Application of a new biological pathogenetic therapy of migraine in clinical practice: expert consensus of the Russian Headache Research Society

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This consensus reviewed the main current issues of clinical application and integration into everyday practice of a new targeted preventive therapy for migraine using monoclonal antibodies (mAbs) to the calcitonin gene related peptide (CGRP) ligand or receptor. These recommendations are based on current scientific and clinical studies and an analysis of the results of several years of clinical use. The main purpose of the consensus is to assist practitioners in prescribing effective prophylactic treatment of migraine using anti-CGRP mAbs and to improve care for patients with various forms of the disease.

Keywords: *migraine; monoclonal antibodies; calcitonin gene-related peptide; consensus.*

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Migraine is a highly prevalent neurological disease and one of the leading causes of impaired quality of life in people under 50 years old and the 2nd leading causing of years lived with disability worldwide [1–3]. About 1 billion people suffer from migraine globally. Migraine remains first among young women under 50 years old [3]. Given its high prevalence, in 18% of women and 8% of men with a peak at the age of 25–55 years old, migraine comes second among all neurological diseases in terms of impairment of daily activities in patients, and medical and social healthcare burden [4]. In the United States of America alone, the average annual migraine-associated costs are estimated at $29 billion, which is higher than for such common conditions as anxiety disorders, depression, asthma, epilepsy, and stroke [5, 6].

Currently, the diagnosis of various types of migraine (migraine without aura, migraine with aura, episodic and chronic migraine, etc.) is based on the clinical criteria of the International Classification of Headache Disorders, 3rd Edition (ICHD-3), and in most cases it is not associated with any significant difficulties [7]. In clinical practice, it is important to be guided precisely by the ICHD-3 diagnostic criteria. Modern algorithms and clinical guidance for both acute treatment of migraine attacks and its preventive therapy are based on a comprehensive personalized analysis of severity and duration of the attacks (pain syndrome and attack-associated symptoms), number of migraine and headache days, and overall impact of quality of life [8,9]. When choosing a preventive treatment strategy, it is important to analyze the number of medications used for acute treatment of migraine attacks, which may reveal a compounding condition, medication-overuse headache [10]. However, due to heterogeneity of clinical phenotypes of migraine, severity, frequency of attacks, intensity of associated symptoms, biomarkers and predictors of efficacy and safety of therapy have not been developed to date. As a result, the process of searching for the optimal approach to treatment for each individual patient can take substantial time and may be associated with a series of unsuccessful, both in terms of efficacy and tolerability, treatment options. These factors may result in decreased adherence and persistence to preventive therapy with increased healthcare resource utilization, financial costs, and ultimate worsening of disease.

Specifics of modern preventive migraine treatment

Introduction of effective targeted biological pathogenetic treatments for migraine (monoclonal antibodies [mAbs] that target the calcitonin gene-related peptide

[CGRP] ligand or its receptor) has evidently led to improvement in efficacy and tolerability of preventive treatment with high adherence and persistence to therapy [9, 11]. Currently, 4 representatives of mAbs targeting CGRP and its receptor (fremanezumab, galcanezumab, eptinezumab, and erenumab) are marketed in the USA and Europe, and fremanezumab and erenumab are also marketed in the Russian Federation [37,38].

Numerous clinical studies and four-year practical experience show that mAbs to the CGRP ligand (fremanezumab, galcanezumab and eptinezumab) and to its receptor (erenumab) are highly effective in the treatment of episodic and chronic migraine. It has also been established that mAbs can be effective in migraine refractory to prior preventive migraine treatments (beta-blockers, anticonvulsants, antidepressants, onabotulinumtoxin A, etc.), and in migraine with medication-overuse headache [12, 13].

Unlike many conventional oral medications for prevention of migraine, CGRP pathway mAbs are targeted treatments that reversibly block CGRP or its receptor, with no immune system involvement [15]. This explains the low incidence of adverse drug reactions (ADRs) and high safety of CGRP pathway mAbs, including in the group of patients with cardiovascular risk factors [11, 14]. The latter circumstance is of particular importance given the high comorbidity and chronic nature of the course of migraine in a high number of patients.

Based on the efficacy (Level of Evidence A) and strong safety profile, CGRP pathway mAbs were included in the group of first-line therapies for migraine prevention according to the Russian National Clinical Guidelines [8]. At the same time, to ensure effective integration of the targeted treatments for migraine into practice, it is important to find answers to the following relevant clinical issues:

1. Identification of predictors and criteria for treatment response/non-response, individual tolerability;
2. Optimal duration of treatment;
3. Indications for a repeated course of treatment;
4. Analysis of real-world evidence in severe refractory types of migraine with medication-overuse headache (MOH).

All of these clinical issues are raised by medical specialists in routine clinical visits. To assist practitioners in terms of effective and safe use of CGRP pathway mAbs, experts from the Russian Headache Research Society (RHRS) have built a consensus on the use of a new (targeted) biological pathogenetic therapy for migraine in clinical practice. The consensus is based on the results of analysis of the latest research and clinical data, as well as practical experience from leading headache centers and specialists in Russia, taking into account a follow-up of more than 600 patients who were treated with CGRP pathway mAbs. This consensus aims to improve current prescribing practices of CGRP pathway mAbs and managing patients with various types of migraine based on currently available data.

Table 1. *Modern criteria for preventive therapy administration [9]*

Preventive treatment	Headache days per month	Disability
To be prescribed	6 or more	Mild
	4 or more	Moderate
	3 or more	Severe
Possibility of the prescription is to be discussed	4 or 5	Mild
	3	Moderate
	2	Severe

The main goals of preventive migraine therapy are as follows [8, 9, 16]:

- Reduce frequency, duration, and severity of migraine attacks
- Improve efficacy of the treatment of migraine attacks, including reduction of the frequency of analgesics use
- Reduce degree of disability and improve the patients' quality of life
- Reduce psychological distress associated with migraine
- Improve patient self-management of the disease
- Reduce direct and indirect migraine-associated costs

When should preventive migraine therapy be prescribed?

According to the current data, the need for prescribing preventive therapy must be reviewed and discussed with the patient in any of the following clinical situations [2, 8, 9]:

- Migraine attacks significantly interfere with the patient's daily activities.
- The patient has migraine attacks with frequency and severity consistent with the criteria presented in Table 1.
- Contraindications, lack of efficacy and/or overuse of analgesics:
- Use of triptans, ergotamine or derivatives, combination analgesics, or any combination of medications to treat migraine attacks during ⩾10 days per month
- Use of NSAIDs or paracetamol during ⩾15 days per month
- Patient's preference

One of the most important criteria for prescribing preventive treatment is a combination of unacceptable (for the patient) frequency and severity of migraine attacks. Currently, the world's leading experts distinguish two clinical situations depending on the ratio of frequency/severity of attacks. In the first case, "preventive treatment is indicated"; in the second case, "discussion with the patient of the need for preventive treatment is indicated" (Table 1) [2, 9]. In the second situation, a comprehensive review of impairment of the patient's quality of life, number and severity of comorbidities, and the frequency of analgesic use is required in order to make a decision.

According to the Russian National Clinical Guidelines for Diagnosis and Management of Migraine, based on the efficacy (Level of Evidence A) and a high level of safety, CGRP pathway mAbs (fremanezumab and erenumab) rank among the first choice medications for preventive treatment of various types of migraine [8]. At this, mAbs against CGRP or its receptor are the only class of drugs for targeted (pathogenetic) therapy currently marketed in the Russian Federation. Fremanezumab and erenumab are administered subcutaneously (SC). Two dosing regimens are available for fremanezumab: 225 mg SC monthly or 675 mg SC every 3 months. Erenumab is administered subcutaneously at a dose of 70 mg or 140 mg monthly [37, 38].

In which groups of patients can targeted preventive biological treatment of migraine be initiated and carried out?

- According to data from randomized clinical trials (RCTs) and real-world evidence from clinical practice, ***CGRP pathway mAbs can be recommended as the first choice for preventive treatment of various types and frequencies of migraine (migraine with/without aura, episodic migraine, chronic migraine, menstrual-related migraine)***, including in the presence of MOH and regardless of prior treatments [8, 9].
- ***CGRP pathway mAbs may be the first choice preventive treatment for previously untreated patients*** [8].
- CGRP pathway mAbs have proven efficacy in patients with episodic and chronic migraine, previously refractory to both oral preventive treatment, and in non-responders to botulinum therapy [11, 17].
- mAbs against CGRP or its receptor have proven efficacy in migraine with MOH [18,20].

Are there any benefits in combination treatment with mAbs?

- It is recommended to use monotherapy (a single medication) for migraine prevention. Currently, there is no convincing evidence of increased efficacy of preventive treatment when using a combination of drugs from different classes [21]. There are few data from observational non-randomized studies that show increased efficacy of preventive treatment using a combination of onabotulinumtoxinA and mAbs against CGRP or its receptor [22–24].
- At the same time, taking into account the data and experience from real-world clinical practice, in severe chronic migraine refractory to ongoing therapy, treatment with mAbs against CGRP or its receptor combined with conventional preventive migraine treatment options in some cases does increase the efficacy of therapy. In order to make a decision to initiate a combination treatment, it is important to make personalized assessments including course and severity of migraine, number and severity of comorbidities, and possible risks and benefits of preventive treatments used in combination.

Specifics of mAbs prescription in MOH

- Targeted preventive treatment may be prescribed BEFORE withdrawal of the drug being overused. It has been shown that the earlier an effective preventive migraine therapy is prescribed, the more successful the MOH treatment [25].
- Withdrawal or limitation of the use (not more than twice a week) of the drug being overused is associated with a higher efficacy of treatment with mAbs against CGRP or its receptor.
- According to the evidence obtained in clinical practice, some patients with migraine and MOH report high efficacy (⩾50% reduction in the number of headache days after 3 months of therapy) of mAbs against CGRP or its receptor before discontinuation of the excessively used acute migraine medications [25].

What are the main criteria for prescribing a CGRP pathway-targeted mAb for migraine?

An important step in initiation of migraine prevention using CGRP pathway mAbs is the development and discussion with the patient of a plan for future therapy. It is important to discuss the need for treatment, mechanisms of action of the medications, waiting period required to achieve significant improvements, duration and realistic expectations from the treatment, duration of persisting therapeutic effect after discontinuation of the prescribed treatments [9, 26].

The criteria for initiation of CGRP pathway mAb treatment in various types of migraine are presented below, based on the results of clinical studies and practical experience [8, 9, 27, 28]:

Table 2. *Criteria for prescribing and patient groups eligible for CGRP pathway mAb treatment*

Treatment initiation may be recommended if criteria A, B are met, and there are no contraindications for prescription of CGRP pathway mAbs in any of the groups C, D, E or F:
A. Treatment is prescribed by a neurologist
B. Patient is aged ⩾18 years old
C. Patients with episodic migraine with or without aura, with ⩾4 migraine days per month and at least moderate impairment of daily activities due to headache (MIDAS[1] score >11 or HIT[2] score >50)
D. Patients with chronic migraine with or without medication-overuse headache
E. Patients with episodic or chronic migraine refractory to prior treatments
F. Female patients with menstrual-related migraine
G. No contraindications for prescription of CGRP pathway mAbs

When is it proper to assess the efficacy of targeted migraine therapy with CGRP pathway mAbs?

The efficacy of CGRP pathway mAb treatment should be assessed not earlier than after 3 months (3 cycles of subcutaneous injections) with a monthly dosing regimen and not earlier than after 6 months (2 cycles of injections) when using fremanezumab at a dose of 675 mg every 3 months [8, 9, 28]. The criteria for evaluating the efficacy of preventive treatment with CGRP pathway mAbs are presented in Table 3. After 3 months with monthly administration (after 6 months with quarterly administration) of CGRP pathway mAbs (fremanezumab and erenumab), after reviewing the efficacy criteria, a decision is to be made whether to continue therapy. In order to assess the efficacy and analyze objectively, it is recommended to use a headache diary and assess disability and functionality scales to determine the level of headache-related impairment of daily activities and impact on quality of life (Migraine Disability Assessment [MIDAS] and Headache Impact Test-6 [HIT-6])[29,30].

[1]MIDAS – Migraine Disability Assessment Questionnaire.
[2]HIT-6 – Headache Impact Test.

What are the main efficacy criteria for targeted preventive migraine treatment with CGRP pathway mAbs?

The main efficacy criteria for targeted preventive migraine treatment with CGRP pathway mAbs are presented in Table 3.

Table 3. *Criteria for the efficacy of targeted preventive migraine treatment with CGRP pathway mAbs (assessment is to be performed after 3 months [3 cycles of subcutaneous injections] with a monthly dosing regimen and not earlier than after 6 months [2 cycles of injections] with a quarterly dosing regimen) [8, 9, 27, 28]*

A. ⩾50% reduction in mean number of days with moderate to severe headache compared to pretreatment in the group of patients with episodic migraine.
B. ⩾30% reduction in mean number of days with moderate to severe headache compared to pretreatment in the group of patients with chronic migraine with/without MOH.
C. Clinically meaningful and significant improvement in the scores of one of the validated questionnaires for assessment of headache-related impairment of daily activities and quality of life (MIDAS and HIT-6 scores).
1. MIDAS:
1.1. ⩾5 scores reduction in case of baseline pretreatment assessment of 11–20 scores
1.2. ⩾30% scores reduction in case of baseline pretreatment assessment of greater than 20 scores
2. HIT-6: ⩾5 scores reduction.

In addition to the above criteria, it is important to assess the treatment efficacy from the patient's individual perspective: these are subjective judgments regarding change in the condition, opinion, and decision that play important roles for the subsequent treatment plan [8, 9, 28]. Additional parameters for analyzing the efficacy of treatment with mAbs against CGRP can include the following:

- Significant reduction in duration of the attacks as assessed by the patient
- Significant reduction in severity of the attacks as assessed by the patient
- Improved response to medications for acute treatment of migraine attacks
- Improved quality of life and reduced psychological stress related to migraine

In addition, at any stage it is important to assess tolerability of the therapy and adverse drug reactions in order to continue the treatment.

How long targeted preventive migraine treatment with CGRP pathway mAbs should be continued?

Based on the results of long-term prospective randomized clinical trials (RCTs) and analysis of data from real-world clinical practice, it is possible to define the mean duration of targeted preventive migraine treatment with CGRP pathway mAbs provided the efficacy criteria are met [31–35]. When discussing the expected duration of treatment with CGRP pathway mAbs, two criteria can be relied on: the disease severity and treatment response rate and depth.

- In low-frequency episodic migraine (4–8 headache days per month) with obvious clinical improvement during the first 3 months of treatment, the duration of therapy may be 6–12 months.
- In high-frequency episodic migraine (8–14 headache days per month), chronic migraine, migraine refractory to prior treatments, or migraine with MOH, the optimal duration of therapy must be 12–18 months.
- The duration of therapy with CGRP pathway mAbs may be longer than 18 months if continued treatment is clinically indicated [35].

When is it possible to prescribe a repeated course of targeted preventive migraine treatment with CGRP pathway mAbs?

Currently, there are insufficient data to reasonably discuss the mean duration of treatment effect after a completed course of therapy with CGRP pathway mAbs. Taking into account the data from real-world clinical practice, it can be noted that in most patients the treatment effect persists for at least 3–6 months after completion of the treatment course [36]. From a practical point of view, it is important to assess the patient's condition and if warranted, change the course of migraine treatment after 3–6 months with CGRP pathway mAbs.

The decision to initiate a repeated course of treatment with CGRP pathway mAbs can be guided by similar criteria that were used at the initiation of preventive migraine treatment with these medications. Thus, if migraine worsens after completion of the treatment course, and there are still indications for prescribing preventive therapy, repeated prescription of CGRP pathway mAbs may be considered.

Limitations associated with prescription of targeted preventive migraine treatment and the spectrum of adverse drug reactions

According to the results of clinical studies and worldwide four-years clinical practice, targeted migraine treatment with CGRP pathway mAbs is further characterized by favorable safety profile. The most common adverse drug reactions (ADRs) are mild and tend to occur at the injection site (i.e. pain, induration, erythema, itching, rash), often resolving spontaneously and not requiring any additional interventions. The prescribing information for erenumab also includes information about the risk of constipation as an ADR, and hence, erenumab is recommended to be administered with caution in patients with a history of severe constipations [35, 37, 38]. According to the available data and recommendations of the European Headache Federation (EHF), CGRP pathway mAbs are contraindicated during pregnancy and lactation. Pregnancy planning is recommended after at least 5 months of completion treatment with CGRP pathway mAbs. It is also recommended that targeted migraine treatment be used with caution in patients with high vascular risk factors and Raynaud's syndrome [35].

What if targeted preventive migraine treatment is not effective?

When analyzing data from real-world clinical practice, much attention is paid to the issue of changing treatment with CGRP pathway mAbs if the efficacy criteria are not met after 3 months (3 cycles of subcutaneous injections) with a monthly dosing regimen or after 6 months (2 cycles of injections) with a quarterly dosing regimen. In order to make a decision, it is necessary to individually discuss with the patient the treatment satisfaction, to review the disease history and previous preventive migraine treatments, persistence of MOH, and comorbidities that can significantly affect the course of migraine. Depending on specific situations, several strategies for continuing preventive migraine treatment are possible [8, 9, 11]:

- Substitution of one CGRP pathway mAb with another, or a dose change. Data from clinical trials and clinical practice show that the medication change leads to significant clinical improvement in the mean of 30% of patients.
- Use of combination preventive treatment. Before initiation of combined treatment, it is necessary to assess the risks, course of migraine, severity of comorbidities, possible risks and benefits of prophylactic treatment with a combination of drugs.
- A course of "detoxification" may be carried out to ensure discontinuation of excessive use of medications for acute treatment of migraine attacks in patients with persisting MOH.

Conclusion

This consensus reviews the main relevant issues of clinical use and integration into everyday practice of a new targeted preventive migraine treatment with CGRP pathway mAbs. These recommendations are based on the current latest data from research and clinical studies, and analysis of the results of several years of experience with these drugs in clinical practice. No doubt, these are not definitive answers to the questions posed, and not all aspects related to the use of CGRP pathway mAbs in migraine. The main purpose of these guidelines is to assist practitioners in prescribing the correct and effective preventive migraine treatment using CGRP pathway mAbs, whilst improving care for patients with various types of the disease.

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