state of Rio Grande do Sul, Brazil.

Methods

The study was conducted at the Neurology and Neurosurgery Service of the city of Passo Fundo, Rio Grande do Sul, Brazil, with a sample of 46 patients undergoing prophylactic treatment of migraine with monoclonal antibodies. The research occurred from July to October 2020 and included all patients in the service, aged over 18, who were in current or previous use of at

least one dose of the monoclonal antibody medications (fremanezumab, galcanezumab, or erenumab) for prophylactic treatment of migraine. Patients who could not be reached by telephone were excluded from the study. The participants' consent was obtained by means of a digital Informed Consent Form, written in a clear and objective manner and sent via e-mail to WhatsApp® or e-mail for electronic signature.

Data were collected through the analysis of clinical records and telephone interviews, in which questions were asked with the objective of evaluating the use of medications and their benefits. Questions were asked about the diagnosis of migraine with or without aura, the number of monthly days of headache before and after the use of medications, duration of treatment, decrease in pain intensity and improvement in work capacity, number of medication for migraine prevention, adverse effects, and the intention to continue the treatment. In this quantitative, retrospective, descriptive study, calculations were made of the exposure variables with the research outcome.

Results

Forty-six patients were selected for the study according to the inclusion criteria. Of these, 44 patients on current or previous anti-CGRP monoclonal antibody use were interviewed, with 90.9% (n=40) being female and 9.3% (n=4) being male. Most of the research participants (39%) were individuals in the age group of 41-50. Two patients were excluded from the study because it was not possible to contact them by telephone.

Of this sample of 44 patients interviewed, 23 (52.3%) have a diagnosis of migraine without aura and 21 (47.7%) of migraine with aura. 61.4% (n=27) have comorbidities, highlighting psychiatric disorders, which add up to 56.8% of the interviewees, being anxiety and depression the diagnoses most reported in the telephone interviews. About healthy individuals, 38.6% (n=17) reported no comorbidity.

Regarding pharmacological therapy with monoclonal antibodies, a higher prevalence of erenumab use was noted, totaling 79% (n=35) of respondents. Of the remaining sample, 14% (n=6) were treating migraine with frenezumab and 7% (n=3) with galcanezumab.

The data about the number of monthly days of headache before the start of monoclonal antibody prophylaxis were filtered out every 5 days for better visualization, since approximately 34% (n=15) of the patients had pain every 26-30 days, this being the highest result. For 23% of the sample, the data show headache for 21-25 days in the month and 30% for 16-20 days in a month.

Approximately 87% of the respondents had symptoms on more than 15 days per month, the average number of monthly days of headache corresponds to 22 monthly days of pain, and the highest frequency of events was 20 days per month.

Given the improvement of symptoms reported in the telephone interviews with the initiation of prophylaxis, the number of monthly days after the start of pharmacological therapy reveals that 5% (n=2) reported no crisis in the whole month, which evidences a 100% reduction of monthly migraine days in some patients. Most respondents, 61% (n=27) only reported 1 to 5 days of headache per month and 14% (n=6) 6 to 10 days per month. Only 11% of the participants reported 16 to 20 days of monthly pain and a sample of 3 people (7%) continued with 26 to 30 days of headache monthly. The data reveal an average of 7.5 monthly headache days in patients who took at least one dose of the anti-CGRP antibodies (Table 1).

Table 1. Monthly pain days before and after prophylaxis

Before prophylaxis			After prophylaxis		
Monthly Days of Pain	Number of patients	Percentage	Monthly Days of Pain	Number of patients	Percentage
0	0	0	0	2	5%
1 to 5	1	2%	**1 to 5**	**27**	**61%**
6 to10	2	4%	6 to 10	6	14%
11 to 15	3	7%	11 to 15	0	0
16 to 20	13	30%	16 to 20	5	11%
21 to 25	10	23%	21 to 25	1	2%
26 to 30	15	34%	26 to 30	3	7%

Patients who used monoclonal antibodies had a reduction in the monthly number of days of headache, on average, from 22 days before therapy to 7 days after at least one dose of the drug, corresponding to a decrease of approximately 67% of monthly days of pain.

Thus, by reducing the number of days of headache per month, the effectiveness of the therapy can be classified as excellent, good, regular, poor, or very poor (Table 2).

Table 2. Effectiveness of therapy

Effectiveness	Excellent	Good	Regular	Poor	Very Poor
Days of pain after prophylaxis	0 to 5	6 to 10	11 to 20	21 to 25	26 to 30
Number of patients	29	6	5	1	3
Percentual	66%	14%	11%	2%	7%

These criteria were created from the patients' reports given in the telephone interviews, considering that those who mentioned headache for more than 20 days a month did not consider it a positive effect and, due to the high cost of the medication, believed that the cost did not outweigh the benefit. Thus, the result was excellent or good in 80% of the patients, regular in 11%, and poor or very poor in 9%.

Regarding the time of use of anti-CGRP antibodies, 54.5% (n=24) of the participants had been taking continuous monthly anti-CGRP antibodies for at least 6 months. The minimum time of therapy was 2 months, corresponding to about 18.2% (n=8) of the respondents.

Regarding pain intensity, Table 3 shows that about 80% (n=35) of the research participants reported a decrease in pain intensity with the use of medication. As for the ability to work, 77% (n=34) responded positively and stated that the use of medication led to an improvement in the performance of daily activities and work.

Table 3. Decreased pain and improved work capacity

	Number of patients	Percentage
Decreased pain intensity	35	80%
Improved work capacity	34	77%

As for previous prophylaxis, 77.3% (n= 34) of the respondents reported five or more previous therapies, mainly, with antiepileptic drugs, antidepressants, and anticonvulsants. The least number of previous treatments was three prophylactics, corresponding to 13.6% (n=6) of the survey participants, which reveals the failure of previous therapies. No patient claimed to have had only one or two previous treatments.

Regarding the adverse effects caused by the therapy, 93.2% of the interviewees reported no adverse effects associated with medication, and only 6.8% attributed adverse effects to medication, such as constipation and weight gain.

Regarding the intention to continue the use of medication, 72.7% (n=32) intend to continue the prophylaxis due to the positive effects on quality of life and only 27.3% (n=12) do not intend to continue due to financial issues, since subcutaneous injections are still expensive, or because they did not achieve the desired effect in the treatment period.

Discussion

Migraine affects women in a 3:1 ratio in relation to men.[4] Likewise, the sample evaluated in this study was mostly female, totaling 90.9% (n=40) of the interviewees and most of them were individuals aged between 41 and 50 years of age (39%).

Like the study by Martelletti and coworkers[5], which presented negative aspects of the disease in social interaction favoring psychic alterations, 56.81% of the population of this study mentioned some psychiatric disorder, with emphasis on anxiety and depression, which were the most reported illnesses in the telephone interviews. Thus, a relationship between migraine and psychiatric disorders is noted, given the social impact and limitations caused by migraine.

Regarding the pharmacological therapies used in migraine, Loder and Rizzoli[10] cite that, most of the time, patients are faced with failed therapies due to factors such as nonspecificity, low tolerability, treatment mal adherence and disease progression. Regarding preventive treatment, non-specific medications for migraine are prescribed, such as antiepileptics, antihypertensives and antidepressants, which often have adverse events and low tolerability.[4]

Data in line with these previous studies reveal the failure of non-specific therapies for migraine, since 77.3% of the patients included in this study reported having already taken five or more previous therapies, especially with antiepileptic drugs, antidepressants, and anticonvulsants. Although not described in the results because they were not part of the questionnaire, several patients reported previous hospitalizations for excessive use of analgesics and the need for intravenous solution medications for pain relief.

In this context, it has become essential to develop new medications given the unmet needs with preexisting treatments.[11] Tepper[12] found that drugs involving the calcitonin gene-related peptide are the first developed specifically to act on pain in the trigeminal system by interfering with the signaling of an important neuropeptide expressed in nerves. They provide relief both in an acute migraine attack with aura and in one without aura, a fact also confirmed in this study, since 52.27% of the patients studied were diagnosed with migraine without aura and 47.72% with migraine with aura.

Four monoclonal antibodies have been created and studied, with erenumab being the only fully human antibody that targets the CGRP receptor. The other three, frenezumab, galcanezumab, and eptinezumab target either the peptide or the CGRP ligand itself. All have gone through phase III studies with positive results and

are primarily employed in migraine refractory to previous treatments.[12] In this study, patients were on current or prior use of at least one dose of the medications, with 79% on erenumab, 14% treating with fremanezumab, and finally 7% on galcanezumab. The greater use of erenumab in the patients studied is probably because the drug had entered the Brazilian market earlier. The study similarly included patients with migraine refractory to previous prophylaxis, since 87% of the participants had more than 15 days of headache per month before monoclonal antibody therapy.

In the study in question, approximately 5% of the patients reported 100% reduction of the monthly days of pain, that is, in an important portion of individuals, the medications completely stopped the pain. Most of the participants, totaling about 61% only reported 1 to 5 days of pain per month, and 14% 6 to 10 days. They reduced the monthly days of headache on average from 22 days before therapy to 7 days after at least one dose of the medication, corresponding to a decrease of approximately 67% of monthly days of pain. Similar data from the analysis of several recent randomized, placebo-controlled studies by Tepper[12], which highlighted the positive response of monoclonal antibodies with a reduction of more than 75% of monthly headache days in most of the patients analyzed.

Therefore, based on the number of monthly days of headache reduction and on the patients' reports in the telephone interviews, the effectiveness of the therapy under study could be classified as excellent, good, regular, poor, or very poor. The result was considered excellent in 66% of the interviewees, who had 0 to 5 days of headache per month.

In this same bias of positive response to medications, most clinical trials analyzed by Henson et al.[13] showed that anti-CGRP monoclonal antibody medications are well tolerated with few or no adverse events, being, allergic reactions at the injection site, fear of needle, and constipation the most frequent reactions and not characterized as serious. Similarly, 93.2% of the interviewees attributed no adverse effects associated with the medication, and only 6.8% reported constipation or weight gain. Weight gain is a factor of low reliability due to the reports of association of well-being caused by pain reduction with appetite improvement, not necessarily being a side effect of the medication.

In view of the impacts on the quality of life of patients using monoclonal antibodies, about 80% of the participants of the mentioned study reported a decrease in pain intensity and 77% obtained a positive response regarding improvement in work capacity. A result also seen in studies by Raffaelli et al.[9] that indicate better functional outcomes in patients who adopted anti-CGRP antibody therapy.

A major challenge of medications is the high cost, in contrast to the cost-effectiveness of therapy.[13] The main reason for treatment discontinuation cited in the telephone interviews was the high investment, which coupled with reports of therapy failure and unsuccessful lawsuits, which prevented the funding of medication through the State, reach 27.3% of dropouts from therapy in the survey. However, the overall data collected shows promise, since 72.7% will continue the prophylaxis due to the positive effects and recognised improvement in quality of life.

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NF, design of the work; acquisition, analysis and interpretation of data for the work; revising it critically; ACF, design of the work; analysis and interpretation of data for the work; revising it critically; final approval of the version to be published.

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