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Guidelines

CROATIAN GUIDELINES FOR SPECIFIC PREVENTIVE TREATMENT OF MIGRAINE WITH MONOCLONAL ANTIBODIES TARGETING CALCITONIN GENE-RELATED PEPTIDE (CGRP) (EPTINEZUMAB, FREMANEZUMAB, AND GALCANEZUMAB) OR THE CGRP RECEPTOR (ERENUMAB)

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SUMMARY – Calcitonin gene-related peptide (CGRP) plays a key role in the pathophysiology of migraine, acting on CGRP receptors in the trigeminovascular system, causing neurogenic inflammation and vasodilation, and promoting nociception. Four specific monoclonal antibodies targeting CGRP are available for prevention of episodic and chronic migraine in adults with at least four migraine days *per* month. The aim of these guidelines is to provide evidence-based recommendations for the use of monoclonal antibodies targeting CGRP in migraine prevention in Croatia. The questions were formulated using the Patients, Intervention, Comparison, Outcome (PICO) criteria, with evidence-based answers. To assess the quality of scientific evidence, a review of the literature available in PubMed was performed. Relevant studies were reviewed by the Expert Group of the Headache Section of the Croatian Neurological Society, and served as the basis for formulating the recommendations outlined in these guidelines. We found high quality evidence for good safety and efficacy of anti-CGRP monoclonal antibodies in the preventive treatment of episodic and chronic migraine. These medications may be considered as first-line prophylactic therapy depending on the patient's history, concomitant diseases, and disease burden. Further real-world studies are needed to elucidate other aspects of their application.

Key words: *Migraine; Prevention; Treatment; Calcitonin gene-related peptide (CGRP); Monoclonal antibody; Guidelines; Eptinezumab; Fremanezumab; Galcanezumab; Erenumab*

Introduction

For many years, migraine prevention has included beta-blockers, amitriptyline, topiramate, valproate, candesartan, and flunarizine. These medications were originally designed for use in other indications but were subsequently shown to be effective in migraine prevention[1-3]. However, such non-specific treatment was insufficiently effective and did not ensure treatment adherence.

In recent years, four specific monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) have become available in migraine prevention with indication for the treatment of episodic and chronic migraine in adults with at least four migraine days a month. CGRP plays a key role in migraine pathophysiology as a vasoactive peptide present in the peripheral and central nervous system, as well as in the trigeminal ganglion and in the walls of the meningeal arteries innervated by it. During an acute migraine attack, CGRP is released in the trigeminovascular system and, by acting on CGRP receptors in the walls of the dural blood vessels, causes neurogenic inflammation and vasodilation, and promotes nociception[4,5]. Before the development of monoclonal antibodies targeting CGRP/CGRP receptor, small molecules of CGRP receptor antagonists were developed, which, in parenteral form, effectively targeted acute migraine attacks compared with placebo[6]. Monoclonal antibodies, i.e., CGRP antagonists, due to their pharmacokinetic mechanism, are used exclusively as migraine prophylactic drugs. Fremanezumab, galcanezumab, and eptinezumab act as humanized monoclonal antibodies that bind to the CGRP-ligand, while erenumab acts as a humanized monoclonal antibody that binds to the CGRP receptor. Erenumab, fremanezumab, and galcanezumab are administered subcutaneously, while eptinezumab is administered intravenously in the form of an infusion. Considering their long half-life[7], these medications are administered once a month, while three-times higher doses of fremanezumab are administered once in three months.

Eptinezumab is an exception as it is usually administered every three months. As their molecular weight is 150 kDa, these medications do not seem to cross the blood-brain barrier, a feature that reduces the possibility of central nervous system side effects[8]. Furthermore, they break down into amino acids in the reticuloendothelial system and do not interfere with the hepatic or renal metabolism, which improves their safety profile.

Methods

The current Guidelines on the application of monoclonal antibodies in migraine prevention have been developed based on scientific principles and previous research. First, we formulated questions using the Patients, Intervention, Comparison, Outcome

(PICO) criteria, with evidence-based answers[9]. To assess the quality of scientific evidence, a review of the literature available on PubMed was performed. The review involved articles published from January 2015 until May 2023. Relevant studies were considered by the Expert Group of the Headache Section of the Croatian Neurological Society and served as the basis for formulating the recommendations outlined in these Guidelines.

The quality of scientific evidence was categorized according to the Grading of Re-commendations Assessment, Development and Evaluation (GRADE) approach as follows: high – the authors of the Guidelines have a lot of confidence that the true effect is similar to the estimated effect; moderate – the true effect is probably close to the estimated effect but there is a possibility that it could be markedly different; low – confidence in the effect estimation is limited[10], the true effect may be markedly different; very low – the authors of the Guidelines have very little confidence in the effect estimation. Besides the four levels of evidence quality, the GRADE system offers two levels of recommendation strength: strong recommendation – most of the clinicians accepted the recommended intervention based on the quality of evidence and it can be recommended in most of the cases. A low recommendation level implies that the evidence is too weak for an intervention to be considered to positively affect every individual patient, but despite this, the intervention is recommended based on the clinical experience of the experts.

Certain clinical questions could not have been formulated according to the PICO criteria due to the lack of evidence, so these questions were answered by expert consensus rather than based on the GRADE system.

Recommendations Based on the Scientific Evidence Review

PICO question 1: In patients with episodic migraine, is preventive treatment with monoclonal antibodies targeting CGRP safe and effective compared with placebo?

Population: patients with episodic migraine.

Intervention: treatment with monoclonal antibodies.

Comparison: placebo.

Outcome: >50% reduction in migraine days or headache days according to a regular headache diary.

In double-blind, randomized-controlled trials, all monoclonal antibodies showed a statistically significant difference compared with placebo in a 50% reduction in migraine days after three and six months of drug administration. The percentage of patients with at least 50% reduction ranged between 39.7% and 63.9%. The results of the trials are shown in Figure 1[11-19].

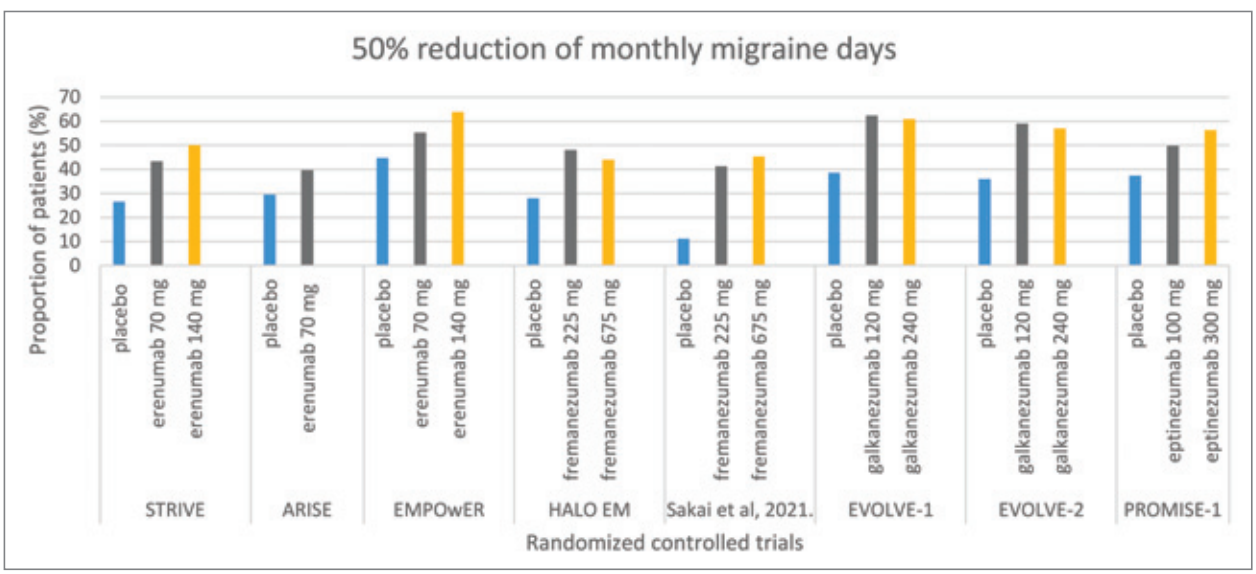

Fig. 1. The efficacy of monoclonal antibodies targeting CGRP/CGRP receptor compared with placebo in patients with episodic migraine in terms of a 50% reduction in monthly migraine days in randomized controlled trials.

CGRP = calcitonin gene-related peptide

Recommendation (level of evidence: high, strength of recommendation: high)

All registered monoclonal antibodies targeting CGRP/CGRP receptor (eptinezumab, erenumab, fremanezumab, galcanezumab) effectively prevent episodic migraine compared with placebo. It cannot be determined whether, in individual subgroups, some of the specific prophylactic drugs are more effective than others. Clinical trials of limited duration show that monoclonal antibodies targeting CGRP/CGRP receptor are safe and well tolerated, but there is insufficient data on their long-term effects.

PICO question 2: In patients with chronic migraine, is preventive treatment with monoclonal antibodies targeting CGRP safe and effective compared with placebo?

Population: patients with chronic migraine.

Intervention: treatment with monoclonal antibodies.

Comparison: placebo.

Outcome: >50% reduction in migraine days or headache days according to a regular headache diary.

In double-blind, randomized-controlled trials, significantly more patients with chronic migraine treated with all monoclonal antibodies compared with placebo showed at least a 50% reduction in the number of migraine days after three months of treatment. The proportion of patients with at least a 50% percent reduction in the number of migraine days ranged from 27.5% to 61.4%. The results of the trials are shown in Figure 2[20-24]. These studies did not involve patients with refractory migraine.

Recommendation (level of evidence: high, strength of recommendation: high)

Based on the available evidence compared with placebo, all four monoclonal antibodies targeting CGRP/CGRP receptor (eptinezumab, erenumab, fremanezumab, galcanezumab) effectively prevented chronic migraine in patients who had not been previously treated with any prophylactic drug or had been unsuccessfully treated with non-specific prophylactics.

Clinical studies of limited duration show that monoclonal antibodies targeting CGRP/CGRP receptor are safe and well tolerated, but there is insufficient data on their long-term effects.

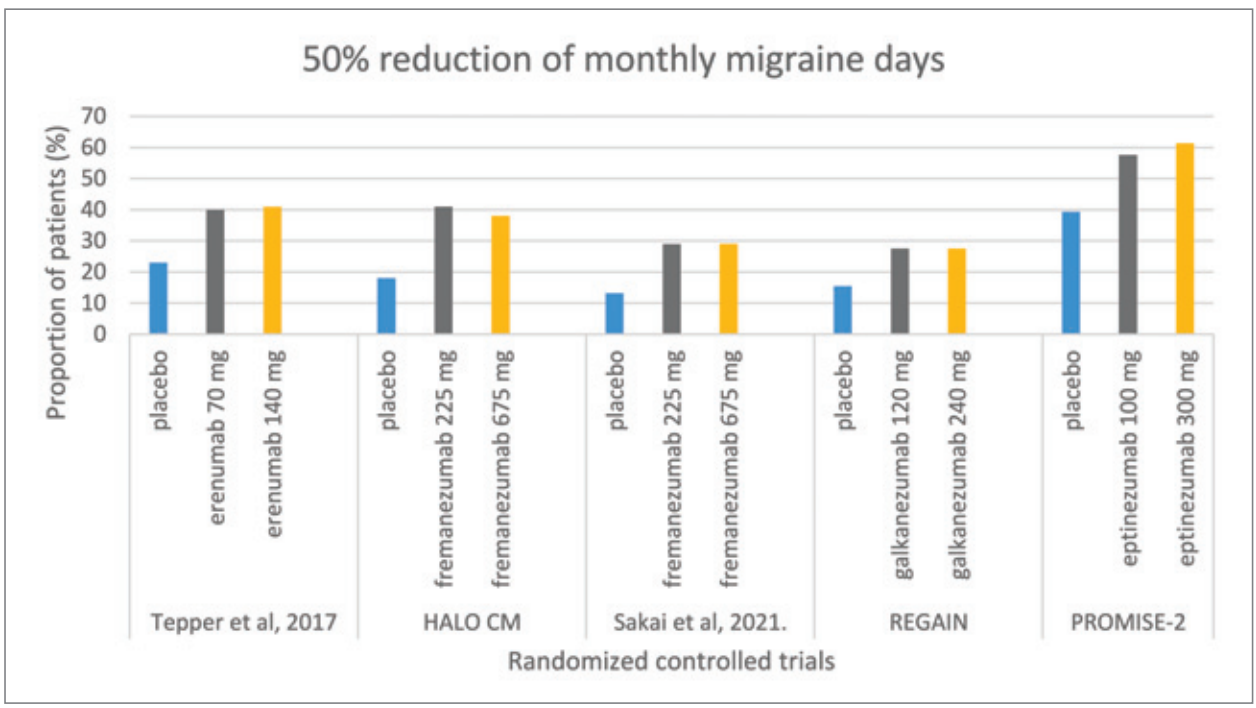

Fig. 2. The efficacy of monoclonal antibodies targeting CGRP/CGRP receptor compared with placebo in terms of a 50% reduction in migraine days per month in patients with chronic migraine in randomized controlled trials.

CGRP = calcitonin gene-related peptide

PICO question 3: In patients with migraine, is preventive treatment with monoclonal antibodies targeting CGRP/CGRP receptor more effective and safer compared with other available preventive treatments?

Population: patients with migraine.

Intervention: treatment with monoclonal antibodies.

Comparison: beta blockers (propranolol, atenolol, metoprolol, timolol), antiepileptics (topiramate, valproate), antidepressants (amitriptyline), calcium channel blockers (flunarizine), and renin-angiotensin system inhibitors (candesartan, lisinopril).

Outcome: >50% reduction in migraine days or headache days according to a regular headache diary, reduction in the use of acute therapy, therapy safety.

There is a lack of valid randomized trials comparing monoclonal antibodies with other medications for preventive migraine treatment. A 24-week HERMES study, conducted in Germany, compared the tolerability and efficacy of erenumab (70 and 140 mg *per* month) with topiramate (50 and 100 mg daily). In the study, 10.6% of patients treated with erenumab discontinued treatment due to side effects compared with 38.9% patients treated with topiramate (p<0.001). Furthermore, significantly more patients treated with erenumab experienced a >50% reduction in monthly migraine days (55.4% *vs*. 31.2%; p<0.001)[25]. However, there are more comprehensive data and indirect real-world comparisons of the efficacy of these two drugs. A meta-analysis by Overeem *et al*. showed an equal efficacy of all available monoclonal antibodies compared with topiramate in patients with episodic migraine, but also a markedly better safety profile of monoclonal antibodies[26]. A retrospective study by Varnado *et al*. showed significantly better adherence to and persistence for monoclonal antibodies compared with other standard oral migraine preventatives[27].

Recommendation (evidence level: low, recommendation strength: high for erenumab and topiramate, weak for other preventatives)

In the prevention of episodic and chronic migraine, erenumab shows better tolerability and efficacy than topiramate. There are no studies directly comparing prophylactic drugs. There is no direct comparison of prophylactic drugs that would show that monoclonal antibodies targeting CGRP/CGRP receptor are more effective or tolerable than topiramate or any other non-specific prophylactics.

Recommendations Based on Expert Consensus

I Clinical question: What is the indication for preventive migraine treatment with monoclonal antibodies targeting CGRP/CGRP receptor?

Clinical studies that served as a basis for registration of monoclonal antibodies targeting CGRP/CGRP receptor involved participants aged 18 to 75. Because of this, drug regulators authorized the use of these medications only in adults. In Croatia, the age of majority is 18. In a small retrospective study in Japan, where the age of majority is 15, the efficacy of migraine prevention with monoclonal antibodies in patients aged 15-17 was about 60%, with good tolerability[28]. However, this study is not significant enough to recommend specific migraine prevention for adolescents younger than 18.

The patient should have at least four migraine days *per* month, as recorded in the headache diary, before monoclonal antibodies are introduced in the preventive treatment of migraine (in studies on erenumab: average during three months before screening[11]; for fremanezumab: during 28 days since the beginning of the study[12]; for galcanezumab during a month since the beginning of the study[15]; and for eptinezumab within any period of 28 days during three months before screening[16]. Due to possible variations in migraine frequencies[29], the Croatian experts reached the consensus that the frequency should be at least four migraine days for two to three consecutive months, as confirmed by the headache diary, before the beginning of treatment. Although international consensus statements on migraine prophylaxis (EAN/EHF Consensus Statement and AHS Consensus Statement) recommend migraine prevention to patients with greater disability or with two to three migraine days a month, there is no clinical study in which the registration of monoclonal antibodies was based on enrolled patients with fewer than four migraine days, so no specific prophylactic drugs can be recommended to these patients.

Recommendation

The indication for preventive migraine treatment with monoclonal antibodies targeting CGRP/CGRP receptor is episodic or chronic migraine in patients with at least four migraine days a month, as documented by the headache diary kept two to three months prior to the beginning of treatment.

II Clinical question: In which sequence should specific prophylactic drugs be administered compared with non-specific prophylactic drugs?

Revised recommendations of the European Headache Federation no longer stipulate the administration of non-specific oral preventive treatment before the administration of monoclonal antibodies in migraine prevention[30]. This recommendation is based on real-world clinical trials that persistently showed efficacy and safety of these drugs in preventive migraine treatment regardless of a failed response to a previous preventive treatment[31-33].

A failed response to migraine treatment with oral prophylactic drugs is considered a non-significant change in migraine frequency (reduction lower than 50%) with a preventive medication taken in an effective or maximum dose for three months, or a treatment termination due to intolerability[34].

The use of botulinum toxin A in the prevention of chronic migraine is deemed as failed if, after two treatment cycles (six months), there is no favorable treatment effect, that is, if there is not at least a 30% reduction in headache frequency in the month after the treatment started[35].

Since monotherapy is the preferred option, the treating physician should carefully choose the first-line preventive treatment taking into account medical history, comorbidities, burden of disease, and motivation for continuous treatment. This means that the first-line treatment for the comorbidity of migraine and depression would be antidepressants; for the comorbidity of migraine and arterial hypertension, these are beta-blockers or renin-angiotensin inhibitors; and for the comorbidity of epilepsy and migraine, these are anticonvulsants. After an interview with the patient, the treating physician should carefully determine the most suitable treatment for the patient's needs based on the European Guidelines for Migraine Prevention and based on treatment availability in the Republic of Croatia (see Tables 1 and 2).

Table 1. Medications for migraine prevention registered in the Republic of Croatia and their availability

Generic medication name	Type of prophylactic drug	Status on the Croatian Health Insurance Fund medication list
Propranolol	Non-specific, beta-blocker	Basic list
Metoprolol	Non-specific, beta-blocker	Supplementary list
Topiramate	Non-specific, anticonvulsive	On the basic list for another indication, not for migraine
Amitriptyline	Non-specific, antidepressant	Supplementary list
Naproxen	Non-specific, only for short-term prevention of menstrual migraine, antirheumatic	Supplementary list
Erenumab	Specific, monoclonal antibody targeting the CGRP receptor	Supplementary list Migraine prevention in adults with four or more monthly migraine days (rimegepant only for episodic migraine) as recommended by a neurology specialist (**pr 11**)
Fremanezumab	Specific, monoclonal antibody targeting CGRP	
Galcanezumab	Specific, monoclonal antibody targeting CGRP	
Atogepant	Specific, gepant	
Rimegepant	Specific, gepant	
Eptinezumab	Specific, monoclonal antibody targeting CGRP	On the hospital list of medications, approved by the hospital committee if guideline **pr 11** is met
Botulinum toxin type A	Prophylaxis for chronic migraine	On the hospital list of medications, approved by the hospital committee

CGRP = calcitonin gene-related peptide; pr 11 guideline for prescribing the specific group of migraine preventive drugs on the Croatian Health Insurance Fund list

Table 2. Medications effective for migraine prevention according to European guidelines but not registered for that purpose in the Republic of Croatia

Generic medication name	Type of preventive drug	Status on the Croatian Health Insurance Fund medication list
Bisoprolol	Non-specific, beta-blocker	On the basic list for another indication, not for migraine
Atenolol	Non-specific, beta-blocker	On the basic list for another indication, not for migraine
Candesartan	Non-specific, renin-receptor blocker	On the basic list for another indication, not for migraine
Valproate	Non-specific, anticonvulsant, contraindicated for women of childbearing age	On the basic list for another indication, not for migraine
Flunarizine	Non-specific, calcium channel blocker	Not available in Croatia

Recommendation

According to the revised opinion of the European Headache Federation, in the absence of contraindications or comorbidities that would call for caution regarding the use of monoclonal antibodies targeting CGRP/CGRP receptor, the treating physician may prescribe these medications as first-line treatment in the prevention of episodic or chronic migraine, as recommended in these Guidelines.

Monoclonal antibodies targeting CGRP/CGRP receptor may be prescribed as the second-line preventive migraine treatment in non-responders to non-specific oral preventive medications, or as the third-line treatment in non-responders to oral preventive medications and botulinum toxin A.

III Clinical question: Can monoclonal antibodies targeting CGRP/CGRP receptor be used concomitantly with other medications for preventive migraine treatment?

In the preventive treatment of migraine, monotherapy is the preferred option since it simplifies the treatment plan and reduces the probability of side effects and drug interactions. Monotherapy also facilitates therapy adherence and reduces treatment costs.

Several placebo-controlled trials of monoclonal antibodies involved patients who were concomitantly taking one[11,21,22] or more[20] oral medications for migraine prevention. A comparison of treatment efficacy between the participants who did and those who did not receive concomitant oral preventive medications was not available when these guidelines were created, but, according to safety profiles from these studies, the combined treatment is generally considered well tolerated. Oral preventive medications in combination with monoclonal antibodies were used more frequently in real-world studies (in 42%-79% of patients)[36]. This is probably because these studies involved patients with migraine who were more resistant to previous preventive treatment than those who were included in placebo-controlled trials. There is insufficient evidence on the efficacy of combination therapies of non-specific oral preventive medications and monoclonal antibodies targeting CGRP/CGRP receptor in the prevention of uncomplicated migraine. However, it is useful and rational to use the concomitant treatment in poor responders or non-responders. This is especially justified if a partial clinical response is obtained with one medication. A combination of medications with different mechanisms of action can also yield good treatment results, decrease the dose of one medication, and thereby minimize the number of side effects of each medication.

The combination treatment of botulinum toxin A (BTA) and monoclonal antibodies targeting CGRP/CGRP receptor was not investigated in placebo-controlled clinical trials, so there is insufficient evidence at the highest level. However, the combination of

BTA and anti-CGRP(-R) was frequently investigated in real-world studies. It seems that in patients with refractory migraine, a good efficacy of this combination treatment is a result of the additive positive effect of each of these medications[37].

Recommendation

There is a consensus opinion that the combination treatment with an oral prophylactic drug and a monoclonal antibody targeting CGRP/CGRP receptor can be used in refractory/resistant chronic and episodic migraine. If monotherapy for migraine prevention is effective, it need not be combined with oral prophylactics. An oral prophylactic drug may be stopped immediately after treatment with a monoclonal antibody targeting CGRP/CGRP receptor starts if the patient has episodic migraine. If the patient has a history of chronic migraine, oral prophylactic drugs should be tapered after the beginning of specific preventive treatment until full treatment efficacy is reached.

Botulinum toxin A should be considered for discontinuation from preventive treatment before the start of chronic migraine treatment with monoclonal antibodies targeting CGRP/CGRP receptor, as there is still no robust evidence on the synergistic effects and safety of the combined use of these two medications.

IV Clinical question: How do we evaluate the effect of treatment with monoclonal antibodies?

Although clinical research has shown that, in some patients, the treatment effect can be observed already in the first few days, some patients will notice the effect only after a few weeks. Generally speaking, clinical studies assessed the effect of medications within the first three months of treatment[38,39]. However, up to one-third of patients who experienced no positive effect in the first three months can experience the effect between the third and sixth month of treatment, so it is rational to allow three additional months for treatment evaluation[40]. In the case of dose escalation from a lower to higher dose for medications that have two possible doses (erenumab 70 mg and 140 mg, and eptinezumab 100 and 300 mg), final evaluation is made at the end of the treatment cycle with the higher dose. The treatment should be evaluated every three months through headache diary. The primary treatment outcome is percent reduction in the average number of migraine days a month. Treatment is considered effective if there is at least a 50% reduction in migraine days a month[41]. Secondary outcomes are significant improvements in the scores of evaluation scales assessing the patient quality of life. Therefore, significant improvement is at least a 30% reduction in the Migraine Disability Assessment Scale (MIDAS) score in patients with an initial score higher than 20. When the initial score is between 11 and 20 points, the treatment is considered effective if there is at least a five-point reduction[42]. Another option is at least a five-point decrease in the Headache Impact Test-6 (HIT-6) score[43]. Since monoclonal antibodies showed significant reductions in MIDAS and HIT-6 scores[44], which correlate with reduction in monthly migraine days, the quality-of-life scales can be used as a secondary measure of therapeutic effect. In any case, the evaluation of treatment response should take into consideration the primary and secondary outcomes since they most accurately predict response to treatment and treatment long-term effect. An Italian study showed that a ≥50% reduction in the number of monthly migraine days and ≥50% reduction in the MIDAS score together increased the probability of a sustained response to erenumab treatment after 12 months of use[45].

Recommendation

Treatment efficacy is evaluated after at least three consecutive doses of medication if the medication is administered once a month/every four weeks (erenumab, fremanezumab, galcanezumab), or after one treatment cycle if the medication is administered once in three months (eptinezumab, fremanezumab). In case of dose escalation from a lower to higher dose due to insufficient efficacy of the lower dose (eptinezumab, erenumab), the efficacy is evaluated after a treatment cycle with the higher dose (after 6 months/24 weeks).

The main criterion for efficacy evaluation in patients with episodic and chronic migraine is at least a 50% reduction in the frequency of migraine days a month in the month after the last drug administration compared with the same period before the first administration. An alternative criterion is significant improvement in the score of validated, specific scales assessing disability, which is demonstrated with at least one of the following criteria:

a) the MIDAS score in the last three months showed:

i) a five-point reduction if the initial score was between 11 and 20 or

ii) a 30% reduction if the initial score was above 20.

b) at least a five-point reduction in the HIT-6 score in the last month of treatment.

After an initial treatment validation, the efficacy is evaluated every three months by determining migraine frequency through the headache diary and/or by determining the degree of disability with validated scales.

V Clinical question: How long should an effective preventive treatment with monoclonal antibodies be continued?

No unambiguous answer can be given to this question. There is no evidence for optimal duration of preventive treatment for all migraine patients. Randomized studies of medication efficacy lasted 12 (most of the studies) to 24 months (STRIVE, EVOLVE-1, and EVOLVE-2), and observed no serious side effects. Considering the possible side effects and adverse effects of long-term medication use, it is recommended that the treatment be paused but no expert consensus exists on when the pause should be made. It remains unclear whether long-term treatment with monoclonal antibodies targeting CGRP/CGRP receptor may modify the disease in people with a long history of chronic migraine and whether it can ensure stable reduction in the frequency of migraine days after the end of treatment. A longitudinal study by Vernieri *et al*. showed that after treatment discontinuation, most patients experienced an increased frequency and intensity of headaches, but the frequency did not return to the level experienced before the introduction of monoclonal antibodies[46]. The European Headache Federation recommends that the treatment be paused between the 12th and 18th month after its start[30]. When it comes to the pause duration, there are varying practices. As a rule, the pause lasts for at least 1 to 3 months until conditions are created for re-introduction of the same or introduction of another monoclonal antibody[36]. In some cases, treatment duration should be adapted to individual needs taking into account the variability of biological response to treatment.

Recommendation

Treatment should be discontinued at the first follow-up examination if the criteria for treatment efficacy are not met. After an effective migraine treatment with monoclonal antibodies targeting CGRP/CGRP receptor lasting for at least 12 months and at most 18 months, a treatment pause should be considered. The treatment pause lasts for 2 to 3 months, i.e., until the frequency of migraine days does not reach the level needed for treatment re-introduction. If considered necessary, the treatment should be continued as long as there is the need for it.

VI Clinical question: Is there an indication for the use of monoclonal antibodies in migraine patients with medication overuse headaches without prior detoxification?

In this case, we are talking about patients who, alongside the overuse of abortive treatment, had an unsatisfying response to several other preventive medications for migraine. There is evidence, especially from post-hoc analyses of randomized trials, supporting a favorable effect of available monoclonal antibodies on the reduction in monthly migraine days and pain intensity in migraine patients with medication overuse headache[47]. This was also confirmed in clinical studies[48-50]. Furthermore, in these patients, the same beneficial effect of monoclonal antibodies was demonstrated regardless of prior detoxification[51].

Recommendation

Treatment with monoclonal antibodies targeting CGRP/CGRP receptor is effective in migraine patients with medication overuse headache, even without prior detoxification.

There is a lack of evidence showing if prior detoxification in migraine patients with medication overuse headache can affect treatment with monoclonal antibodies targeting CGRP/CGRP receptor.

VII Clinical question: If treatment with a monoclonal antibody targeting CGRP/CGRP receptor in migraine prevention fails, does it make sense to switch to another monoclonal antibody?

There is insufficient evidence from randomized studies or registries to answer this question. The main difference among the four monoclonal antibodies is that one blocks CGRP signaling by binding to the CGRP-receptor, whereas the others directly target the ligand. This could lead to various effects since erenumab blocks only the CGRP-receptor, while the other three block signaling not at the CGRP receptor but also at

the amylin 1 (AMY1) receptor. It is currently unclear if amylin is involved in migraine mechanism and whether suppression of the mechanisms mediated by CGRP on the AMY1 receptor has any effect in migraine prevention. However, this could be a possible explanation for the observed differences in efficacy after monoclonal antibody switching.

A few smaller retrospective studies showed a ≥30% reduction in the number of monthly migraine days in a subset of patients after switching from the anti-receptor monoclonal antibody to anti-ligand monoclonal antibodies and *vice versa*[52-54]. Another possibility is to intravenously administer eptinezumab instead of the monoclonal antibodies that are administered subcutaneously in patients with particularly debilitating migraines who need immediate treatment. Theoretically, when intravenous administration is used, a maximum drug concentration is reached within an hour, thus leading to faster onset of the medication effect[55].

There is no consensus on the duration of the period between discontinuation of an ineffective monoclonal antibody and start of treatment with another monoclonal antibody. In the case of monoclonal antibody switching due to drug intolerability, the manufacturers recommend a treatment pause of three to six months. A recent study showed that three months after the end of a prolonged treatment with monoclonal antibodies targeting CGRP/CGRP receptor, total plasma concentration of CGRP significantly decreased compared with the treatment period, and the concentration of the freely circulating CGRP did not differ from the concentration before treatment[56].

Recommendation

In the case of treatment failure with a monoclonal antibody targeting CGRP/CGRP receptor, especially in patients with refractory/resistant episodic or chronic migraine, the antibody in question may be switched to another medication from the same group but with a different mechanism of action, and the recommended treatment pause should last for three months.

VIII Clinical question: What are the contraindications and precautions for the use of monoclonal antibodies in migraine prevention?

The use of monoclonal antibodies is not recommended in minors and pregnant or breastfeeding women, as these groups were not included in clinical studies on this issue. According to some studies, monoclonal antibodies (erenumab) cross the placenta[57] and CGRP affects the uteroplacental circulation in normal pregnancy[58]. There are no reliable data on the presence of monoclonal antibodies in breast milk. It is also unknown how long it is safe to conceive after discontinuation of a monoclonal antibody, but this period is estimated to last between five and six months (the half-life of monoclonal antibodies targeting CGRP is about one month, and it takes about 5.5 half-lives to completely eliminate the medication from the body)[59]. These medications are not recommended for women of childbearing age if they are unable to practice effective birth control[60]. In the postmarketing period of monoclonal antibodies targeting CGRP/CGRP receptor, there were reports on new-onset or worsening of preexisting hypertension, and severe constipation in individual patients treated with erenumab. As a result, a warning was issued by the US Food and Drug Administration: erenumab should be cautiously administered in patients with a history of hypertension or constipation, and all patients treated with erenumab should have their blood pressure periodically monitored and asked about the symptoms of constipation[61]. Hypertension can appear within the first week of treatment, and the risk is relatively low[62]. Constipation can appear early or late in treatment, it is mostly mild, and does not require treatment termination[63]. According to a large retrospective analysis in the US, the risk of constipation in patients treated with erenumab is 0.46% at the beginning of treatment and is somewhat higher compared with other monoclonal antibodies[64]. CGRP has an important vasodilatory effect in cerebral and coronary blood vessels, so caution is advised as monoclonal antibodies targeting CGRP/CGRP receptor could deteriorate the existing vascular disease in patients at an increased risk. These patients were also not involved in clinical trials assessing the efficacy of monoclonal antibodies targeting CGRP/CGRP receptor. Furthermore, caution is required in patients with peripheral vascular disease, including patients with Raynaud's phenomenon. In these patients, considerable disease deterioration was observed after the use of monoclonal antibodies[65]. Since patients can independently administer the medication with auto-injectors, it is necessary for them to be in a stable mental state to receive the prescribed dose of

the medication at the designated location in a timely manner.

Recommendation

The use of monoclonal antibodies targeting CGRP/CGRP receptor is not recommended in children, adolescents, women who are planning pregnancy, and pregnant or breastfeeding women. Caution is required in people older than 65 and women of childbearing age. Furthermore, as a precaution due to possible vasoconstrictive action, the use of monoclonal antibodies targeting CGRP/CGRP receptor should be considered on an individual basis in patients with coronary heart disease, after ischemic stroke, after subarachnoid hemorrhage, in patients with occlusive peripheral artery disease, arterial hypertension, and with Raynaud's syndrome.

When erenumab is used in patients with a history of obstipation and in patients with new-onset arterial hypertension or with worsening of existing hypertension, caution and clinical follow-up are required. The use of monoclonal antibodies targeting CGRP/CGRP receptor is not recommended in alcohol or drug addicts and in patients with severe psychiatric disorders.

IX Clinical question: Which individuals and institutions are responsible for prescribing and administering specific migraine treatment with monoclonal antibodies targeting CGRP/CGRP receptor?

Monoclonal antibodies targeting CGRP/CGRP receptor are specific medications for migraine prevention. During the registration process, the regulators have specified that the treatment is to be prescribed by a physician experienced in diagnosing and treating migraine. In Croatia, the physicians responsible for migraine treatment are specialists in neurology who in the same manner prescribe specific abortive migraine treatment – triptans. Besides prescribing the treatment, neurology specialists are required to regularly assess treatment efficacy and decide, based on these Guidelines, on treatment discontinuation. Neurology specialists and their expert teams, in collaboration with family medicine teams, should educate patients and their families on drug administration, possible side effects, and keeping a headache diary.

As erenumab, fremanezumab, or galcanezumab are administered subcutaneously, the administration can be performed outside a healthcare institution by educated patients themselves or by another educated person. If the patient requests it, the treatment should be administered by a professional in a healthcare institution.

The intravenous administration of eptinezumab should be performed in a designated healthcare institution.

A designated institution for the administration of eptinezumab is a facility with minimal space and personnel requirements for storing and administration of medications, and monitoring of the effects of intravenous treatment supervised by a neurology specialist.

Recommendation

The individuals responsible for prescribing the treatment with monoclonal antibodies targeting CGRP/CGRP receptor are specialists in neurology. Monoclonal antibodies targeting CGRP/CGRP receptor in a parenteral form that are administered subcutaneously (erenumab, fremanezumab, and galcanezumab) can be administered outside a healthcare institution by an educated patient or another educated person. Intravenous administration of eptinezumab should be carried out in a designated healthcare institution by professional healthcare personnel.

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Sažetak

HRVATSKE SMJERNICE ZA SPECIFIČNO PROFILAKTIČKO LIJEČENJE MIGRENE MONOKLONSKIM PROTUTIJELIMA NA PEPTID POVEZAN S KALCITONINSKIM GENOM (CGRP) (EPTINEZUMAB, FREMANEZUMAB I GALKANEZUMAB) I NA CGRP RECEPTOR (ERENUMAB)

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Peptid povezan s kalcitoninskim genom (CGRP) igra ključnu ulogu u patofiziologiji migrene djelujući na CGRP receptore u trigeminovaskularnom sustavu, time uzrokujući neurogenu upalu i vazodilataciju, uz promociju nocicepcije. Četiri specifična monoklonska protutijela koja djeluju na CGRP su dostupna u profilaksi epizodne i kronične migrene u odraslih osoba s najmanje četiri migrenozna dana na mjesec. Cilj ovih smjernica je pružiti preporuke zasnovane na dokazima za primjenu monoklonskih protutijela koja djeluju na CGRP u prevenciji migrene u Hrvatskoj. Pitanja su formulirana primjenom kriterija PICO (*Patients, Intervention, Comparison, Outcome*), uz odgovore zasnovane na dokazima. Kako bismo procijenili kvalitetu znanstvenih dokaza pretražili smo literaturu u bazi podataka PubMed. Pronađene relevantne studije analizirala je Stručna skupina Sekcije za glavobolju Hrvatskoga neurološkog društva i služile su kao osnova za oblikovanje preporuka navedenih u ovim smjernicama. Pronašli smo visokokvalitetne dokaze u smislu dobre sigurnosti i učinkovitosti monoklonskih protutijela na CGRP u profilaksi epizodne i kronične migrene. Ovi lijekovi se mogu razmatrati u prvoj liniji profilaktičke terapije, ovisno o bolesnikovoj povijesti bolesti, supostojećim bolestima i opterećenosti bolešću. Daljnje studije u kliničkim uvjetima potrebne su kako bi se rasvijetlili dodatni aspekti njihove primjene.

Ključne riječi: *Migrena; Prevencija; Liječenje; Peptid povezan s kalcitoninskim genom (CGRP); Monoklonsko protutijelo; Smjernice; Eptinezumab; Fremanezumab; Galkanezumab; Erenumab*