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The importance of an early onset of migraine preventive disease control: A roundtable discussion

Christopher Gottschalk[1], Anirban Basu[2], Andrew Blumenfeld[3], Bradley Torphy[4], Michael J Marmura[5], Jelena M Pavlovic[6], Paula K Dumas[7], Nim Lalvani[8], and Dawn C Buse[6]

Abstract

Background: Newly approved migraine preventive therapies have allowed for rapid control of migraine activity, offering potential to minimize the burden of migraine. This report summarizes a roundtable discussion convened to analyze evidence for early onset of prevention, ascertain its clinical relevance, and provide guidance for healthcare professionals in crafting goals and treatment expectations for patients with migraine initiating preventive therapy.

Methods: A virtual roundtable meeting of migraine clinicians, researchers, and patient advocates convened in October 2020. Participants reviewed and discussed data summarizing patient and healthcare professional perceptions of migraine prevention and evidence from the peer-reviewed and gray literature to develop corresponding recommendations.

Summary: Evidence from clinical studies of anti-calcitonin gene-related peptide monoclonal antibodies (erenumab, fremanezumab, galcanezumab, and eptinezumab) and the chemodenervation agent onabotulinumtoxinA indicate that patients may experience reduction of migraine activity within 7 days of drug administration and early attainment of disease control is associated with improvements in clinically important outcomes. The roundtable of experts proposes that early onset be defined as demonstration of preventive benefits within 1 week of treatment initiation. We recommend focusing discussion with patients around "disease control" and potential benefits of early onset of prevention, so patients can set realistic preventive therapy goals and expectations.

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Introduction

Migraine is a common and disabling neurologic disorder that affects more than 1 billion individuals worldwide.[1] It is the most disabling disease in people under the age of 50 years[2] and was second only to low back pain as the leading cause of disability globally in 2016.[1] Migraine affects multiple areas of functioning (e.g., family and other relationships, career trajectories, educational achievement, financial security),[3] may limit participation in healthy lifestyle choices (e.g., moderate or vigorous physical activity),[4,5] and imposes a significant economic burden on individuals and on society as a whole.[6–9]

The negative impacts of migraine often persist despite treatment.[10] Poorly controlled migraine not only extends the burdens described above, it is also associated with acute medication overuse (MO)[11,12] and medication overuse headache (MOH)[13–16]; it may result in the transformation or chronification of migraine,[17–22] the latter of which likely arises from neuroinflammation and central sensitization resulting from repeated and prolonged exposure to migraine activity in genetically susceptible individuals.[23,24] While some studies suggest that poorly controlled migraine may worsen or chronify, other studies suggest that the prevalence of daily headache may stabilize, with 69% of participants with migraine aged 19–20 manifesting the same predominant headache subtype over a 30-year period.[25] Furthermore, in a longitudinal population-based study of 9,944 participants, remission from chronic headache was observed in 58.2% and was associated with female sex, and no medication overuse compared to participants with persistent chronic headache.[26]

The impact of migraine increases with increasing monthly headache day frequency.[3,27–30] It has long been recognized that patients diagnosed with chronic migraine (CM) carry much higher levels of disability than those diagnosed with episodic migraine (EM); however, recent investigations have shown that patients with high-frequency episodic migraine, defined as 8–14 or 10–14 headache days per month, have levels of disability similar to CM, prompting a proposal to lower the threshold for CM diagnosis.[27,28,31,32]

The American Headache Society consensus statement (2021)[33] recommends that preventive treatment be offered to patients who experience 6 or more headache days per month regardless of the degree of associated disability. It further advises that preventive treatment (both pharmacologic and nonpharmacologic) be offered to/considered for patients with less frequent attacks that significantly interfere with daily life (associated disability) as well as for patients who cannot use, do not use, or use more than the recommended dosage of acute therapies. The goals of preventive therapy for patients with migraine are not only to reduce headache frequency and duration, but also to reduce attack severity; improve response to acute treatment/avoid escalation of use and reliance on poorly tolerated, ineffective, or unwanted acute treatments; reduce associated disability and costs; improve functioning; and to reduce headache-associated psychological distress, enable patients to self-manage migraine, and improve quality of life.[33]

The introduction of migraine-specific preventives with demonstrated early onset of preventive disease control has the potential to vastly improve the lives of patients with migraine, who in the past may have had to wait 2 to 6 months to recognize the benefits of available preventive therapies.[34–36]

The objective of this report is to summarize discussions and recommendations from a roundtable of experts convened to analyze available evidence related to early onset of preventive disease control, ascertain its clinical relevance, and provide guidance for healthcare professionals in crafting goals and treatment expectations for patients with migraine initiating preventive therapy.

Methods

A virtual roundtable meeting attended by migraine clinicians, researchers, and patient advocates was convened and hosted by H. Lundbeck A/S and Lundbeck Seattle BioPharmaceuticals, Inc. on October 8, 2020. The objective of the meeting was to discuss migraine preventive therapies, with a specific focus on the early onset of migraine prevention. Participants (the authors of this report) reviewed and discussed data summarizing patient and physician perceptions of migraine preventive disease control and evidence from the peer-reviewed, gray (i.e., from government, academic, business, and industry sources),[37] and consumer literature on the benefits of an early onset in migraine preventive disease control, with an emphasis on issues relevant to prevention in clinical practice (Table 1). Identified data were reviewed in order of scientific merit and integrity, as well as relevance. Recommendations were then developed by the authors, based on their knowledge of identified literature as well as clinical expertise. These recommendations are described in this report, highlighted in italics. All authors contributed to this meeting summary.

Results/discussion

Appropriately defining "early onset of prevention": Disease control

The authors recommend that migraine prevention should be broadly defined as "*the control of disease activity, including benefits beyond reductions in attacks/days per month frequency, such as reductions in acute medication use or in non-pain symptoms present during and between attacks as well as improvements in patient functionality, satisfaction, and quality of life. Early onset denotes demonstration of preventive benefits within one week of treatment initiation.*"

Table 1. Relevant questions raised during roundtable discussion for migraine preventive disease control in clinical practice.

- What impact would the early onset of prevention be expected to have on the patient's quality of life?
- Does a preventive therapy that offers a rapid reduction in migraine severity have clinical benefits?
- How would early prevention impact a patient's ability to work/return to work?
- What benefits on overall patient outcomes would you expect to see with an early onset of prevention?
- How would the early onset of prevention be expected to impact acute medication use?
- Can an early preventive effect reverse disease chronification?
- How is the effect of early prevention different from the overall reduction in migraine frequency?
- What clinical outcomes (apart from monthly migraine days) could be utilized to evaluate the benefits of early prevention?
- How important is an early preventive effect in the goal of preventing disease chronification?
- How meaningful is it that the migraine preventive agent has an impact on the current attack?
- Would an impact on medication overuse headache be an indicator of early prevention?
- How would an early onset of prevention impact personal and overall healthcare costs?
- How would a patient's personal relationships be affected by an early onset of prevention?
- Would an early onset of preventive effect be expected to have an impact on non-migraine comorbidities?

We believe that the term "prevention" may be potentially misleading, since many patients would naturally, if unconsciously, infer that the goal of preventive intervention is to eliminate the chance of having a migraine. For this reason, we recommend that prevention be more broadly defined as "disease control"; that is, its goal is not necessarily to eliminate all migraine attacks (an unrealistic expectation for a chronic disease), but rather to reduce overall migraine frequency, attack duration and severity, migraine-related disability, and disease-related psychological distress. When disease control is achieved, patients often experience enhanced response to acute treatment and improved functioning in key domains and in overall health-related quality of life. These goals are consistent with those enumerated by the American Headache Society in their 2021 consensus statement.[33]

The onset of preventive benefits with traditional oral migraine preventive therapies is typically expressed in months, if not longer. Based on trial design and the resulting clinical data for these agents, current guidelines and the American Headache Society consensus statement recommend that patients who are prescribed oral preventive therapies should continue treatment for at least 8 weeks "after achieving the target or usual effective dose."[33] Further, the guidelines recommend that patients who are experiencing a partial response at that 8-week timepoint be advised that the medication(s) may take 6 to 12 months to achieve a full preventive effect.[33] In contrast, evidence from studies of the anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs; erenumab, fremanezumab, galcanezumab, and eptinezumab) and the chemodenervation agent onabotulinumtoxinA indicate that patients receiving these newer injectable agents may experience clinically relevant preventive benefits much sooner—as early as Day 1 and consistently by Day 7 post-administration.[38–60] As such, based on the availability of clinical evidence, we propose that early onset be defined as the demonstration of preventive benefits within 1 week of treatment initiation. In the following discussion, we describe outcomes supportive of this definition.

Impact on migraine and headache attack/day per month frequency

We acknowledge and agree that "*CGRP-targeted mAb for migraine prevention significantly reduces both migraine and headache frequency early in the course of treatment (as early as Day 1 with eptinezumab, Days 1–2 with fremanezumab and galcanezumab, and Week 1 with erenumab) and provides sustained preventive effects for up to 12 weeks post-administration. OnabotulinumtoxinA reduces headache frequency as early as Week 1 after the first dose.*"

A common primary study endpoint is change in migraine days over a predefined period (e.g., 4 weeks, 12 weeks, etc.) that is traditionally based on regulatory guidance and requirements.[61] We believe, however, that a reduction in total headache days, severity, or duration (including migraine and other headache) could be a more clinically relevant marker of early onset of preventive disease control for patients than migraine days, because patients more often focus on "days without a headache."

CGRP-targeted mAbs for migraine preventive disease control significantly reduce both migraine and headache frequency early in the course of treatment—as early as Day 1 with eptinezumab, which also demonstrated efficacy after 2 hours when administered during a migraine attack, Day 1–2 with fremanezumab and galcanezumab, and Week 1 with erenumab—and provide sustained preventive disease control for up to 12 weeks post-administration.[42,44–60,62,63] For example, in the PROMISE studies, eptinezumab 100 mg and 300 mg reduced the likelihood of a migraine attack in the 24 hours post-infusion 50% versus baseline and significantly more than placebo (EM, 14.8% and 13.9% vs 22.5%; CM, 28.6% and 27.8% vs 42.3%, respectively).[42,55] In the HALO studies, nearly 80% of patients with EM and 70% of patients with CM who received fremanezumab reported no headache of at least moderate severity by the next day following the first injection, versus 67% and 61% of the placebo groups, respectively.[45,59] Similarly, reductions in migraine headache days were greater with galcanezumab than with placebo each day of the first week following injection in the EVOLVE studies.[48]

OnabotulinumtoxinA has also demonstrated an early onset of preventive efficacy, significantly reducing headache frequency as early as Week 1 after first dose (–0.9 days/week [onabotulinumtoxinA] vs –0.7 days/week [placebo] compared with the week before treatment; $p = 0.046$ vs placebo).[41]

Reduced acute medication use

We agree that "*a rapid reduction in migraine and headache frequency can reduce reliance upon acute medications (including over-the-counter and prescription) and result in fewer medication trials in the quest to find one that works, less medication overuse, less frequent development of medication overuse headache, and fewer side effects and drug interactions.*"

The side effects of acute medications—wooziness/dizziness, fatigue, chest and throat pressure, chest pain, impaired concentration, and upset stomach, among others[64,65]—have likely negatively impacted the quality of life of thousands of patients over the past 50 years, and can be especially detrimental in patients with comorbid conditions. The potential for gastrointestinal side effects, including gastric ulceration, may preclude acute non-steroidal anti-inflammatory drug (NSAID) use for acute migraine in some patients, particularly those with peptic ulcer, bowel diseases, or hemorrhagic stroke.[64] Caffeine-containing combinations may permit reduced NSAID doses but can also lead to gastrointestinal disturbances as well as anxiety and motor unrest.[64] Triptans have been associated with many central nervous system, gastrointestinal, and skin-related side effects, as well as chest tightness and pain.[64] Among patients with EM, acute opioid or barbiturate use increases the risk for transformation to CM.[66] Opioids may also increase the risk for comorbidities. In the population-based American Migraine Prevalence and Prevention (AMPP) study, depression, anxiety, and cardiovascular disease risk factors were higher among opioid users than among nonusers, as was headache-related healthcare resource utilization.[67] And, as is always the case with opioids, the potential for abuse and dependence is an obvious concern. While migraine treatment utilizing acute medications may lead to the side effects described above, it is important to emphasize that not treating migraine may result in worsening in disease symptoms and overall functioning.[3–5,17–22]

Acute medication overuse is common and may contribute to transformation from EM to CM. In the Migraine in America Symptoms and Treatment (MAST) study, a longitudinal cross-sectional survey of adults with migraine in the United States, 2107/13,649 participants (15.4%) reported acute medication use that met the definition for overuse; that is, they were using a triptan, opioid, barbiturate, isometheptene, ergot alkaloid, or combination analgesic ≥10 days/month or an NSAID or simple analgesic ≥15 days/month.[15] A similar proportion of patients in the Chronic Migraine Epidemiology and Outcomes (CaMEO) study met the criteria for acute medication overuse (2975/16,789 [17.7%]).[68] Although the factors contributing to transformation are likely complex, reports indicate that patients with MOH are up to 19.4 times more likely than non-overusers to experience migraine transformation.[19,22]

To this end, data from erenumab, eptinezumab, and fremanezumab clinical studies have demonstrated reductions in acute medication use that were consistent with rapid reductions in migraine frequency. In the ARISE study,[49] which was conducted in patients with EM, erenumab significantly reduced acute migraine–specific medication treatment days as early as Month 1 ($p < 0.05$) with further reductions at Week 12 (–1.2 days vs –0.6 days from baseline in the erenumab and placebo groups, respectively [$p = 0.002$]); Week 12 reductions were of even greater magnitude when only patients with baseline acute migraine–specific medication use were considered (–2.1 days vs –1.2 days, respectively [$p = 0.002$]). In a CM study, patients who received erenumab experienced greater reductions in acute migraine–specific medication treatment days than did patients who received placebo, whether or not they had acute medication overuse at baseline. This effect was present at Month 1, with differences achieving statistical significance by Month 3 (without overuse, –0.9 [$p < 0.05$] to –2.4 [$p < 0.001$] vs placebo; with overuse, –2.8 [$p < 0.001$] to –3.3 [$p < 0.001$] vs placebo).[69]

Similarly, eptinezumab reduced acute medication use (ergots, triptans, and analgesics) more than placebo as early as Month 1 after treatment and across 6 months of treatment in patients with EM in the PROMISE-1 study, with greater reductions by Month 6 observed in patients with higher (≥10 days/month) baseline use (eptinezumab 100 mg, –4.0 days; eptinezumab 300 mg, –7.4 days; placebo, –4.1 days).[70] For those with CM and ≥10 days of acute headache medication use during PROMISE-2 at baseline, reductions at Month 1 were –8.7 (100 mg) and –9.4 (300 mg) days with eptinezumab versus –5.1 days with placebo, which was sustained out to Month 6 (eptinezumab 100 mg, –8.9 days; eptinezumab 300 mg, –11.1 days; placebo, –7.9 days).[71]

Additionally, a recent post hoc analysis of patients in PROMISE-2 who were prospectively diagnosed with MOH found that eptinezumab reduced total days/month of acute medication use from 20.6 (100 mg) and 20.7 (300 mg) at baseline to 10.8 (100 mg) and 12.2 (300 mg) over the first dosing interval (Weeks 1–12) versus from 19.8 to 14.8 with placebo.[72] These reductions were sustained or further improved with eptinezumab over the second dosing interval. In fact, 50.5% (100 mg) and 49.5% (300 mg) of eptinezumab-treated patients, versus 27.1% of those receiving placebo, consistently used acute headache medication at frequencies that were below the diagnostic thresholds for MOH for all 6 months of treatment.[73]

Further, when preventive treatment with eptinezumab was initiated during a migraine attack in patients with

migraine (in the RELIEF study), the likelihood of acute medication use for that ongoing attack was reduced within the first 24 hours after the start of infusion.[63]

Among patients who overused acute medications at baseline in the fremanezumab HALO studies (13% of patients with EM and 54% of patients with CM), significant proportions reverted to no acute medication overuse at Month 6 (EM, 61% to 85%; CM, 59% to 65%); this benefit was maintained through Month 12 (EM 77% to 86%; CM 66% to 68%).[74,75] In both HALO studies, reductions in migraine frequency were evident by Week 4,[51,74] as was reversion from medication overuse to no medication overuse in the CM study.[76]

Increased functionality/decreased disability and improved quality of life

The authors agree that "*available data indicate that the CGRP inhibitors and onabotulinumtoxinA increase function, reduce disability, and improve quality of life.*"

For patients with migraine, we believe that waiting 4 to 12 weeks for medications to work, let alone longer, can have serious negative implications. For many patients, the inability to work for extended periods can adversely impact job, school, and financial opportunities and success and place additional strain on relationships, all of which can lead to loss of self-efficacy and hope. Thus, medications that quickly address the effects of migraine on the ability to function have the potential to significantly improve the lives of these patients. Patients may be able to confidently return to work or school sooner and be more productive while there. They may be better able to cope with attacks, care for their children, make healthy lifestyle choices (e.g., increase level of physical activity), and plan and consider opportunities at work or in social settings. It seems reasonable to expect that increases in days free from headaches could translate into improvements in one or more of these parameters. In the non-interventional National Health and Wellness Survey,[77] each incremental increase in headache-free days was associated with a 5% reduction in work days missed and days of household activities missed. Further, if not managed appropriately, i.e., quickly, migraine may have long-term clinical and pathophysiological implications for patients, such as worsening of headache/migraine day frequency, increased acute medication use, and structural brain changes.[78–84]

Tools to directly assess impact of migraine and treatment on functionality/disability and quality of life are sometimes included in clinical trials of preventive migraine interventions[85]; many are also useful in clinical practice.[86] A variety of both general health and migraine-specific patient-reported outcome measures (PROMs) have been utilized for these purposes,[86,87] such as the 36-item Short-Form Health Survey (SF-36) and Migraine-Treatment Optimization Questionnaire. These PROMs vary in parameters covered, response categories, and recall time frames, making selection and interpretation challenging based on context.[87] We believe that standardized use of PROMs in future clinical trials will be invaluable in evaluating the benefits of an early onset of prevention in patients with migraine.

Available data indicate that the CGRP inhibitors increase function, reduce disability, and improve quality of life (reviewed in Gottschalk et al.[88]). These achievements would be expected to provide patients with even more benefits—those that are not easily captured with available measures. For example, increased functionality would be expected to provide patients with more time to spend on healthy lifestyle activities (vs having to rest), which could further improve their disease control. They could also potentially aid relationships by giving patients greater ability to make and fulfill familial and social commitments and by reducing their reliance upon others for support. Additional studies are needed to examine these potential effects as well as to determine how quickly these benefits manifest and whether or not they extend to the periods between attacks.

The PREEMPT trials—randomized, double-blind, placebo-controlled studies of onabotulinumtoxinA for the treatment of CM—indicated functional improvement as well. In one report, 44.1% of patients who received onabotulinumtoxinA versus 25.4% of patients who received placebo had a ≥5-point reduction from baseline in the 6-item Headache Impact Test (HIT-6[89,90]) total score at Week 24 (difference vs placebo, $p < 0.001$).[43] Similarly, all role function domains of the Migraine-Specific Quality-of-life Instrument (MSQ[91,92]) were improved more with onabotulinumtoxinA than with placebo at Week 24 (all $p < 0.001$).[43] For both measures, improvements continued through Week 56, but differences between the groups that received onabotulinumtoxinA and placebo in the double-blind phase (both followed by open-label onabotulinumtoxinA) were no longer statistically significant.[43]

Reduced anxiety and depression (comorbidities)

The authors agree that "*data from fremanezumab and onabotulinumtoxinA studies suggest that these preventive agents may reduce the symptoms of anxiety and depression in patients with migraine; however, additional studies are needed to clarify the impact of the early onset of prevention on these comorbidities.*"

Because anxiety and depression are likely related to headache pain frequency and intensity,[93] early control of migraine activity would be expected to reduce the severity of these comorbidities. Comorbidities of migraine increase as headache day frequency increases.[27,93] Few studies have, however, assessed this potential benefit. In the HALO-CM trial,[76] fremanezumab improved MSQ–Emotional Function domain scores 19.7 to 22.4 points from baseline to Month 12 (vs 16.7 to 17.3 points in the placebo groups) and reduced 9-item Patient Health Questionnaire

(PHQ-9) scores 2.3 to 2.8 points from baseline to Month 12 (vs 1.6 to 2.4 points in the placebo groups). Patients also self-reported improvements in anxiety in a long-term fremanezumab extension study.[94] In a pilot study conducted in patients with comorbid depression, onabotulinumtoxinA significantly improved symptoms of depression and anxiety as early as Week 12.[95] In the larger open-label COMPEL trial,[96] onabotulinumtoxinA treatment was associated with improvements in symptoms of depression (PHQ-9; 3.7- to 6.3-point reductions) and anxiety (Generalized Anxiety Disorder [GAD-7]; 5.2- to 8.0-point reductions) over a 2-year period.[96] The speed of onset of these effects likely varies from patient to patient and is an area requiring further study.

Increased patient satisfaction and persistence with therapy

The authors highlight that the "*early control of migraine activity provides patients with more timely validation that the preventive treatment is working, improving persistence with therapy.*"

Patients who fail to experience benefits of preventive therapies early and patients who experience side effects (sometimes before benefits) are likely to be dissatisfied with the treatment and may fail to give the therapy an adequate trial. This was demonstrated in the Second International Burden of Migraine Study (IBMS-II), in which 24.0% of patients with EM and 40.8% of patients with CM discontinued traditional preventive therapy (i.e., antidepressants, anti-epileptics, beta blockers, and calcium channel blockers), 36.8% to 48.2% (EM and CM, respectively) because they believed the medications were not working, and 34.2% to 53.2% because of side effects.[97] A 2017 retrospective analysis of inpatient, outpatient, and pharmacy claims for patients with CM indicated that many patients make the decision to discontinue or switch oral preventives early—with 50% doing so within 60 days of initiation.[98] There is a real benefit in feeling rapid improvement, as it provides the patients with more timely validation that the preventive is working. This may help explain why dropouts in the primary study periods of CGRP-targeted therapy trials were low (≤18%).[42,49–51,53,55,57,75,98–101]

Reduced healthcare utilization/direct costs

The authors agree that "*the effects on healthcare resource utilization and direct costs have yet to be examined in clinical studies of the newer preventive therapies for patients with migraine.*"

Patients who experience early control of migraine are likely to use less acute medication than are patients who must wait for their preventive treatment to start working. This could also mean fewer emergency department and urgent care visits, acute intravenous infusions, neuroimaging studies, and hospitalizations during this time period and overall. Because patients often seek medical help not only for headaches, but also for other migraine-related features, there is a need for studies to explore relationships between onset of effect with respect to the full range of disease variables (e.g., attack frequency, disability, and associated symptoms and comorbidities) and healthcare resource utilization and costs.

Effects on healthcare resource utilization and direct costs have yet to be examined in clinical studies of newer preventive therapies; however, the costs of these preventive medications, particularly for patients with chronic migraine, can be high.[102] It is interesting to note that in an analysis of data from the non-interventional US National Health and Wellness Survey, there was no significant relationship between headache-free days and direct costs observed.[77] This finding underscores the need to examine the impact of the full range of treatment effects on these outcomes in future preventive medication trials.

Reduced non-medical costs

The authors similarly agree that "*the effects of an early onset of preventive benefits on non-medical costs have yet to be examined in clinical studies of patients with migraine.*"

Likewise, effects on non-medical costs have yet to be examined in clinical studies of newer preventive therapies. Data from the US National Health and Wellness Survey indicated that greater freedom from headache (headache-free days) was associated with lower non-medical costs. Specifically, each headache-free day was associated with a 4% reduction in non-medical costs related to reduced work productivity; annualized non-medical costs were $16,975, $12,564, and $6,919 when stratified by 0–10, 11–20, and 21–26 headache-free days per month, respectively.[77]

Reduced risk of transition/chronification

The authors highlight that "*the ability to rapidly control migraine activity with CGRP-targeted agents would be expected to reduce migraine transformation; however, this potential benefit has not yet been evaluated in clinical studies of patients with migraine.*"

There are several identified risk factors associated with increased rates of progression from EM to CM.[19,22–24,103] Sociodemographic characteristics (e.g., female sex and low family socioeconomic status), lifestyle factors (e.g., caffeine consumption, major/stressful life events), comorbidities (e.g., obesity, depression, asthma, noncephalic pain, head and neck injury), headache day frequency, non-optimized acute treatment, and overuse/increasing use of acute migraine medications are all associated with an increased risk of transformation. Although the effects of modification of risk factors on the new onset of CM have

not been established, we believe that it remains good clinical practice to do so. Thus, education and lifestyle modifications remain an important aspect of migraine management, as do interventions to treat comorbidities, minimize migraine frequency and duration, and optimize acute medication use.

Whereas the ability to rapidly control migraine activity with CGRP-targeted agents would be expected to reduce migraine transformation, this potential benefit has not yet been evaluated in clinical studies. It is notable that persistent reversion from CM to EM was reported in post hoc analysis of data from a long-term erenumab clinical study in which patients receiving erenumab were more than twice as likely as patients receiving placebo to revert to EM during the initial 12-week double-blind phase of the study, and nearly 96.9% of those experiencing early reversion maintained this benefit throughout the subsequent 52-week open-label study period.[104]

Additional benefits

We anticipate that there may be additional clinical benefits of an early onset of migraine preventive disease control, including reductions in the intensity of average headache pain, interictal allodynia and neck pain and cognitive impairment, migraine symptom frequency and duration (during and between attacks), and prodromal symptoms, as well as prolongation of the duration of interictal periods. Outcomes assessing these potential benefits should be included in future migraine prevention studies.

Discussing the benefits of an early onset of prevention with patients

We strongly recommend that *"clinicians take time to ensure that patients with migraine have a clear understanding of realistic rates of improvements to expect with preventive therapy and when they may expect to see the benefits from treatment."*

We believe that clinicians should take time to ensure that migraine patients have a realistic understanding of the rates and amount of benefits they may experience with preventive therapy and the estimated timing. We recommend focusing discussion with patients around "disease control"; that is, not necessarily *curing* or eliminating *all* migraine attacks (an unrealistic expectation for a chronic disease), rather describing the benefits of an early onset of migraine prevention as described above. Clinicians should also help patients establish realistic expectations for treatment efficacy and disease control. For example, with traditional preventives, many patients experience some benefits early and then continue to improve over the first 3 to 6 months of treatment. Thus, they should be advised that this might be the case. Education about time to benefit with respect to other migraine symptoms—particularly the patient's most bothersome symptom—or with a comorbidity,

such as anxiety, is also important. Satisfaction and compliance with therapy may be enhanced when a patient recognizes that the time to improvement with respect to these benefits may differ from time to improvement in headache.

Conclusion

The goals of migraine management have long focused on the control of attacks and associated functional impairment using both acute abortive and preventive therapies. Despite the potential burden that migraine has on the individual patient, limited guidance has been provided regarding the importance of the clinical benefits that patients are provided with the earliest onset of preventive disease control. Based on the available evidence with the anti-CGRP mAbs (erenumab, fremanezumab, galcanezumab, and eptinezumab) and chemodenervation agents (onabotulinumtoxinA), we suggest that a broader approach regarding the goal of early control of migraine activity be undertaken in managing patients with migraine—one that encompasses effects on clinically important outcomes, such as acute medication use, patient function, satisfaction, quality of life, and comorbidity.

Attainment of disease control early in the process can reduce both the impact on daily life and potential for transformation that arises from repeated migraine attacks. We anticipate that these benefits will translate into improved adherence and persistence with therapy as well as reduced acute medication use, healthcare resource utilization, and associated costs. Additional studies are needed to fully elucidate the extent of these effects.

Author contributions

CG, AB, AB, BT, MJM, JMP, PKD, NL, and DCB contributed to the conception and design of the manuscript. All authors reviewed and provided critical revision of all manuscript drafts for important intellectual content, as well as read and approved the final manuscript for submission.

Authors' Note

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Lundbeck selected the chairperson, Dr. Christopher Gottschalk, who steered the content development, moderated the roundtable, and served as lead author for this manuscript.

Declaration of conflicting interests

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