Prevention of migraine with monoclonal antibodies against CGRP or the CGRP receptor

Addition to the S1 guideline: Therapy of migraine attacks and prevention of migraine. Recommendations of the Germany Society of Neurology and the German Migraine and Headache Society

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Abstract
Monoclonal antibodies against the calcitonin gene-related peptide (CGRP) receptor (Erenumab) or against CGRP (Eptinezumab, Fremanezumab, Galcanezumab) are new substances for the preventive treatment of migraine. They represent an extension of the therapeutic options, which already exist in migraine prevention. In randomized, placebo-controlled studies, the efficacy and good tolerability of these specific substances have been demonstrated in patients with episodic and chronic migraine. The following treatment recommendation presents a summary of the pivotal studies. Recommendations are provided for the targeted selection of patients as well as for the evaluation of therapeutic success and the duration of treatment. Finally, possible restrictions on the use of this new substance group are discussed.
This guideline is an abridged and translated version of the guideline published by Diener H-C, May A et al., Prevention of migraine with monoclonal antibodies against CGRP or the CGRP receptor, Supplement to S1 Guideline Therapy of Migraine Attack and Prevention of Migraine, 2019, Deutsche Gesellschaft für Neurologie (eds.), Guidelines for Diagnostics and Therapy in Neurology. A complete version of this guideline can be found on the website of the Deutsche Gesellschaft für Neurologie (www.dgn.org/leitlinien) and the AWMF (Arbeitsgemeinschaft wissenschaftlicher Medizinischer Gesellschaften).
This guideline has been approved by the German Neurological Society (DGN) and the German Migraine and Headache Society (GMHS) and was reviewed by the two societies.

Keywords: Episodic migraine, Chronic migraine, Migraine prevention, CGRP, Monoclonal antibodies, Guideline
Introduction
This guideline is an abridged and translated version of the guideline published by Diener H-C, May A et al., Prevention of migraine with monoclonal antibodies against CGRP or the CGRP receptor, Supplement to S1 Guideline Therapy of Migraine Attack and Prevention of Migraine, 2019, Deutsche Gesellschaft für Neurologie (eds.), Guidelines for Diagnostics and Therapy in Neurology [1]. A complete version of this guideline can be found on the website of the Deutsche Gesellschaft für Neurologie (www.dgn.org/leitlinien) and the AWMF (Arbeitsgemeinschaft wissenschaftlicher Medizinischer Gesellschaften). The original guidelines was published in August 2019 and the guidance is valid until 1 September 2022.

Recently, three monoclonal antibodies against CGRP and the CGRP receptor have become available for the medicinal prophylaxis of migraine. A further one (Eptinezumab) was approved in the USA. Therefore, the existing guideline for the treatment of migraine attack and prophylaxis of migraine of DGN and DMKG had to be updated. This guideline deals with the therapeutic use of antibodies against CGRP or the CGRP receptor for the prophylaxis of episodic or chronic migraine. The patient group for whom this guidance is most relevant are those patients with migraine in whom previous drug therapies have been ineffective, were not tolerated or are contraindicated. The scope of application of the guideline covers outpatient, day-care and inpatient care and the recommendations of the guideline are aimed at neurologists and pain therapists who treat patients with therapy-refractory migraine.

Patients with frequent or severe migraine attacks require non-drug and/or drug migraine prevention in addition to effective treatment of the acute migraine attack [1]. Until now, according to the Guidelines of the German Society of Neurology and the German Migraine and Headache Society, the beta-receptor blockers propranolol, metoprolol and bisoprolol, the calcium antagonist flunarizine, the anticonvulsants valproic acid and topiramate as well as the tricyclic antidepressant amitriptyline have been available for this purpose with a high degree of evidence [1]. A complete version of this guideline can be found on the website of the Deutsche Gesellschaft für Neurologie (www.dgn.org/leitlinien). The original guidelines was published in August 2019 and the guidance is valid until 1 September 2022.

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the size of the antibodies, as they do not cross the blood-brain barrier to a relevant extent and do not have central nervous system side effects. Due to their degradation to amino acids, they do not interact with other drugs by bypassing hepatic and renal elimination steps. Monoclonal antibodies have to be administered either subcutaneously or intravenously, with the corresponding dosing intervals depending on the half-life and dose-ranging between 4 weeks and 3 months for Fremanezumab and Eptinezumab.

**Methods of guideline development**

Research, selection of proven scientific evidence: First, seven questions were formulated on the use of monoclonal antibodies against CGRP or the CGRP receptor and a systematic literature search was conducted for these
questions. The terms CGRP, CGRP antibody, monoclonal antibody against CGRP, CGRP-receptor antagonist, Erenumab, Fremanezumab, Galcanezumab, Eptinezumab, episodic migraine, chronic migraine, safety, tolerability, adverse events, medication overuse headache were used. The literature review covered the period from January 2015 until mid-August 2019. Selection of evidence: The relevant literature was selected by the authors who formulated the respective section of the guideline.

The guideline is an addition to the S1 DGN–DMKG guideline: Therapy of migraine attacks and prevention of migraine (AWMF-Registry number 030/057).

The guideline was released on 30 August 2019 and is valid until 1 September 2022.

These are joint recommendations of the Germany Society of Neurology and the German Migraine and Headache Society. Both societies reviewed the guideline.

The external review of the guideline was carried out by three members of the DGN Guidelines Commission and additionally by two independent external reviewers of the DGN.

Recommendations

The treatment algorithm for prevention of migraine with monoclobal antibodies can be seen in Fig. 3. The seven different recommendations are explained below.

1. Are monoclonal antibodies (MOAB) against CGRP or the CGRP receptor effective for the prevention of episodic migraine?

Monoclonal antibodies against CGRP (Eptinezumab, Fremanezumab, and Galcanezumab) or the CGRP receptor (Erenumab) are superior to placebo treatment in the preventive treatment of episodic migraine. The reduction of migraine days per month in episodic migraine ranges between 2.9 and 4.7 days. The 50% responder rate after 3–6 months is between 30 and 62%. The 50% responder rate for placebo is between 17 and 38%. The effectiveness can be evaluated within 4–8 weeks. A direct comparison of the monoclonal antibodies with each other has not been performed, nor is a comparison with the traditional migraine preventive drugs available so far.

2. Are monoclonal antibodies against CGRP or the CGRP receptor effective in the prevention of chronic migraine?

Monoclonal antibodies against CGRP (Eptinezumab, Fremanezumab, and Galcanezumab) or the CGRP receptor (Erenumab) are superior to placebo treatment in the prevention of chronic migraine. The reduction of migraine days per month for chronic migraine is between 4.3 and 6.6 days. The 50% response rate after 3 months ranges between 27 and 57%. The 50% response rate for placebo is between 15 and 40%. Efficacy has also been shown for
patients with chronic migraine and medication overuse. A direct comparison of the monoclonal antibodies with each other was not performed, nor is a comparison with traditional migraine preventive drugs available to date.

3. Which patients should receive a monoclonal antibody for migraine prevention?
Monoclonal antibodies are approved in Germany for the treatment of migraine with at least four migraine days per month. According to the decision of the German Federal Joint Committee (GBA), a prescription is possible in patients with episodic migraine if at least 5 substances from the 4 available, approved pharmacological groups such as beta-blockers (Metoprolol or Propranolol), Flunarizine, Topiramate, valproic acid or amitriptyline were not effective, not tolerated or if there are contraindications or warnings against their use. Regarding patients with chronic migraine, it is recommended that they have not additionally responded to therapy with OnabotulinumtoxinA.

4. How is the therapy success evaluated?
In episodic and chronic migraine, treatment success is defined as a reduction in the average monthly headache days by 50% or more compared to pre-treatment for a period of at least 3 months (diary documentation is recommended) [13].

Alternative clinically acceptable criteria are significant improvements in validated, migraine-specific, patient-related outcome measures such as: 30% reduction of the MIDAS [14] score for those with baseline values above 20. Reduction of the score in the 6-point headache impact test (HIT-6) [15] by at least 5 points.

5. How long should preventive therapy be performed?
The therapy should initially be carried out for 3 months. If there is no satisfying therapy effect, the therapy will be terminated. If the therapy is effective, interruption of therapy should be considered after 6–9 months to check whether the therapy is still necessary.

6. What are the contraindications and warnings for the use of monoclonal antibodies?
Monoclonal antibodies against CGRP or the CGRP receptor should not be used in pregnant women and during lactation. They should not be used in women who have no or insufficient contraception. Furthermore, as a precaution, they should not be used in patients with coronary heart disease, ischemic stroke, subarachnoidal hemorrhage or peripheral arterial occlusive disease. For children and adolescents, there is no information on tolerability and safety to date. Monoclonal antibodies should not be used in patients with inflammatory bowel disease, COPD, pulmonary hypertension, Raynaud's syndrome, wound healing disorders or transplant recipients until further notice. Since the available studies have so far only included patients without relevant previous diseases, patients with chronic diseases should be treated with caution.

7. Does it make sense to switch to a CGRP receptor antagonist if therapy with a CGRP antagonist does not respond and vice versa?
There are no data on this question from the randomized studies or registries. The attempt to change therapy seems justified.
remuneration, which, however, is not published. A self-assessment no longer took place. All declarations of interest were reviewed by an anonymous, independent and knowledgeable conflict of interest officer of the DGN for potential relevant thematic interests. The information was examined with regard to an existing thematic reference, thematic relevance, type and intensity of the relationship and the absolute amount of the remuneration. The following evaluation criteria were applied:

- Paid assessor/consultant work for industrial companies
- Participation in a scientific advisory board: paid work for industrial companies
- Lectures: paid for by the industry
- Authorship or co-authorship: only if industry-driven
- Research projects/conducting clinical studies: directly or partially financed by industrial companies
- Ownership interests (patents, shareholdings) with reference to guidelines
- Indirect interests with relevance

The 50% rule of the DGN is a special requirement of the DGN since May 2014 which stipulates that for a balanced composition of the guideline group, at least 50% of the participants in the guideline must have no or only minor conflicts of interest relevant to the guideline. The DGN has decided to introduce the 50% rule because it prevents any overlap of individual interests in voting.

Evaluation of the interests presented

The editorial committee consists of 14 members, including two lead authors. Of the total group, 9 members are free of conflicts of interest or have only minor thematically relevant conflicts of interest. 5 contributors with moderate conflicts of interest were not involved in the formulation of the guidelines text. They had an advisory and/or corrective function. The 50% rule of the DGN was observed. For reasons of transparency, the interests of the parties involved and their assessment by DGN conflict of interest officers are listed a summary table on the webpage of the guideline.

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