Onabotulinumtoxin A (ONA-BoNT/A) in the treatment of chronic migraine

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ABSTRACT
Migraine is a common primary headache disease, which reduces quality of life. About 8% of migraineurs suffer from chronic migraine (CM), which is the most severe and troublesome type. It has been proven that onabotulinumtoxinA (ONA-BoNT/A) significantly improves CM, presumably inhibiting the release of calcitonin gene-related peptide (CGRP) and other neurotransmitters from c-fibres endings, and thus decreasing activation of nociceptive pathways and transmission of pain. The aim of this position paper was to assess the place of ONA-BoNT/A for the prophylaxis of CM in adults. The authors have compared the efficacy, safety and tolerance of the toxin to those of classical oral preventive therapies as well as to recently introduced anti-CGRP-pathway monoclonal antibodies. The results of randomised controlled studies of ONA-BoNT/A have been compared to open label (real world practice) trials.

Key words: chronic migraine, botulinum toxin type A, onabotulinumtoxin A, prophylactic treatment, monoclonal antibodies, CGRP

Introduction
Migraine, as the second leading cause of disability, reduces quality of life, increases the economic burden, and decreases productive capacity [1–4]. Chronic migraine (CM) is the most severe and troublesome type of this disease [5]. According to the International Headache Society, CM is defined as a headache occurring on 15 or more days per month for more than three months a year, which, on at least eight days per month, has the features of migraine without or with aura [6]. The overall prevalence of CM ranges from 1.4% to 2.2% of the general population, which reflects 8% of all individuals suffering from migraine [7, 8]. In women, the prevalence of CM peaks at 18–29 years and again at 40–49 years [9]. Chronic migraine in most cases evolves from episodic migraine, with a conversion rate of 2.5% to 3% a year [10]. Published studies have demonstrated that onabotulinumtoxinA (ONA-BoNT/A) has a particular effect on the prevention of CM, although the mechanism is not fully understood [11–14]. Recently, new effective therapeutics based on monoclonal antibodies against Calcitonin Gene Related Peptide or its receptor (anti-CGRP-mAbs/CGRP-R-mAbs) have been approved. The aim of this review was to assess the position of ONA-BoNT/A among other licensed medications for CM, and to make recommendations on treatment pathways.

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Impact of CM on patients’ lives

While neurological disorders as a group are a significant cause of disability and death worldwide [15], migraine, alongside lower-back pain, is associated with the highest number of disability-adjusted life-years (DALYs) [16]. The Global Burden of Disease (GBD) estimates that in 2016 migraine was responsible for 45.1 million years lived with disability (YLDs) [16, 17]. Migraine, especially CM, has a significant impact on patients’ lives in terms of their professional work, social activities and private lives [18]. The social cost of migraine is high for a number of reasons. These include inefficiency at work, reduced functionality, medication use, and outpatient, inpatient and emergency medical visits. The total costs include both direct (medications, visits, examinations), and much higher, indirect costs (absenteeism, presenteeism) resulting in decreased productivity [19]. A very large disproportion between direct costs and indirect costs is visible. Indirect costs are many times greater. In the indirect cost category, the costs of presenteeism are many times greater than the costs of absenteeism. The conclusion is therefore that the primary cost implication of migraine is the cost of significantly reduced productivity. Most people with a migraine attack come to work or develop a migraine attack at work and then carry out their duties and activities with significantly limited productivity. This limitation can result in 50% performance loss or more. This generates high costs of presenteeism in the group of people suffering from migraines. The estimated annual cost of presenteeism for one person suffering from episodic migraine in Poland is PLN 2,149.22, and the estimated cost of presenteeism for one person suffering from CM is PLN 10,225.14.

The higher cost of presenteeism for people suffering from CM may result not only from migraine attacks, but also from ailments resulting from other diseases. It should be taken into account that the estimated number of economically active people suffering from episodic migraine in Poland exceeds 2 million, and the number of people suffering from CM may exceed 350,000. This means costs in the range of 6-8.5 billion PLN annually, i.e. 0.3-0.4% of the annual Gross Domestic Product (GDP). An additional problem is the coexistence of migraine with other diseases, including mental, neurological, vascular and cardiological disorders [15]. Among psychiatric disorders, depressive disorder (MDD) is the most common disorder observed in patients with migraine [20]. Migraine as an ‘almost whole life-lasting’ debilitating and disabling disorder has a significant influence on well-being and social/healthcare system costs [21].

Pharmacoeconomic aspects of chronic migraine

Pharmacoeconomics is an increasingly important part of the evaluation of migraine therapies [22, 23]. Taking into account the therapeutic approach before the era of ONA-BoNT/A and anti-CGRP-mAbs/anti-CGRP-R-mAbs, such costs related to hospitalisations/ED visits, healthcare provider visits, procedures and medications in chronic migraineurs are globally three times as much as in patients with episodic migraine. In the USA, the aforementioned mean annual sub-costs of chronic migraine are as follows: $86.7, $498.4, $557.1, and $3,002.4, with a mean total annual cost of $4,144, and $187.2, $178, $127.3, and $1,040.4 in episodic migraine respectively, with a mean total annual cost of $1,533 [24]. In Canada, as well as in European countries, the proportions between the mean costs of treatment of chronic migraine and episodic migraine are similar [23, 24]. According to the data of the Social Insurance Institution, in 2017, 97,349 sick leave days due to migraine were financed in Poland [25]. It follows that the costs of sickness absenteeism were four times higher than the direct medical costs incurred by the taxpayer in 2017.

CM treatment — review of recommendations

Current recommendations developed by the European Neurological Society and the American Academy of Neurology, as well as the International Headache Society, include traditional medication and complementary drug treatments. It has been estimated that c.40%people with migraine would benefit from preventive therapy, but with chronic one probably less than 65%. Unfortunately, about half of those who would be candidates for preventive treatment are prescribed prophylactic treatment instead [26, 27].

Drugs that have the strongest evidence supporting their effectiveness as chronic migraine prevention (category A evidence) include antiepileptic drugs (valproate and topiramate). According to the European Medicines Agency (EMA) recommendations, valproic acid should not be used in women with childbearing potential (US Food and Drug Administration (FDA) Category X) [28, 29]. Amitriptyline is probably effective as a preventive in CM (category B evidence). In the recommendations (level A/B) for CM, ONA-BoNT/A was considered a drug with well-documented effectiveness in a placebo-controlled clinical trials [30]. Monoclonal anti-CGRP antibodies (mAbs-CGRP) are a new therapeutic option for CM. Like ONA-BoNT/A, they show a good adherence profile as they are injected once a month or once a quarter. The safety profile and tolerability of both ONA-BoNT/A and anti-CGRP/CGRP-R mAbs are excellent and comparable, with good compliance and adherence to these therapies. Moreover, they both act in patients who have experienced previous treatment failures, in patients with MOH, and in individuals with comitant depression and/or anxiety, having an additional benefit in the latter. The results from randomised, placebo-controlled trials (RCT) are additionally confirmed by real-world studies (RWS) discussed in this paper. Substantial studies which have been published on mAbs against CGRP/CGRP-R locate this class of therapeutics in a very strong position in the options for the treatment of migraine.
Possible mode of action of ONA-BoNT/A in migraine

The analgesic effect of ONA-BoNT/A has been shown in cervical dystonia, where pain relief precedes the muscular effect. Therefore, it is not only due to muscle relaxation, but probably also due to sensory nerves involvement [31]. Nevertheless, the possible mode of action of ONA-BoNT/A in migraine is not yet fully understood.

There are several different mechanisms underlying this effect, such as axonal transport and transcytosis, inhibition of key neurotransmitters release, and modulation of receptors and chronic inflammation [32]. The majority of studies showing these possible mechanisms are based on animal models. The pretreatment of a skin area with ONA-BoNT/A injection in a capsaicin pain model reduced the trigeminal pain intensity, secondary hyperalgesia, blood flow and skin temperature compared to normal saline [33]. ONA-BoNT/A retrograde transport to the central nervous system has been proven, and colchicine, an axonal transport blocker, is able to inhibit this effect. In a formalin model, unilateral and contralateral injections decreased pain showing both peripheral and central desensitisation effects. Peripheral scalp injections may therefore result in retrograde transportation through the connections (skull sutures) to the meninges, Gasserian trigeminal ganglion and occipital nerves through dorsal roots to the cervical spine [32–34].

The protocol for migraine treatment with ONA-BoNT/A injections utilises this proximity of trigeminal and occipital nerves endings [32]. Several animal studies show that ONA-BoNT/A also inhibits the release of a number of neurotransmitters associated with migraine such as CGRP and substance P (SP), serotonin, glutamate, gamma aminobutyric acid (GABA), noradrenaline, dopamine, enkephalin and glycine. CGRP has a crucial role in peripheral and central sensitisation in migraine. Due to the retrograde ONA-BoNT/A transportation, these effects may be both peripheral and central [32, 35].

ONA-BoNT/A blocking peripheral neurotransmitter release may result in peripheral sensitisation of nociceptors. A consequence of this would be an indirect reduction of central sensitisation as well [36]. ONA-BoNT/A has been shown to inhibit the surface expression of numerous nociceptive receptors such as TRPV1, TRPM8, TRPA1, P2X3, and GABA-A, and is an agonist of α-opioid receptors. The last one agonistic opioid effect diminishes the pain, but the mechanism how ONA-BoNT/A may block α-opioid receptors remains unknown. TRP channels activation resulting in the release of both CGRP and SP, and therefore this inhibition effect of ONA-BoNT/A may theoretically decrease this effect. A clinical trial of a TRPV1 antagonist in acute migraine showed it was ineffective, but it was not tested in chronic migraine patients [32].

The release of CGRP during neuronal activation of the trigeminal system stimulates the satellite glia cells, which in turn release proinflammatory cytokines, thereby further modulating the neuronal response. This process is believed to participate in the maintenance of chronic migraine [37]. ONA-BoNT/A downregulates pronociceptive interleukins IL-1β and IL-18 in the dorsal root ganglion, and upregulates antinociceptive interleukins IL-1RA and IL-10 in the spinal cord [28, 32, 38]. This may explain why ONA-BoNT/A is so effective in chronic, but not episodic, migraine or in tension type headaches.

The mechanisms of BoNT/A in chronic migraine are still unclear and a uniform concept is not yet possible, but they have translated successfully into clinical trials with ONA-BoNT/A in patients with chronic migraine.

Randomised clinical studies of ONA-BoNT/A in treatment of CM

The PREEMPT-2 trial was the first to prove good efficacy and safety of ONA-BoNT/A in the preventive therapy of CM [39]. The rationale underlying the concept of multiple administrations of the medication over 31–39 injection-points, of 5 U each, was derived from the hypothetical suppressive/inhibitory effect of ONA-BoNT/A on the release of neurotransmitters within the nociceptive pathways in the brain and the dura mater, presumably in peptidergic neurons containing calcitonin gene-related peptide (CGRP). The injections were made in the vicinity of five groups of muscles, in the frontal, temporal, parieto-occipital areas of the skull, the area of the paraspinal muscles of the upper neck, and the region of the upper part of the trapezius muscles. The minimum number of injection-sites was 31, and there were up to eight optional, additional injections to be given in a ‘follow-the-pain’ mode. In pooled analysis from Part 1 and Part 2 of the PREEMPT study, the primary goal and the secondary goal were achieved. These included fewer monthly headache days, monthly migraine days, monthly moderate and severe headache days, monthly cumulative number of hours with headache, and number of triptans taken. The only parameter which initially failed (due to an incorrect methodological assumption) was the number of days with abortive drug taken. The differences between the ONA-BoNT/A treatment group and the placebo group were statistically highly significant. Such statistical differences were equally high both in ‘pure CM’ patients as well as in CM with concomitant Medication Overuse Headache (MOH) individuals.

Long-term open-label observational studies and real-world studies of ONA-BoNT/A in treatment of CM

The paradigm of injections from the PREEMPT study has become the standard for many subsequent studies, both RCT, and observational, real-world evaluations of this treatment. RWS producing ‘real-world data’ (RWD). In 2018, the initial results of COMPEL, a real-world study, were
published [40]. This assessed the impact of ONA-BoNT/A on CM parameters over two years. This model confirmed the high efficacy of the drug previously demonstrated in the PREEMPT trial in terms of reduced headache days per month, and a significant improvement in headache impact on daily activities as assessed by the Headache Impact Test-6 (HI-T-6) evaluating the effect of headaches on professional activities, activities at school, housework, as well as social and personal activities. The safety and tolerability of the medication was equally good as in the placebo-controlled study, even though the duration of COMPEL was twice that of PREEMPT. Only a few cases of transient blepharoptosis, local pain, muscle tension, and transient neck pain were reported.

In the PREEMPT trial, there was a slightly higher reduction in headache days after 52 weeks (11.7 days) than after 60 weeks of open-label treatment in the COMPEL study (9.2 days). We speculate that this was related to the total dose of the drug, because in the COMPEL trial all patients received a total dose of 155 U into 31 fixed injection points, whereas in the PREEMPT study it was acceptable to administer up to an additional 40 U in a ‘follow-the-pain’ manner. Thus some patients received as much as 195 U. A higher efficacy of 195 U of ONA-BoNT/A compared to 155 U was demonstrated in another open-label trial [38]. The better effect of a 195 U dose compared to a 155 U dose was shown not only in reducing headache days per month, but also in reducing migraine days a month, and in HIT-6 score Extended results of COMPEL study focused on co-morbidities of CM as depression, anxiety and sleep disorders [41].

In other studies, CM is associated with depression and anxiety in a high proportion of patients: in 41% and 30% [42] or even as high as 47% and 58% respectively [44]. Also, the risk of developing major depression within two years in migraine patients is more than five times greater than in the population without migraine [45]. This issue was addressed in the open-label REPOSE study [46], which demonstrated a statistically significant trend towards a reduction of the total score of health state self-perception (EQ-5D), which also included symptoms of depression and anxiety in CM patients treated for two years with ONA-BoNT/A. Similar findings were found in the COMPEL study: compared to the baseline, in week 108 of ONA-BoNT/A treatment using the 155 U dose, 78% of migraine patients experienced a significant reduction in depression symptoms when assessed by the PHQ-9 questionnaire [42]. At the same time 81.5% of those patients showed a significant decrease in anxiety symptoms measured by the GAD-7 test. The effect of ONA-BoNT/A treatment on depression symptoms increased over the course of the therapy, being present in 61.8% of patients after 12 weeks, in 66.8% after 48 weeks, and in up to 78% after 108 weeks. This applied to patients with mild, moderate, moderate-to-severe and severe depression symptoms. Anxiety symptoms, mild, moderate and severe, also improved at the same study points: after 12 weeks in 69.3%, after 48 weeks in 78%, and after 108 weeks in up to 81.5%.

In the COMPEL study, a reduction in depression symptoms was observed in all patients: in those with a reduction in headache days of at least 50%, in those with a reduction of headache days of at least 25%, and in those who did not respond to treatment (i.e. with an improvement of less than 25%). However, after 48 weeks of treatment of patients with a reduction in the frequency of headache days of at least 50%, improvement in depression and anxiety was significantly higher than in patients without response in headaches of at least 50%. A similar phenomenon with regard to non-responders was observed in the group achieving reduction of headache days of at least 25% [42].

In recent years, there have been a number of long-term clinical evaluations of ONA-BoNT/A effect in the treatment of CM, most of which were not RCT, but RWD i.e. observational studies. In the meta-analysis published by Tassorelli et al. in 2018 [45], the data presented came from five studies lasting 18–48 months, in which MOH was present in a substantial proportion or even in 100% of patients. All studies proved the significant effectiveness of ONA-BoNT/A in CM, including when it is complicated by MOH. In several RWD publications with ONA-BoNT/A in CM from single centres or single countries (Italy, Greece, Australia), the data obtained has shown comparable improvements in terms of fewer monthly days with headaches, and/or number of days with moderate to severe headaches, and/or monthly mean hours with headaches [46–50]. The numbers of 50% responders or 75% responders progressively increased over the course of long therapies. Consequently, the number of abortive drugs taken because of headaches, including migraine, also decreased over the course of treatment with ONA-BoNT/A [46–50]. Concomitantly to clinical improvement achieved over long therapies, questionnaires evaluating quality of life (HIT, MIDAS) have revealed parallel improvements [47, 49, 50].

Apart from the clearly beneficial effect of ONA-BoNT/A on the prevention of headaches in CM, some of the above-mentioned studies have also found its effect on abortive treatment. This is pronounced by progressive shortening of the latency time between intake of abortive drug (triptan) and the relief of headache [47, 50].

**Comparison of effectiveness of ONA-BONT/A and anti-CGRP monoclonal antibodies in treatment of CM**

Four monoclonal antibodies for migraine therapy have already been developed: one against the CGRP-R (erenumab) and three against the CGRP peptide or ligand (optineumab, fremanezumab and galcanezumab).

At present, there are no reliable ‘head-to-head’ studies comparing the effectiveness of ONA-BoNT/A and monoclonal antibodies (mAbs) anti-CGRP/anti-CGRP-R in the treatment
of CM. However, we can expect the first such analyses in the near future: She et al. published in January 2020 in the Journal Medicine the protocol they have adopted into their study on the comparison of ONA-BoNT/A and anti-CGRP/CGRP-R antibodies in the prophylactic treatment of CM, which will be a systematic review and meta-analysis of available studies [51].

To date, ONA-BoNT/A in the treatment of CM has only been compared to that of some preventive oral medications. In 2018, a meta-analysis of available studies on the treatment of CM with ONA-BoNT/A was published in the Cochrane database, in which its effectiveness was successfully compared to a placebo, and, for non-inferiority, to comparators comprising valproic acid, topiramate and histamine, showing also better safety and tolerability profiles than oral prophylactics [52].

Clinical trials have shown that all four CGRP/CGRP-R mAbs have a favourable safety and tolerability profile, as well as high efficacy, and they are recommended for the treatment of episodic migraine with frequent attacks (≥ 4 pain days per month) as well as CM [53]. In all studies, mAbs has demonstrated greater efficacy in reducing the number of migraine days per month compared to placebo, a higher proportion of patients with at least a 50% reduction in the number of migraine days, and a significant reduction in the number of abortive medications used.

The efficacy of erenumab in CM has been assessed in a Phase II study which compared doses of 70 mg and 140 mg administered subcutaneously every month. Both doses achieved a statistically significant difference in the reduction of migraine days compared to the placebo group, which was 2.5 days. The endpoint of at least 50% reduction of migraine/headache days was achieved by 40% of patients receiving erenumab at a dose of 70 mg, and by 41% of patients receiving erenumab at a dose of 140 mg [54]. Tepper et al. continued to evaluate the effectiveness of both doses of erenumab in a long-term, 52-week, open-label study [53]. Clinically significant reductions from the double-blind treatment phase baseline (about half) were observed for monthly migraine days and migraine-specific medication days. Achievement of 50%, 75% and 100% reductions from the double-blind treatment phase baseline in monthly migraine days at week 52 were reported by 59.0%, 33.2% and 8.9% of patients, respectively. A numerically greater benefit was observed with 140 mg compared to 70 mg at weeks 52 [55]. In patients with CM, 12 weeks of treatment with fremanezumab at doses of 225 mg monthly and 675 mg quarterly was associated with a significant decrease in the number of migraine days, on average by 2.1 and 1.9 days compared to the placebo group, and a higher percentage of patients with an at least 50% reduction in the number of migraine days: 27.6% vs. 15.4% [58]. The effectiveness of fremanezumab and erenumab has also been assessed in CM that was refractory to previous pharmacological treatment. Fremanezumab, in the 12th week of treatment, showed a significant reduction in the number of days with migraine compared to placebo (3.2 days and 3.8 days in relation to the doses of 675 mg quarterly and 225 mg monthly) [59]. Treatment with erenumab following previous treatment failures was associated with an average of 4.7 days reduction in the number of migraine days [60]. A summary of the effectiveness of anti-CGRP antibodies is set out in Table 2.

**Conclusions**

Data obtained from RCT and RWD suggests that ONA-BoNT/A effectively reduces the frequency of migraine days, of headache days and the total number of hours with headaches in patients with CM. It is currently recommended to apply treatment with ONA-BoNT/A also to CM patients with concomitant medication overuse headache.

With regard to the original RCT PREEMPT study (along with a number of RWD reports following the PREEMPT study), it can be concluded that:

1. **Long-term (up to four years) treatment of CM with ONA-BoNT/A is safe, well tolerated, and effectively decreases the number of headache days per month compared to baseline.**
2. **Numeric values show comparable, and in some studies even better, effect of ONA-BoNT/A if used in RWS conditions than in RCT.**
3. **In all reported RWS, significant clinical improvements in relation to baseline were observed with regard to: monthly mean reduction of headache days, migraine days, days with moderate to severe headache, and days when abortive drugs were used.**
4. **A 195 U dose administered in ‘real world’ conditions over two years according to the paradigm used in the PREEMPT study seems slightly more efficacious than a 155 U dose.**
5. **Numerous trials have also demonstrated significant improvements during 2–4 years of treatment in the perceived negative impact of CM on selected parameters of quality of life, especially on activities associated with work, education, housework, social activities and personal lives.**
6. **In addition to the beneficial effect on migraine headaches, ONA-BoNT/A has a favourable impact on the**
reduction of concomitant symptoms of depression and anxiety, irrespective of whether or not the patient has achieved a satisfactory reduction in headache days. This phenomenon, however, is more pronounced in patients who have achieved a good effect in terms of frequency of headaches, and more significant reductions are observed with increasing treatment durations. An alternative explanation, however, takes into consideration the direct effect of ONA-BoNT/A on depression and anxiety [61, 62].

A summary of the most important results (‘end-points’) of several RWD outcomes compared to the PREEMPT study as the standard RCT trial with ONA-BoNT/A in CM is shown below in Table 1.

NICE (The National Institute for Health and Care Excellence) recommends the use of ONA-BoNT/A to treat CM that has not responded to at least three prior pharmacological prophylactic therapies [63]. A similar approach in the treatment of CM in regard to ONA-BoNT/A is recommended by the Polish Headache Society [64].

Thus today we believe that it is not justified to position ONA-BoNT/A in relation to CGRP/CGRP-R, or to recommend one of them being used ahead of the other. However, taking into account the pharmacoeconomic aspects, NICE suggests the use of ONA-BoNT/A first and, if it fails, then to try mAbs.

According to this consensus, therapy with ONA-BoNT/A and CGRP/CGRP-R mAbs should not be combined. In patients with CM treated with ONA-BoNT/A with inadequate treatment response, it is suggested to stop onabotulinumtoxinA before the initiation of mAbs [53]. However, a growing number of reports suggest the beneficial effect of combined therapy. The dual mechanisms of both medication actions seem to offer a greater chance of controlling CM [65].

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**Table 1.** Summary of most important results (‘end-points’) of several RWD outcomes compared to PREEMPT study as standard RCT trial with ONA-BoNT/A in CM. Data presented as mean change in 28-day treatment vs. baseline.

<table>
<thead>
<tr>
<th>End point</th>
<th>RCT</th>
<th>RWD</th>
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<tbody>
<tr>
<td></td>
<td>PREEMPT</td>
<td>COMPEL</td>
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<tr>
<td></td>
<td>REPOSE</td>
<td>Dikmen 2018</td>
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<td></td>
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<td>Negro 2016</td>
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<td></td>
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<td>Santoro 2019</td>
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<td>Stark 2019</td>
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<td></td>
<td></td>
<td>Vikelis 2019</td>
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<tr>
<td>Mean change in headache days</td>
<td>–8,4</td>
<td>–8,0</td>
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<tr>
<td></td>
<td>–7,4</td>
<td>–13,0</td>
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<td>–14,7</td>
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<td>–13,6</td>
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<td>Mean change of migraine days</td>
<td>–8,2</td>
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<td></td>
<td></td>
<td>–9,4</td>
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<tr>
<td>Mean change of moderate/</td>
<td>–7,7</td>
<td>–6,5</td>
</tr>
<tr>
<td>severe headache days</td>
<td></td>
<td>–11,9</td>
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<td></td>
<td>–9,4</td>
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<td></td>
<td></td>
<td>–8,2</td>
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<tr>
<td>Mean change of HIT-6 score</td>
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<tr>
<td></td>
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<td></td>
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<td>–6,9</td>
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<td>–11,8</td>
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<tr>
<td>Mean change of days with abortive</td>
<td>–10,1</td>
<td></td>
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<tr>
<td>drugs</td>
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<tr>
<td></td>
<td></td>
<td>–11,1</td>
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<td>–11,8</td>
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<td></td>
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<td>–11,0</td>
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</tbody>
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The data presented as the mean change in 28 day treatment vs. baseline. With courtesy of Allergan.

**Table 2.** Summary of effectiveness of anti-CGRP/CGRP-R antibodies in CM.

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication/phase</th>
<th>Medication/dose</th>
<th>Comparator</th>
<th>MMD difference (p value)</th>
<th>MHD difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tepper et al. 2017</td>
<td>CM Phase II</td>
<td>Erenumab 70 mg monthly</td>
<td>Placebo</td>
<td>–2.5 (&lt; 0.0001)</td>
<td>–2.2 (&lt; 0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>140 mg monthly</td>
<td></td>
<td>–2.5 (&lt; 0.0001)</td>
<td>–2.3 (&lt; 0.0001)</td>
</tr>
<tr>
<td>Tepper et al. 2020</td>
<td>CM Open-label</td>
<td>Erenumab 70 mg monthly</td>
<td>–</td>
<td>–8.5</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>140 mg monthly</td>
<td></td>
<td>–10.5</td>
<td></td>
</tr>
<tr>
<td>Silberstein et al. 2017</td>
<td>CM Phase III</td>
<td>Fremanezumab 225 mg monthly</td>
<td>Placebo</td>
<td>–1.8 (&lt; 0.001)</td>
<td>–2.1 (&lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>675 mg quarterly</td>
<td></td>
<td>–1.7 (&lt; 0.001)</td>
<td>–1.8 (&lt; 0.001)</td>
</tr>
<tr>
<td>Detke et al. 2018</td>
<td>CM Phase III</td>
<td>Galcanezumab 120 mg monthly</td>
<td>Placebo</td>
<td>–2.1 (&lt; 0.001)</td>
<td>–1.8 (&lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>240 mg monthly</td>
<td></td>
<td>–1.9 (&lt; 0.001)</td>
<td>–1.6 (&lt; 0.001)</td>
</tr>
<tr>
<td>Lipton et al. 2020</td>
<td>CM Phase III</td>
<td>Eptinezumab 100 mg quarterly</td>
<td>Placebo</td>
<td>–2.0 (&lt; 0.0001)</td>
<td>–1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 mg quarterly</td>
<td></td>
<td>–2.6 (&lt; 0.0001)</td>
<td>–2.3</td>
</tr>
<tr>
<td>Ferrari et al. 2019</td>
<td>refractory EM, CM Phase IIIb</td>
<td>Fremanezumab 225 mg monthly</td>
<td>Placebo</td>
<td>–3.8 (CM group)</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>675 mg quarterly</td>
<td></td>
<td>–3.2 (CM group)</td>
<td></td>
</tr>
<tr>
<td>Raffaeli et al. 2020</td>
<td>refractory CM</td>
<td>Erenumab 70 mg monthly</td>
<td>–</td>
<td>–4.7</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Open trial</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

MHD — mean headache days; MMD — mean migraine days.
To sum up, ONA-BoNT/A is an effective treatment for CM, the position of which is defined as level A, and it might be considered as a first-line therapy in CM.

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ASI has served as an expert on Advisory Boards and as a lecturer for the following companies: Allergan, Novartis, Teva, Sanofi, Biogen, Boehringer Ingelheim, Bayer;

JS has contracted advisory boards, consultations and lectures for Allergan, Ipons, Merz, Novartis and Teva;

MBJ has contracted advisory boards, consultations and lectures for Allergan Abbvie, Merz, Novartis and Teva;

ASł has served as an expert on Advisory Boards and as a lecturer for Allergan, Ipsen, Merz, Novartis and Teva;

KR has served as an expert on Advisory Boards and as a lecturer for the following companies: Allergan, Abbvie, Novartis, Teva, Elli Lily;

JG declared no conflict;

JFR has served as an expert on Advisory Boards and as a lecturer for the following companies: Allergan, Abbvie, Novartis, Teva, Elli Lily.

### References


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