Therapeutics and Clinical Risk Management

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REVIEW

Eptinezumab for the Prevention of Migraine: Clinical Utility, Patient Preferences and Selection – A Narrative Review

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Abstract: The new Calcitonin Gene-Related Peptide (CGRP)-targeted therapies have proven high efficacy and tolerability in episodic and chronic migraine. Eptinezumab is a humanized monoclonal antibody that selectively binds CGRP with high affinity. Eptinezumab was approved by the Food and Drug Administration on February 21st, 2020, for the preventive treatment of migraine in adults. It is administered intravenously over 30 minutes with a standard dose of 100 mg and has a T-max of 30 minutes-1 hour and a half-life of 27 days. These pharmacological properties allow for a very rapid onset of effect and a quarterly administration. It is the first time that a preventive treatment for migraine can be offered as an intravenous administration. As the range of therapeutic possibilities in migraine is expanding, the treatment process must include common decision-making, where physicians should explain in detail to patients the different characteristics of treatment options beyond efficacy and side effects. Patients can now express a preference on a range of opportunities: pharmacological versus non-pharmacological approaches, route of administration, frequency of administration, efficacy, rapidity, side effects, costs, the possibility of titration or dosing, and durability of effectiveness at suspension. Also, patient preferences can be influenced by age, country, migraine severity, and earlier experience with CGRP-targeted therapies. Besides, adherence may be influenced by several factors, including route and the schedule of administration. This narrative review describes a new perspective from the patient's point of view. Clinicians should ally with patients to select treatments that meet each patient's needs and thus apply a tailored approach, addressing not only headaches. In this way, physicians would care for the patients globally and stand out their preferences on different aspects of treatment. Besides, healthcare professionals shall be aware that patients' beliefs about therapies are subject to change with increasing experience with new therapeutic approaches.

Keywords: eptinezumab, CGRP, preference, adherence

Introduction

Migraine occurs as recurrent headache attacks of pulsating pain of moderate/severe intensity, which aggravates with movement and is associated with bothersome accompanying symptoms such as nausea and photo- and phonophobia.[1] Together with tension-type headache and medication-overuse headache (MOH), it is the most common type of headache worldwide.[2]

The high recurrence of migraine attacks can result in chronic migraine (CM),[3] a condition the patients can experience together in the context of other overlapping chronic pain disorders and somatic conditions.[4,5] In some patients, chronic migraine can be complicated by MOH, defined as a headache occurring for ≥15 days per month in patients with pre-existing primary headache and regular excessive use for >3 months of one or more drugs used for the acute or symptomatic treatment of headache.[3] The disability caused by migraine and MOH is also associated with a high risk of anxiety (19% and 39%, respectively), depression (7% and 17%), or both (5% and 14%), conditions that significantly impact migraine patients, especially during their working years.[6]

Received: 5 September 2023
Accepted: 18 November 2023
Published: 23 November 2023

All of the above easily explains why, despite the paroxysmal nature without permanent neurological sequelae and no impact on mortality, the Global Burden of Diseases (GBD) placed migraine as the most disabling condition in the world in individuals of both genders in the age group between 14 and 49 years who have the need for greater productivity in work, study, and social activities.[7]

Therapeutic Strategies

According to international guidelines, individuals with ≥4 headache days per month should be treated with migraine preventive treatment (MPT).[8] Criteria for identifying candidate patients for MPT are based on multiple factors: the frequency of the attacks, the degree of disability, the interference of headache with patients' daily routines, and the presence or the risk of drug overuse. The aim of starting (or switching) a preventive therapy for migraine is to reduce, as much as possible, the monthly headache frequency and the analgesics intake, reducing disability and improving the patient's quality of life over time.

Despite many MPT being available, optimizing the treatment for different types of patients is still challenging. When prescribing an MPT, several aspects should be taken into account: age, vital signs, comorbidities, patient's lifestyle and work habits, ease of use, and patient preference.[9]

Besides, migraine should be considered an evolving condition, with a rate of progression from episodic migraine (EM) to CM of 2.5%/year.[10] Thus, an MPT should be offered early in the disease course.[11]

For many years, prophylactic therapy for migraine relied on non-specific drugs for migraine belonging to pharmacological classes such as antiepileptics (valproic acid and topiramate), beta-blockers (propranolol and metoprolol), calcium antagonists (eg, flunarizine), antidepressants (eg, amitriptyline), and in the last decade botulinum toxin indicated only for chronic migraine.[12] Although these drugs can be very effective, their mechanisms of action remain not completely understood. They were not designed ad hoc to act specifically on the pain pathways and are often discontinued because of emerging side effects.[13,14]

The Calcitonin Gene-Related Peptide (CGRP) pathway is the most well known among the pathophysiological mechanisms responsible for pain. This neuropeptide is abundant in trigeminal ganglion neurons and is released from the peripheral nerve and central nerve terminals as well as being secreted within the trigeminal ganglion. Peripherally, it promotes the activation of the cascade of nitric oxide and, thus, neuronal inflammation and vasodilation with trigeminal terminal sensitization. Within the trigeminal ganglion, CGRP release activates with adjacent neurons and satellite glial cells to amplify peripheral sensitization and can induce central sensitization of the second-order neurons.[15,16]

The introduction of therapies against the CGRP pathway in the pharmacological landscape of migraine prophylaxis has finally renovated the therapeutic possibilities, significantly improving the quality of life of patients with few side effects.[17] These are molecules that can bind to the ligand or its receptor. The CGRPr is constituted of three subunits: the calcitonin receptor-like receptor (CALCRL), the receptor activity-modifying protein 1 (RAMP1), and the receptor component protein (RCP).[18] The CALCRL is a G protein-coupled receptor for CGRP and adrenomedullin. However, CGRP does not bind it effectively unless CALCRL forms a heterodimer with RAMP1. RAMPs are single transmembrane-spanning proteins that modify the functions of G protein-coupled receptors, including pharmacological properties and cell trafficking. The CGRP binds the CGRPr ligand cleft in the interface between CALCRL and RAMP1. Once CGRPr is activated, RCP facilitates the coupling of the Gαs subunit of the G-protein, which in turn initiates intracellular adenylyl cyclase and cAMP-dependent signaling, and, in the cerebral vessel smooth muscle, ultimately produces an increase in c-AMP resulting in vasorelaxation.[16]

The new class of drugs acting on the CGRP pathway was proved highly efficacious by randomized controlled trials (RCTs).[19] The first monoclonal antibodies directed against the CGRP pathway available for clinical use were formulated as subcutaneous injections to be administered once a month (erenumab, galcanezumab, fremanezumab).[9,20] Real-life studies have shown that these safe, well-tolerated drugs are even more effective than proved by RCTs.[21–23] Eptinezumab is the only intravenous monoclonal antibody approved by the Food and Drug Administration (2020).[24]

This narrative review addresses the role of eptinezumab and other preventive therapies from a new perspective: the patient's point of view. With this aim, we have conducted a PubMed search for "eptinezumab [and] RCT", "migraine [and] patient [and] preference", and "migraine [and[adherence".

Eptinezumab

Eptinezumab (ALD403) is a humanized monoclonal antibody that selectively binds Calcitonin Gene-Related Peptide (CGRP) with high affinity resulting in effective and sustained inactivation of the CGRP[25] It is a humanized IgG1 monoclonal antibody produced by recombinant DNA techniques within yeast cells of Pichia pastoris.[24] Eptinezumab was approved by the Food and Drug Administration (FDA) on February 21st, 2020, for the preventive treatment of migraine in adults, based on the results of RCTs (Table 1). The drug is administered intravenously over 30 minutes every three months with a standard dose of 100 mg, although a 300 mg dose may also be considered for patients and has a half-life of 27 days.[24] Eptinezumab's 30-minute infusion presents bioavailability of 100% by its end, with a T-max of 30 minutes-1 hour.[26] These pharmacokinetic properties are not influenced by factors such as age, sex, race, or body weight.[25] Eptinezumab is indicated for the preventive treatment of migraine in adults, with pivotal Phase 3 studies establishing efficacy and safety in patients with Episodic Migraine (EM) (PROMISE-1)[27] and Chronic Migraine (CM) (PROMISE-2).[28]

Table 1 A Summary of Clinical Evidence Supporting the Efficacy and Safety of Eptinezumab in Migraine Prevention

Study Name and Registration	Citation	Population	Age	Study Group	Intervention	Results	Conclusions
PROMISE-1 NCT02559895	Ashina et al, 2020[27]	N=888	18–75 ys.	EM	RCT eptinezumab 30 mg, 100 mg, 300 mg, or placebo for up to four doses administered every Q12W	Reduction in mean MMDs across all eptinezumab treatment doses. Adverse events evenly dispersed across the groups.	Efficacy in reducing MMDs, good tolerability and safety profile
PROMISE-2 NCT02974153	Lipton et al, 2020[28]	N=1072	18–65 ys	CM	RCT Eptinezumab 100 mg, 300 mg, or placebo administered on day 0 and week 12	Reduction in mean MMDs over treatment period. Reduction to severe headache-related life impact.	Efficacy in reducing MMDs, good tolerability and safety profile
PREVAIL NCT02985398	Kudrow et al, 2021[29]	N=128	18–65 ys	CM	OPEN LABEL Eptinezumab 300 mg Q12W for up to 8 doses.	Improvements in PROs were observed at first assessment (week 4) and generally sustained through week 104	Early and sustained improvement in migraine-related burden and health-related quality of life over 2 years. Good safety profile, limited long-term immunogenicity
DELIVER NCT04418765	Ashina et al, 2022[30]	N=891	18–75 ys	EM/CM with at least 4 MMDs and 2 to 4 previous preventive treatment failures	RCT Eptinezumab 100 mg, 300 mg, or placebo	Reduction in mean MMDs vs placebo. Adverse events evenly dispersed across the groups	Significant preventive effects with acceptable safety and tolerability,

Abbreviations: EM, episodic migraine; CM, chronic migraine; RCT, randomized clinical trial.

The Prevention Of Migraine via Intravenous Eptinezumab Safety and Efficacy-1 (PROMISE-1) study was a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Adults aged 18–75 years with EM with a history of migraine for at least 12 months, with 4–14 headache days per month, in the 3 months prior to screening were enrolled. Patients were randomized to receive Eptinezumab 30 mg, 100 mg, 300 mg, or placebo intravenous (IV) every 12 weeks (Q12W) for up to 4 doses. The primary endpoint was the change in Monthly Migraine Days (MMDs) from baseline over weeks 1–12. A total of 888 participants in 84 study sites received treatment.

The mean MMDs during the 28-day screening period were around 8.6 across treatment groups. Treatment with Eptinezumab 100 mg and 300 mg significantly reduced MMDs across weeks 1–12 compared with placebo (30 mg, −4.0 MMDs; 100 mg, −3.9 MMDs [p = 0.0182]; 300 mg, −4.3 MMDs [p = 0.0001] vs placebo, −3.2 MMDs). Hence, the study met the primary endpoint.

A migraine preventive effect of Eptinezumab was already seen on the first day after dosing, when 17.3% of patients in the Eptinezumab 30 mg group, 14.8% of patients in the Eptinezumab 100 mg group, and 13.9% of patients in the Eptinezumab 300 mg group had migraine compared to 22.5% in the placebo group (p = 0.1539, p = 0.0312, and p = 0.0159 vs placebo).

Results in both primary and secondary endpoints for the 30mg group were not statistically significant from those of the placebo group. Subsequent exposure-response analysis has shown 100mg as the lowest effective dose, with a similar efficacy between 100mg-300mg doses due to a plateauing effect.[25] Adverse events experienced by patients in the Eptinezumab groups were similar to those in the placebo group. There were no serious adverse events attributed to the study drug. The authors concluded that Eptinezumab (100 mg or 300 mg) significantly reduced migraine frequency, was well tolerated, and had an acceptable safety profile when used for the preventive treatment of migraine in patients with EM.

The Prevention Of Migraine via Intravenous Safety and Efficacy-2 (PROMISE-2)[28] study is a phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Adults aged 18–65 years with migraine diagnosis at or before 50 years of age with a history of CM for ≥12 months before screening were eligible for participation. Patients with CM and Medication Overuse Headache (MOH) were also eligible for inclusion, except for the overuse of barbiturates or opioids. A total of 1.072 patients were randomized to receive Eptinezumab 100 mg, or 300 mg, or placebo administered IV on day 0 and week 12. The primary endpoint was a change from baseline in MMDs over weeks 1–12, and the efficacy of Eptinezumab was measured over a 24-week period following drug administration.

The baseline mean number of MMDs was ≈16.1 across treated groups. Treatment with Eptinezumab (both at 100 and 300 mg) showed statistically significant reductions in MMDs during weeks 1 to 12 (p < 0.0001), with MMDs decreasing from 16.1 to 8.5 days in the Eptinezumab 100mg group, from 16.1 to 7.9 days in the Eptinezumab 300 mg group, and from 16.2 to 10.5 days in the placebo group. The migraine preventive effect of Eptinezumab was statistically significant after the first day after dosing for both doses of Eptinezumab (100 and 300 mg) compared to placebo. During the screening period of 28 days, the average daily percentage of participants with migraine was 58%. On the day after dosing, the percentage of subjects with migraine was reduced to 28.6% in the Eptinezumab 100 mg group and 27.8% in the Eptinezumab 300 mg group vs 42.3% in the placebo group (both p < 0.0001 vs placebo).

Moreover, patients who received Eptinezumab reported fewer mean MMDs from the baseline (of 16 MMDs) during both the first dosing interval (weeks 0–12; −7.7 days for 100mg, −8.2 days for 300mg vs −5.6 days for placebo) and the second dosing interval (weeks 13–24; −8.2 days for 100mg, −8.8 days for 300mg vs −6.2 days for placebo). The 100mg and 300mg Eptinezumab groups showed statistically significant improvements in migraine frequency across 24 treatment weeks compared to the placebo group. Furthermore, treatment with Eptinezumab reduced acute medication days from baseline to week 12 (−3.3 days for 100 mg, −3.5 days for 300 mg). Improvement was also registered as measured by the Headache Intensity Test (HIT-6), which is a questionnaire generally used to evaluate disability related to headache episodes in migraineurs. Indeed, patients showed significant improvement in severe headache-related life impact, showing a reduction from a baseline of 89.6% to 43.5% by week 24 in the 100mg group, from a baseline of 88.6% to 39.7% in the 300mg group and from a baseline of 87.4% to 55.3% in the placebo group.

There were no significant differences in Treatment Emergent Adverse Events (TEAEs) in the Eptinezumab groups vs the placebo group, and the only serious TEAE reported was worsening visual aura in a patient with a history of migraine

with aura. In addition, the safety profile of the first dose was unchanged by the second dose at week 12. The authors concluded that eptinezumab 100 and 300 mg was associated with a significant reduction in MMDs from the day after iv administration through week 12 in patients with CM and that Eptinezumab was well tolerated and demonstrated an acceptable safety profile.

Evidence of efficacy and safety in patients with MOH emerges from a subgroup analysis of PROMISE-2.[31] A total of 431 CM patients (139, 147, and 145 participants in the Eptinezumab 100 mg, 300 mg, and placebo groups, respectively) had a diagnosis of MOH at screening (40.2% of the total PROMISE-2 population [n = 1.072]). In patients with CM and MOH, both Eptinezumab 100 mg and 300 mg were associated with clinically meaningful improvements in mean HIT-6 total scores starting at week 4 and throughout the 24-week study. Responder rates for individual HIT-6 items were greater in patients treated with eptinezumab than with placebo at all time points. At week 12, patients treated with eptinezumab indicated the Patient Global Impression of Change (PGIC) was "much" or "very much" improved almost twice than placebo (58.5% for the 100 mg group and 67.4% for 300 mg group vs 35.8% for placebo group). Participants treated with Eptinezumab showed numerically greater improvements in the Patient-Identified Most Bothersome Symptom (PI-MBS) and in the 36-item Short-Form Health Survey (SF-36 scores) compared with placebo. This subgroup analysis in subjects with CM/MOH at baseline suggests that Eptinezumab is associated with early, prolonged, and clinically meaningful improvements measured by patient-reported outcomes (PROs) questionnaires.

The PREVAIL study[29] evaluated the long-term safety, immunogenicity, and impact on PROs of repeated doses of Eptinezumab in subjects with CM. The authors concluded that Eptinezumab 300 mg demonstrated a favorable safety profile, limited long-term immunogenicity, early and sustained reductions in migraine-related burden, and improvements in health-related quality of life over 2 years in adults with CM.

While safety and tolerability of Eptinezumab were shown in phase 3 trials (PROMISE-1 and PROMISE −2), the benefits in the subpopulations of migraine patients with previous preventive treatment failures have been explored in the DELIVER trial.[30] DELIVER is a phase 3b, multicenter, multi-arm trial including a 24-week double-blind, placebo-controlled phase and a 48-week dose-blinded extension. Adults aged 18–75 years with EM or CM with at least 4 MMDs (as per International Headache Society guidelines) and documented evidence of failures of 2–4 previous preventive treatments within the past 10 years were recruited from 96 sites across Europe (n = 93) and the USA (n = 3). A total of 891 subjects were randomly assigned and received at least one dose of the study drug (safety population; eptinezumab 100 mg n = 299 [34%], eptinezumab 300 mg n = 294 [33%], placebo n = 298 [33%]). The primary efficacy endpoint was the change from baseline in mean MMDs in weeks 1–12. A total of 865 patients completed the placebo-controlled period. The change from baseline to weeks 1–12 in mean MMDs was −4.8 with eptinezumab 100 mg, −5.3 with eptinezumab 300 mg, and −2.1 with placebo. The difference in change in mean MMDs from baseline was significant with eptinezumab 100 mg (−2.7; $p < 0.0001$) and eptinezumab 300 mg (−3.2; $p < 0.0001$) when compared to placebo. Adverse events occurred in 42% of patients treated with eptinezumab 100 mg, in 41% of patients treated with eptinezumab 300 mg, and in 40% of patients treated with placebo. Serious adverse events were rare and occurred in 2% of patients in the eptinezumab 100 mg group, 2% in the eptinezumab 300 mg group, and 1% in the placebo group.

The authors concluded that eptinezumab provided significant migraine preventive effects in adults with migraine with 2 to 4 previous preventive treatment failures, acceptable safety, and tolerability. Hence, eptinezumab is an effective treatment option for this population.

Patient-reported outcomes and quality of life were also explored from DELIVER study population. Subjects with 2–4 prior preventive treatment failures who received eptinezumab reported greater improvements in well-being, quality of life, and most bothersome symptoms compared to placebo.[32] Eptinezumab effect on self-reported work productivity was also explored in DELIVER study population. Treatment with eptinezumab 100 mg and 300 mg IV every 12 weeks (Q12W) improved absenteeism and presenteeism and decreased work productivity loss and activity impairment compared to placebo, as demonstrated by the Work Productivity and Activity Impairment questionnaire specific to migraine (WPAI:M).[33]

Finally, a recent meta-analysis compared the efficacy and safety of eptinezumab 300 mg vs 100 mg in patients with migraine. Compared with eptinezumab 100 mg, eptinezumab 300 mg was associated with substantially reduced MMDs ($p < 0.00001$), increased 75% responder rate ($p = 0.008$), and 50% responder rate ($p = 0.02$) but no remarkable influence

on migraine 1 day after dosing (p = 0.52), adverse events (p = 0.62) or serious adverse events (p = 0.40). These findings suggest that eptinezumab 300 mg may provide additional benefit to eptinezumab 100 mg for treating migraine in selected patients.[34]

As per its pharmacological characteristics, eptinezumab iv administration takes only 30–60 minutes to reach the T-max[35] so that it can bind CGRP very rapidly and effectively. The RELIEF study assessed the efficacy and safety of eptinezumab when infused during an active migraine attack in subjects with a monthly migraine frequency rendering them eligible for preventive migraine treatment per current guidelines. RELIEF is a phase 3, multicenter, parallel-group, double-blind, randomized, placebo-controlled trial conducted at 47 sites in the USA and Georgia.[36] Patients aged 18–75 years with a history of migraine longer than 1 year and 4–15 days of headache per month in the 3 months before screening were treated during a moderate-to-severe migraine attack. Eptinezumab 100mg (n = 238) or placebo (n = 242) was iv administered within 1–6 hours of the onset of a qualifying moderate-to-severe migraine attack. The study results demonstrated that the infusion of eptinezumab was also able to significantly stop a migraine attack reaching the headache pain freedom ($p < 0.001$) and the absence of most bothersome symptoms ($p < 0.001$) faster than placebo.[37] At 2 hours after infusion, pain freedom was achieved by 23.5% with eptinezumab and 12.0% with placebo. Most participants considered the reduction in the likelihood of migraine offered by eptinezumab on day 1 postdosing to be at least as important as a clinically relevant reduction in migraine days the first-month postdosing[38]

Post-hoc analysis of eptinezumab phase 3 RCTs addressed other important issues.

Beyond headache pain, associated symptoms can be very disabling.[1] Among patients with CM in the PROMISE-2 study, those treated with eptinezumab reported more remarkable improvement in the severity of their most bothersome symptoms compared with placebo recipients, and this improvement correlated strongly with scores of patient global impression of change (PGIC) scale.[39]

The baseline patients' characteristics seem not to interfere with the efficacy (ie, ≥50% migraine responder rate) of eptinezumab in adults with episodic or chronic migraine except for obesity, which seems to reduce the therapeutic gain compared to placebo,[40] as also observed for other monoclonal antibodies targeting the CGRP pathway.[41,42]

Also, the vascular safety of eptinezumab is supported by the results of a post hoc analysis of four clinical trials for eptinezumab at different doses (up to 1000 mg, more than 3 times the highest approved dose) showing that no clinically relevant changes in vital signs or in concomitant cardiovascular medication usage were observed, and the incidence of cardiovascular treatment-emergent adverse events was comparable to placebo.[43] Moreover, the efficacy and safety profile in patients with migraine with aura were similar to those without aura.[44]

Clinical Utility, Patient Selection and Preferences

Patient Preferences

In a therapeutic era when several therapeutic approaches are finally available for migraine prevention, patients should play a key role in the selection of the most appropriate treatment strategies. Several aspects should be openly discussed by doctors together with patients when prescribing a new MPT, fully exploring the range of opportunities: pharmacological versus non-pharmacological approaches, route of administration, frequency of administration, efficacy, rapidity, side effects, costs, the possibility of titration or dosing, and durability of effectiveness at suspension (Figure 1).

Different studies addressed patients' preferences regarding MPT prescriptions. Patients can have varying preferences depending on the person's age, sex, cultural and socio-economic aspect, and underlying health conditions.

Most studies showed that efficacy is the priority,[45] more relevant than tolerability or the route of administration.[46] In a US and German study with an online discrete choice experiment survey, treatment effectiveness, and consistency were the main drivers of patient choice. Overall, patients placed the least importance on avoiding side effects and preferred an oral tablet over injectables, in line with earlier observations.[46] However, patient preferences were influenced by age, country, migraine severity, and previous experience with mAbs (Figure 2). Younger patients considered less important the route of administration (intravenous vs oral).[47] Interestingly, patients are favorably predisposed to MPT with multiple dosing.[48]

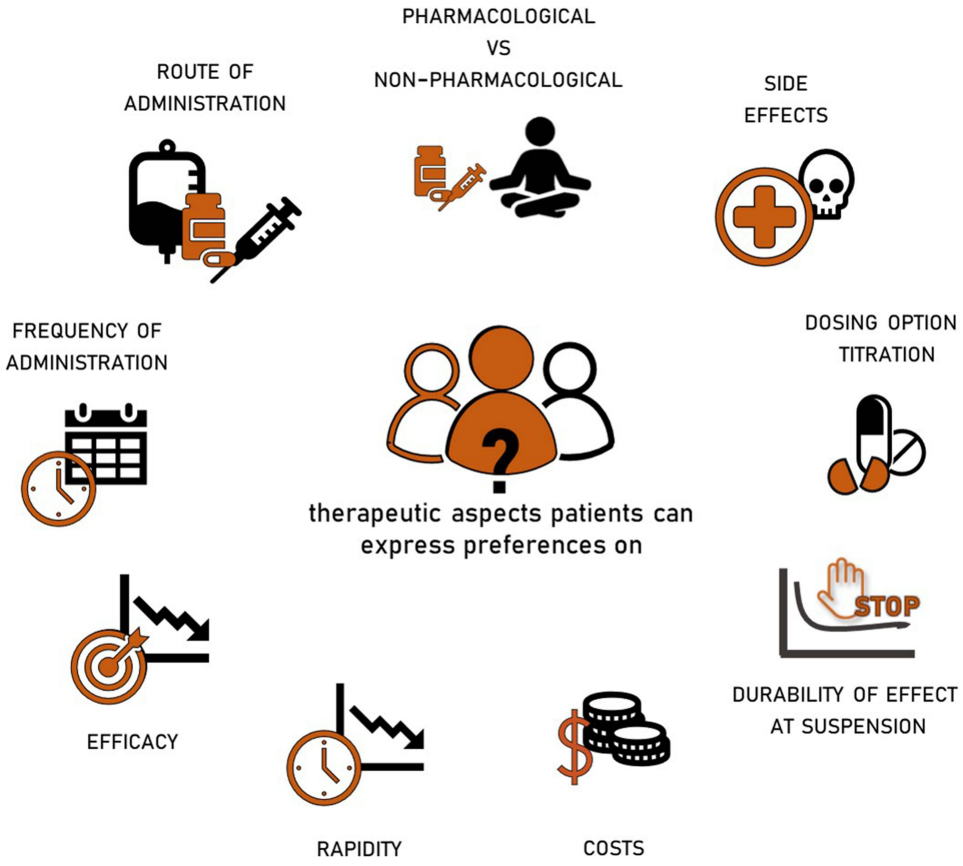

Figure 1 Therapy aspects that the patients can express preferences on.

In an electronic survey on 466 Italian migraine patients, the presence of adverse events, duration of the treatment effect, reduction of the intensity of the symptoms, speed of the effect, and cost borne by the patient were, in that order, the attributes considered most relevant by the respondents. Compared to men, women had significantly higher preferences for faster treatment efficacy and limited adverse events and reported higher preferences for costly treatments.[49] In another sample including 300 respondents,[50] among side effects, weight gain was considered the most important to avoid, more than memory and thinking impairment. Respondents preferred a once-monthly injection or daily pill to a twice-monthly injection. Patients were willing to pay some costs for a therapy lacking these side effects. Urtecho et al[51] also highlighted that beyond maintaining or improving function and avoiding side effects, other important aspects are the potential for addiction to medications, pain reoccurrence, and a positive effect on non-headache symptoms such as nausea, vomiting, and sensitivity to light or sounds.

As nowadays the range of therapeutic possibilities in migraine is expanding, the treatment process must include common decision-making, where physicians should explain in detail to patients the different characteristics of treatment options beyond efficacy and side effects. Clinicians should ally with patients to select treatments that meet each patient's needs. On this basis, it would be possible to apply a tailored approach, not addressing only headaches, where clinicians take care of the patients globally and stand out their preference on different aspects of treatment. Besides, healthcare professionals shall be aware that patients' beliefs about therapies are subject to change with increasing experience with new therapeutic approaches.

Preventive Treatment Adherence

Although MPT is strongly recommended since the early stage of migraine,[52] only half of males and a third of females who are candidates for prophylactic therapy receive it.[53,54] Patients with migraine were consistently described as unlikely

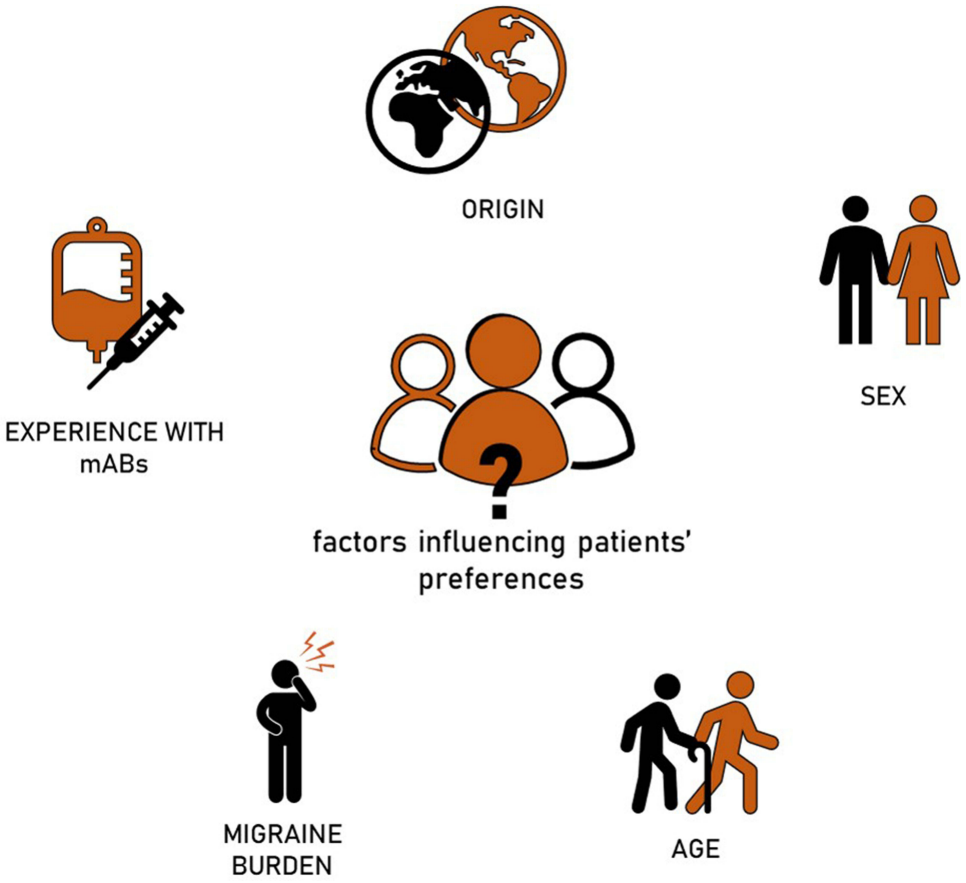

Figure 2 Factors influencing patients' preferences on therapies.

users of preventive medications, and among users, only a few seemed to take preventive medications continuously.[55] For all MPT classes, the most frequent cause of discontinuation was an adverse event or poor effect.[56,57]

According to a retrospective study on 8707 adult patients, 86% of patients discontinued these therapies.[13,58] The discontinuation occurs already after 30 days with a sharp decline curve and about half of the patients discontinued at 60 days. Similar trends have also been described after the 2nd and the 3rd cycle of preventive therapy.

A few strategies were proposed to improve adherence, including close follow-up and self-monitoring, patient education, and self-management skills training. In an online survey, coping ability and trust in the attending physician and treatment concept were significantly associated with adherent behavior in migraine patients.[57] Cognitive–behavioral therapy techniques can also be employed to improve medication adherence.[59]

Despite these efforts, adherence to oral MPT seems poor, even in newly diagnosed patients. In a study conducted between January 1, 2016, and December 31, 2018, among 12,894 migraine subjects, only 18.9% of patients were prescribed MPT, and of these, only 26.2% adhered to the initial treatment. These results are in line with another Italian and a US study recently performed, highlighting still an unmet need in the management of migraine: the vast majority of patients did not receive MPT or presented a high rate of discontinuation at 90 days.[60,61]

Interestingly, adherence can be poor also to non-pharmacological therapy, such as cognitive behavioral approaches. Several factors were hypothesized to explain this observation: attitudes and beliefs, lack of motivation, poor external locus of control, poor self-efficacy, low levels of acceptance, and engagement in maladaptive coping styles.[62]

Since onabotulinumtoxinA has become available for the treatment of chronic migraine, a new perspective has opened up also for patients who had not benefited from previous, non-specific oral MPT.[35] OnabotulinumtoxinA showed high efficacy and safety also in the long term[63,64] and patients with frailty.[65] These patients also displayed higher adherence than that usually observed for oral MPTs, suggesting that even if patients seem to prefer oral intake, other factors are often more relevant to increase adherence (ie, efficacy, tolerability, relying on physicians, and scheduled treatment cycles; Figure 3).

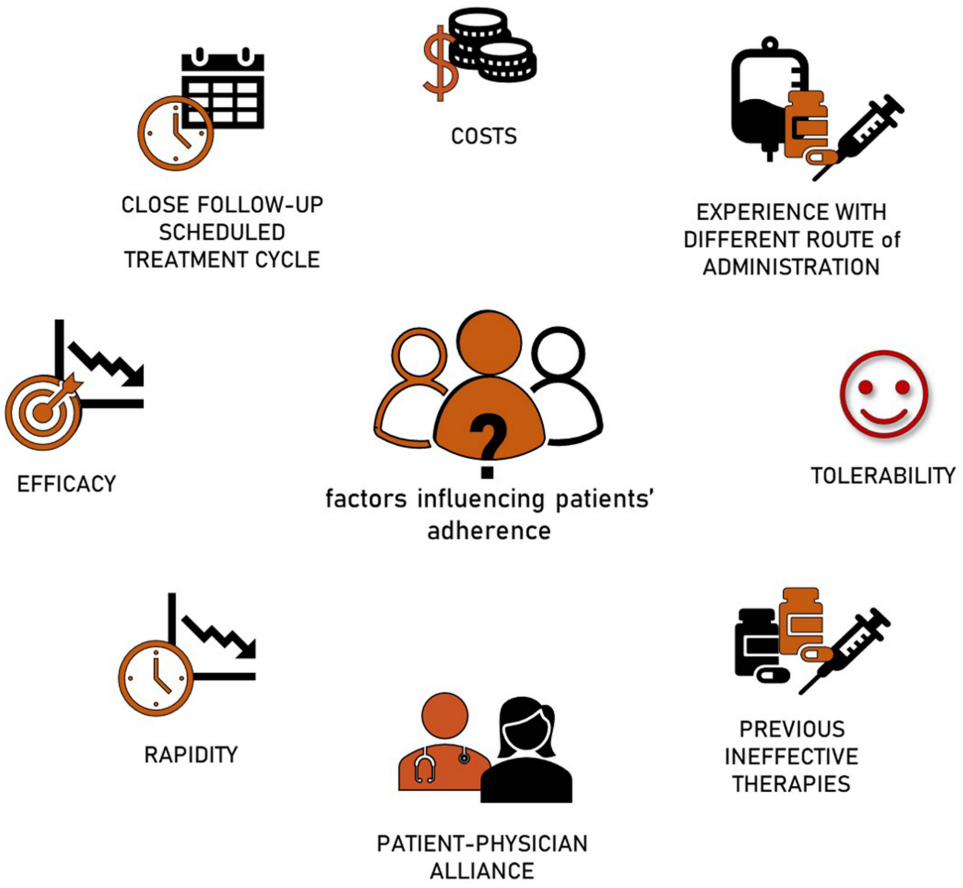

Figure 3 Factors influencing patients' adherence to therapies.

This landscape has undergone further improvements since the introduction of monoclonal antibodies anti-CGRP pathways.

The open-label extension phase of RCTs demonstrated a high adherence in the long term for erenumab (85%),[66] fremanezumab (79%),[67] and galcanezumab (81%).[68] Real-life observations confirmed a high rate of adherence (above 85%) also in everyday clinical practice.[22,23,69]

The high adherence to the new CGRP targeted therapy is explained by a more favorable rate between efficacy and side effects, as suggested by a non-direct comparison of clinical studies.[14,70]

Only erenumab was directly compared to topiramate in a double-blind, double-dummy multicenter study. In this study, 777 patients were randomized to receive topiramate (50–100 mg daily) + placebo injection or erenumab (70 or 140 mg monthly) + placebo tablets. After 3 months in the erenumab group, 55.4% of patients achieved a significant >50% reduction in monthly migraine days from baseline compared to 31.2% in the topiramate group. Only 10.6% discontinued medication due to adverse events compared to 38.4% in topiramate group.[71]

Other observational studies are ongoing. The APPRAISE is a prospective, randomized, open-label study comparing the sustained benefit of erenumab with the standard of care oral MPT in episodic migraine. The results showed a sustained superior efficacy of erenumab compared to oral preventives over one treatment year.[72]

The TRIUMPH is an ongoing, prospective, observational study in episodic and chronic patients who initiated an oral traditional MPT. In the interim analysis at three months, patients initiating or switching to galcanezumab had significantly better response rates than those receiving oral MPT, despite greater disability in the galcanezumab cohort at baseline.[73]

The rapidity of action of MPT could also influence long-term adherence: a patient perceiving an early benefit is most predisposed to continue the therapy. This is particularly true in patients who have experienced previous treatment failures[74] and may have important relevance in MOH.[75]

The time of action of monoclonal antibodies anti-CGRP pathways is very fast, within the first week or even on Day 1,[11] while patients treated with oral MPT (like beta-blockers, tricyclic antidepressants and antiepileptics) may have to wait several weeks for their clinical effect, with the double risk of prolonged high levels of migraine activity and potential overuse of acute medication.[76] For their rapid efficacy, the monoclonal antibodies anti-CGRP pathway allowed an early and consistent relief also in patients with CM or medication overuse, often making detoxification unnecessary.[77–79]

Clinical Utility and Patient Selection

In the new scenario where anti-CGRP pathway monoclonal antibodies with subcutaneous self-injection greatly improved migraine management,[19] one can wonder which is the clinical utility of a therapeutic approach that involves an in-hospital intravenous administration. Indeed, several aspects should be considered.

Despite the great advantages of CGRP-targeted therapies, patients still experience a residual migraine burden that deserves consideration.[80] Increasing real-life experiences show that switching from one antibody to another can bring additional clinical benefit in selected cases.[81,82] Thus, a new antibody with a different route of administration and pharmacokinetics represents a relevant therapeutic opportunity.

Secondly, the long-time real-life practice with onabotulinumtoxinA[83] suggests that an in-hospital administration is not necessarily a drawback, especially if it involves a trimestral schedule. For some patients, especially those experiencing a severe burden, an in-hospital infusion might meet the need to rely on the healthcare professional, increasing the patient-physician alliance.

Nevertheless, overall, patients may prefer subcutaneous over intravenous injections,[84] and self-injectable therapies are more cost-sustainable. Even considering intravenous administration a limit, eptinezumab speed of action could be especially useful in some settings.

Post-hoc analyses of the PROMISE-2 trial assessed the efficacy of eptinezumab in patients with a dual diagnosis of CM and MOH. Half of the patients reverted to an episodic condition without medication overuse for the entire 24 weeks of therapy.[85] In the whole group, days with acute medication intake were reduced by half.[86] Eptinezumab treatment was also associated with early, sustained, and clinically meaningful improvements in patient-reported outcomes, increasing patients' satisfaction.[31]

The observed efficacy on patients with CM and MOH makes eptinezumab specifically suitable for rapidly treating these patients. The RESOLUTION trial is an ongoing interventional, randomized, double-blind, parallel-group, placebo-controlled, phase-4 trial (NCT05452239) aiming to primarily assess the change from baseline in the number of monthly migraine days in the first 4 weeks after infusion of eptinezumab or placebo in add-on to a brief educational intervention.[87] The study is expected to end in May 2024.

Conclusions

The scenario of migraine management is rapidly evolving. The new CGRP-targeted therapies have produced a relevant change in the physician's mindset. With the increasing number of treated patients, we should also expect their perspectives to undergo profound changes. Patients' preferences may evolve in favor of injectable therapies, also in an in-hospital setting, if an effective treatment, rapidly acting and with sustained effect, is offered quarterly. Clinicians should be aware that considering together patients' needs and preference is fundamental when prescribing an MPT, as it may strengthen the therapeutic alliance and adherence. With the widening of the therapeutic offerings, headache specialists should inform the patients of the various treatment options, fully educating them about different aspects (eg, pharmaceutical vs non-pharmaceutical, costs, time of action, route, and schedule of administration, and side effects) in order to achieve the best tailored management. Future RCT and real-life studies are necessary to evaluate the best option in specific conditions (eg, MOH, elderly, relevant comorbidities).

Disclosure

Claudia Altamura is associated editor for Frontiers of Human Neuroscience, and received travel grants and/or personal fees for advisory boards and speaker panels, from Novartis, Eli-Lilly, Lundbeck, Teva, Lusofarmaco, Laborest, AbbVie/Allergan, Almirall. Luisa Fofi received travel grants, honoraria for advisory boards, and speaker panels, from Novartis,

Eli Lilly, and Teva. Fabrizio Vernieri received travel grants, honoraria for advisory boards, speaker panels, or clinical investigation studies from Allergan/AbbVie, Amgen, Angelini, Eli- Lilly, Lundbeck, Novartis, and Teva. The authors report no other conflicts of interest in this work.

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