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Original

A framework for decision making of migraine treatment with anti-CGRP monoclonal antibodies: a guide for real-world practice and public policies

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Abstract

Anti-CGRP monoclonal antibodies have been developed for migraine preventive treatment. There is evidence of good efficacy and safety of these medications; however, cost is a factor that interferes with the choice of treatment. This paper proposes a framework in order to better assist the decision-making processes on the use of these drugs in developing countries without coverage of health care costs for migraine. The framework was built after reviewing phase II and III studies on episodic and chronic migraine treatment with erenumab, galcanezumab and fremanezumab.

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Introduction

Migraine is a common and debilitating disorder, which affects a significant proportion of the population worldwide.[1,2] Abortive and preventive treatment strategies are often combined using pharmacological and nonpharmacological methods. The most commonly used medication categories are: antidepressants, beta blockers and anticonvulsants.[3,4] The poor quality of life of these patients interferes in their functional status. There are losses in work performance, school, family, relationships, in addition to affecting daily concentration, generating fatigue and mood alterations. These medications lead on average to a 50% frequency reduction in 50% of patients, and their use are limited due to side effects or contraindications.[5] Four monoclonal antibodies (mAbs) have been developed: one targeting the calcitonin gene-related peptide receptor (erenumab) and three targeting the calcitonin gene-related peptide (eptinezumab, fremanezumab, and galcanezumab).[6]

Erenumab, galcanezumab, fremanezumab and eptinezumab have yielded positive results concerning episodic and chronic migraine prevention.[7,8] The new drugs have already been approved in the United States and other countries worldwide. Erenumab was approved in May, 2018 in the US, in August, 2018 in Europe, while galcanezumab and fremanezumab were approved in September, 2018 in the US, and in November, 2018 in Europe. Eptinezumab was approved in February, 2020?

Headache care lacks universal coverage even in developed countries.[9]

From the estimated 1 billion migraine sufferers across the globe, at least half do not have full coverage even of essential health services.10 About 100 million people worldwide have been pushed into extreme poverty because they have to pay for health care.[11] Migraine treatment and health care policies should be planed according to patients' access.

Although studies on phase II and III clinical trials have revealed a protocol or a way of prescribing migraine by administering subcutaneously injections every month for 3 to 6 months, there is scarce information regarding when to stop medication, dosing strategies, management involving refractory patients or non-responsive patients, and other issues yet to be examined.[12] Administration and use of new monoclonals are expected to vary according to the environment, physicians experience, patient's responses, and financial aspects. Headache related health care policies are not available worldwide, and patient access is still a matter of intense debate. Medical systems across the globe have country specific regulations for patient access, reimbursement and price policies.[13] Therefore, CGRP monoclonal antibodies protocols should consider not only the pre-fixed protocols studied in clinical trials, but should be customized for the real-world practice, individualized according to the medical system.

In order to account for socio-economic factors, a decision tree algorithm for migraine preventive treatment with mAbs should be generated. In this paper we suggest a framework for improving the decision making process in real life and for public policies.

Methods

This is an opinion article in which the authors propose a framework for improving the decision making in choosing steps for the management of preventive treatment of migraine with monoclonal antibodies. This could be a ground for gathering opinions and collecting data towards cost-benefit analysis, aiding decisions in the context of limited financial resources. The framework was built after reviewing phase II and III studies on episodic and chronic migraine treatment with erenumab, galcanezumab and fremanezumab.

Information regarding dosage, timing, half-life and administration protocol were reviewed. Eptinezumab data were excluded due to its approval in limited countries.

The authors created an algorithm that summarizes strategies for the treatment of migraine with anti-CGRP monoclonal antibodies.

Evaluating the response pattern according to the percentage of reduction in pain days, three categories were considered:

Group 1: Poor response, less than 25% reduction;
Group 2: Partial response, reduction between 25% and 75%;
Group 3: Good response, more than 75% reduction.

The framework was set in order to facilitate the opinion on the following questions:

1. When should treatment be offered?
2. How long to maintain treatment in cases of good response?
4. How long to maintain treatment until no response is established?
5. In cases of partial response, what steps can be taken in order to increase efficacy?

After analyzing data, we modeled an algorithm so a framework could be the basis for clinical migraine prevention decision-making in different health care scenarios.

Results

We propose an algorithm to clarify the phases in migraine management through anti-CGRP monoclonal antibodies. The decision tree is intended to support the clinical practice and was developed according patient's response. We tried to generate an approach that is based on efficacy data but also could be taken different economic scenarios into account. Erenumab, galcanezumab and fremanezumab half-life is around 25-30 days, regarding subcutaneous injections perfomed in the abdomen, thigh, or upper arm. The recommended dose are: erenumab, 70 mg or 140 mg monthly; fremanezumab 225 mg monthly or 675 mg every three months; and galcanezumab 120 mg monthly. Framanezumab can be also administered quarterly. Galcanezumab can be started with a loading dose of 240 mg (Table 1).

Treatment with monoclonal antibodies should be offered to what kind of patients? Should only to those who have failed two classes of preventive treatment: antidepressant, anticonvulsant or beta-blocker? Once the treatment with monoclonal antibodies is decided, following the protocol studied is the obvious indication, therefore galcanemuzab would be administered with a loading dose (240 mg). But what if the medication cost is dose dependent? Should starting with 120 mg be cost effective?

The next step is to measure the clinical response and classify the patient in the three groups. For group 3, in which the patient presents substantial improvement in the first month, we suggest repeating the dose as soon as reducing the effectiveness for less than 50%.

For group 2, in partial response, should the same dose be repeated within a month? For group 1, with no response, twice the dose of erenumab and the same dose of galcanezumab and fremanezumab should be prescribed? In the following month, patients must be reclassified, according to the response rate. Patients who remain in group 1 would be advised not to continue treatment, within a context in which financial resources are limited? How much more time should we insist in the trial? In this group, patients should be reassessed in an attempt to confirm the diagnosis and identify other factors that contribute to pain refractoriness, such as mood disorders, sleep, postural errors, physical inactivity or exposure to triggering factors.

For groups 2 and 3, the optimal or partial response is an opportunity to optimize non-pharmacological treatment measures and the pharmacological treatment kept for how long? At least six months for chronic migraine? Three to six in episodic migraine (Figure 1).

Discussion

Data from available clinical trials indicate that erenumab, fremanezumab and galcanezumab are safe and effective for the prevention of episodic chronic migraine.

Monoclonal antibodies present a good tolerability profile, low incidence of side effects and easy application, which may lead to patients who prefer such prophylaxis. The high cost, however, does not allow their use as first choice option in most cases.[14]

Regarding the question about when should treatment be offered, most studies of prophylactic use of monoclonal antibodies have as exclusion criteria patients that have failed with two or more prophylactic medication. However, an analysis in the subgroup of chronic migraine with erenumab showed effectiveness of the medication, even in patients that failed the previous prophylactic treatments, showing that such medications can be considered in case of refractory migraine.[15] In our opinion, to achieve a cost effective treatment for migraine, we should first try a preventive treatment with low cost medication.

The loading dose is propose to galcanezumab, but in the context of limited resources, after analyzing clinical outcomes, one may have to evaluate the cost benefit of 120 mg and 240 mg doses of galcanezumab.[16]

Table 1. Characteristics of approved anti-CGRP drugs

Generic name	Commercial name	Study phase	Regulatory status	Doses studied	Half-life	Administration protocol	Mechanism of action
Erenumab	Pasurta	Phase 3	Approved	70mg/ 140mg	28 days	SC/monthly	CGRP receptor
Galcanezumab	Emgality	Phase 3	Approved	120mg/ 240mg	25-30 days	SC/monthly	CGRP
Fremanezumab	Ajovy	Phase 3	Approved	225mg/ 675mg	31-39 days	SC/monthly or quarterly	CGRP

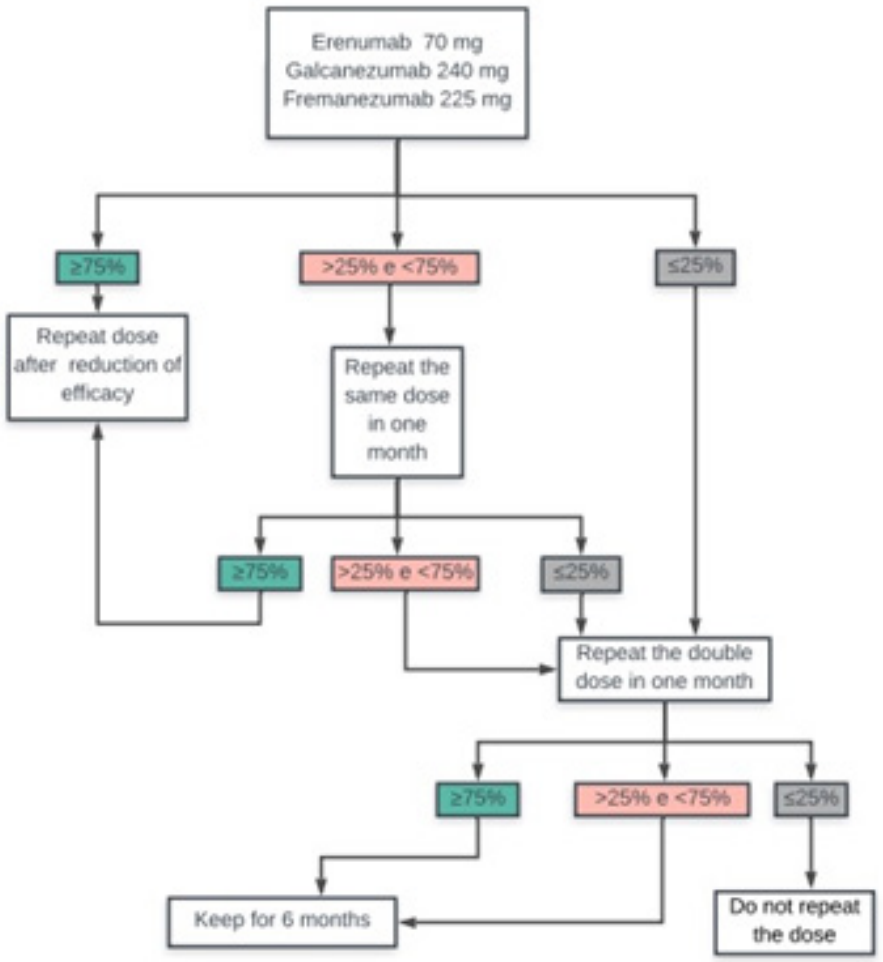

Figure 1. Framework for improvement of decision making in migraine prophylaxis through anti-CGRP monoclonal antibodies.

Regarding the time to determine the response, in the clinical trials, the duration of the treatment varied from 3 months to 1 year. There were reports of persisting benefits during the whole period. Studies with galcanezumab (EVOLVE-1, EVOLVE-2 and REGAIN study) have shown satisfactory responses of patients in continuous treatment.[16-18] These patients responded in a modest way in the first dose application and have reached better responses in the following months.[19] In another open clinical trial[20] that verified the satisfaction of participants with the use of galcanezumab, it was shown an enhancement in the positive response in the visits of first, sixth and twelfth month. Although the studies concluded the main outcome for longer periods, improvement can start to be observed as early as the first week; therefore, we consider that by the end of the first month it is possible to classify patients in group 1, 2 or 3.

Future directions

Ideally, this framework should be field tested, and clinical trials be done. The opinion of general practitioners, family physicians, policy makers, neurologists, headache specialists in several countries should besought and studied.

Divergence or controversy is expected as for what steps of the algorithm should be followed. This is, however, only the first steps in clarifying this issue.

Conclusion

The framework is intended to provide an easier approach for a better decision making in real life and regulatory affairs.

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