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Strategies to Improve Migraine Treatment Results

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Abstract

The purpose of this review is to describe strategies for optimizing the use of available agents for acute migraine therapy. Patient satisfaction with migraine therapy depends on obtaining rapid and complete resolution of pain and preventing headache recurrence, making 2-h pain free and sustained pain free more relevant endpoints than 2-h pain relief for assessing acute migraine therapies. Many treatment guidelines recommend a step-care approach to migraine management, that is, starting with a simple analgesic, followed by various combination analgesics, allowing a migraine-specific drug (e.g. a triptan) only after the patient has demonstrated an inadequate response to non-specific treatments. This can result in prolonged morbidity and patients lapsing from care. In the stratified-care approach, the initial treatment is selected according to the individual patient's migraine severity and associated disability, promoting the use of migraine-specific treatments as first-line agents for patients with disabling migraines. Another strategy, triptan treatment during mild headache pain, has been shown to improve treatment success rates compared with treatment delayed until pain is moderate to severe. Treatment before the development of central sensitization is thought to underlie the improvement in outcomes. In conclusion, migraine treatment strategies such as the stratified-care approach and the administration of medication while pain is mild will help increase treatment success rates and substantially reduce patient suffering and disability.

1. Introduction

The development of the triptan class of drugs for the acute treatment of migraine has been a great advancement in therapy for this condition. Although triptans have been shown to have significantly greater efficacy than placebo,[1,2] the endpoints emphasized in the registration trials of triptans may not encompass all of the treatment attributes necessary for patients to achieve their therapeutic goals.[3] A new focus on endpoints relevant to patients is needed to increase patient-defined treatment success.

Triptans are not being utilized to their full therapeutic potential for a number of reasons. These drugs are not being used as first-line agents in many patients who need them, such as patients with high levels of migraine-associated disability.[4] Triptan treatment attributes vary in subtle ways that may be meaningful to individual patients,[2] but there has been little guidance on matching triptan treatment attributes with patients'

specific treatment goals. Finally, triptan treatment regimens based on the protocols from registration trials, in which patients are instructed to delay treatment until headache pain is moderate to severe in intensity, may not provide the optimal treatment strategy.[5]

Triptan treatment strategies need to evolve with the availability of new data on therapeutic regimens that can improve patient satisfaction. This article will explore therapeutic endpoints and treatment goals relevant to patient satisfaction, the use of stratified care based on the level of migraine-associated disability, the appropriate use of triptans as first-line therapy, choosing a triptan based on treatment attributes, and the initiation of therapy during mild headache pain.

2. Appropriate Endpoints for Acute Migraine Therapy

In light of the numerous clinical trials investigating acute migraine therapy with triptans and other agents, there has been some discussion of what the appropriate clinical endpoints should be to achieve patient satisfaction. Probably the most commonly used endpoint in triptan trials has been pain relief 2 h after the treatment of moderate to severe headache pain. Two-hour pain relief is defined as a change from severe or moderate pain to mild or no pain. This endpoint is not considered optimal, however, because some patients achieving this endpoint still have mild headache pain.[3]

The 2-h pain-free response is a better indicator of what patients want from acute migraine therapy than 2-h pain relief because it entails the complete and rapid resolution of pain.[6,7] Another feature of acute migraine treatment that patients consider important is freedom from migraine-associated symptoms; the complete relief endpoint combines this feature with 2-h pain free (figure 1).

The 2-h pain-free response does not include several other treatment attributes important to patients. For greater satisfaction, patients want to be free from headache recurrence, clinically defined as the onset of headache pain after 2-h pain free has occurred and within 24 h of treatment. Headache recurrence often necessitates the use of rescue medication, something patients wish to avoid. The sustained pain free (SPF) endpoint has therefore been recommended as the appropriate endpoint to use in clinical trials of triptans.[1,2] It is defined as pain free 2 h after treatment, with no headache recurrence or the use of rescue medication from 2 to 24 h after dosing. As illustrated in figure 1, patients' satisfaction with treatment increases as the endpoints for migraine therapy become more stringent and more challenging to achieve.[8]

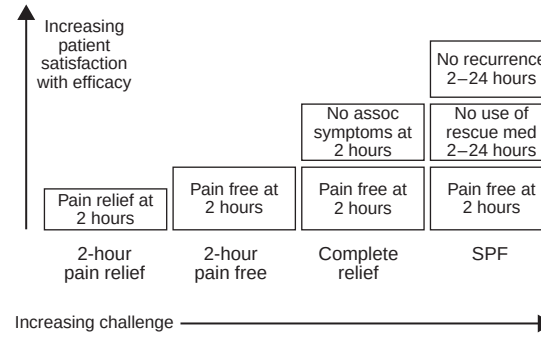

Fig. 1. Patient satisfaction with acute migraine therapy according to endpoints used in triptan clinical trials.

3. Step Care Versus Stratified Care of Migraine

The step-care approach, across attacks or within attacks, is a frequently used strategy for migraine management. In step care, a physician starts a migraine sufferer with a non-specific medication. If the non-specific treatment is unsuccessful, another agent is given, and this step is repeated until an effective agent is found. When step care is given across attacks, the patient who is not satisfied with the initial treatment must wait until the next attack to receive a different agent. With step care within attacks, the patient with initial treatment failure may take another agent during the same attack.[9,10]

The step-care approach aims to prevent the overtreatment of migraine and minimize treatment

costs by restricting the use of the more expensive specific agents (e.g. triptans) only to patients who require their efficacy. Step care for migraine management has been promoted in a number of treatment guidelines, including the French Recommendations for Clinical Practice: Diagnosis and Therapy of Migraine. These recommendations provide comprehensive guidelines for managing migraineurs and are evidence based as they were developed from internationally published clinical literature on migraine therapy.[4]

According to the French guidelines, during the initial consultation, patients who have been treating their migraines with non-specific medications are asked four questions regarding their current treatment strategy: Do you have significant relief within 2 h after taking the medication?; Is the medication well tolerated?; Do you take only one dose?; and Two hours after taking the medication, can you resume normal occupational, social, and family activities? A patient who responds 'Yes' to all four questions can continue using non-specific agents; this patient does not need any change to the current therapeutic regimen.

A patient who responds 'No' to one or more of these questions requires a treatment change, and the guidelines recommend a step-care approach within attacks with the restricted use of triptans. This patient should receive a prescription for a non-steroidal anti-inflammatory drug (NSAID) and a triptan, with instructions to take the NSAID first during the next attack. The patient is not to take the triptan unless the attack is not sufficiently relieved 2 h after taking the NSAID. Patients must demonstrate poor response or poor tolerability with an NSAID to receive a prescription for a triptan as first-line therapy for subsequent attacks. For patients with severe, disabling migraines, triptans are not recommended as first-line therapy because, despite a large body of medical and economic data,[4,10,11] the framers of these recommendations did not achieve consensus on this issue.

The step-care approach, as illustrated in the French recommendations, has a number of disadvantages. Step care is based on the faulty premise that most migraineurs have basically the same treatment needs. In reality, the nature, severity, and associated disability of migraine varies greatly among individual patients.[9] The step-care approach mistakenly assumes that all patients who require second or third-line therapies will have sufficient motivation to continue to pursue therapy; however, patients may not follow up with their physician when a treatment fails and instead may lapse from medical care.[9,12] This approach also requires that these patients have confidence that the prescribing physician will be able to identify an effective treatment, which is not always the case.[12,13] Finally, the step-care approach assumes physicians will have the tenacity to continue exploring second or third-line agents.[9]

In the real-world migraine consultation setting, first-line non-specific therapy appears to be ineffective as the average patient receiving step care for migraine experiences 4.6 treatment failures before finding an effective therapy.[14] The step-care approach thus prolongs patients' suffering and disability.[9]

An alternative strategy for migraine management is stratified care. The goal of stratified care is to match the therapeutic regimen efficiently to the individual patient's treatment needs. For example, patients can be categorized according to the level of migraine-associated disability. Migraineurs whose attacks are associated with low levels of disability receive non-specific therapy. Patients whose migraine attacks are significantly disabling receive specific agents (e.g. triptans).

The stratified-care approach has been thought to be more expensive than the step-care approach, which aims to reduce costs by steering patients to less expensive first-line therapies. In practice, however, the high level of treatment failures occurring with the step-care approach has been associated with increased medical expenditures, whereas stratified care has been associated with fewer physician visits and new prescriptions.[9–11,15,16]

The clinical benefits of a stratified-care and a step-care approach to migraine management have been compared in a randomized, controlled,

parallel-group, multicentre clinical trial conducted by the Disability in Strategies Study Group.[10] Patients ($N = 835$) from 13 countries with a Migraine Disability Assessment Scale (MIDAS) grade of II, III, or IV were randomly assigned to stratified care, step care within attacks, and step care across attacks for the treatment of six attacks. Stratified care consisted of aspirin 800–1000 mg plus metoclopramide 10 mg for patients with MIDAS grade II migraine, and zolmitriptan 2.5 mg for those with MIDAS grade III and IV migraine. Step care consisted of an initial treatment with aspirin 800–1000 mg plus metoclopramide 10 mg. Patients randomly assigned to step care within attacks could use zolmitriptan 2.5 mg if the migraine attack did not respond to the initial treatment at 2 h. Those randomly assigned to step care across attacks who did not respond to aspirin plus metoclopramide at 2 h in at least two of the first three attacks then received zolmitriptan 2.5 mg to treat the next three attacks.

Across the six attacks, stratified care was associated with a significantly greater rate of pain relief at 2 h (53%) compared with step care within attacks (41%; $P < 0.001$) and step care across attacks (36%; $P < 0.001$). Disability time (defined as the area under the disability versus time curve) across six attacks was significantly lower for patients receiving stratified care compared with those receiving step care within attacks and step care across attacks ($P < 0.001$ for both comparisons). These results support the use of a stratified-care approach to increase headache response and reduce disability time.

Ultimately, the success of a stratified-care approach requires that physicians identify the migraine-associated factors relevant to the patient's therapeutic needs. Patients differ with respect to the severity of headache pain, the types and intensity of associated symptoms such as nausea and vomiting, and the sensitivity to and willingness to tolerate side-effects.

A basis for the stratification of migraine to help guide treatment decisions is provided in figure 2. The severity of headache pain (mild, moderate, or severe) is a key factor in stratification. The time to the peak of the attack ('crash migraine' in which there is a rapid onset of symptoms, intermediate onset, or slow onset) is also factored in. The presence of associated symptoms and the timing of their onset are also taken into consideration. The overall level of disability (mild, moderate, severe) is determined. Finally, the frequency of migraine attacks is used to determine the need for prophylaxis.

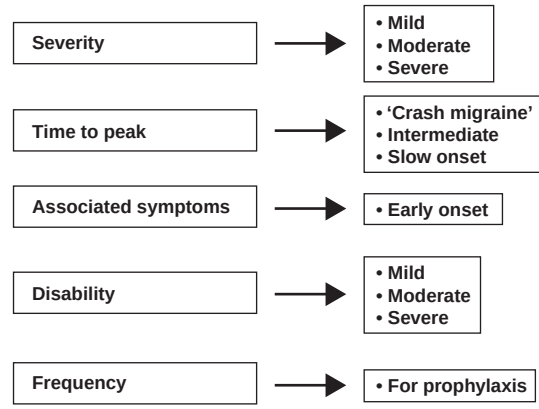

Fig. 2. Basis for migraine stratification according to various migraine characteristics including level of migraine-associated disability.[9]

4. Matching Triptan Attributes With Patient Needs

Although the triptans as a class are efficacious and generally well tolerated at marketed doses for the acute treatment of migraine, the individual triptans are not interchangeable. As demonstrated in the meta-analysis of 53 randomized, double-blind, controlled (active or placebo) oral triptan trials by Ferrari and colleagues,[2,17] these agents differ with respect to specific efficacy parameters, consistency of effect, and their association with adverse events.

In that meta-analysis, almotriptan 12.5 mg, eletriptan 20, 40, and 80 mg, naratriptan 2.5 mg, rizatriptan 5 and 10 mg, sumatriptan 25 and 50 mg, and zolmitriptan 2.5 and 5 mg were compared with sumatriptan 100 mg. Sumatriptan was chosen as the reference drug because, as the first triptan to be

Table I. Triptan meta-analysis: comparison with sumatripan 100 mg[2]

Triptan	2-h PR	SPF	Consistency of effect	Tolerability
Almotriptan 12.5 mg	=	+	+	++
Rizatriptan 10 mg	+	+	+(+)[a]	=
Eletriptan 80 mg[b]	+(+)	+	=	−
Eletriptan 40 mg	=/+	=/+	=	=
Zolmitriptan 2.5 mg	=	=	=	=
Zolmitriptan 5 mg	=	=	=	=
Rizatriptan 5 mg	=	=	=	=
Sumatriptan 50 mg	=	=	=/−	=
Naratriptan 2.5 mg	−	−	−	++
Sumatriptan 25 mg	−	=/−	−	+
Eletriptan 20 mg	−	−	−	=

PR = Pain relief; **SPF** = sustained pain free. − Inferior; =/− possibly inferior; = no difference; =/+ possibly better, + better; +(+) possibly much better; ++ much better compared with sumatriptan 100 mg.
[a] The unusual design of the rizatriptan trial makes it difficult to compare its consistency of effect with other drugs.
[b] Not an approved single dosage in most countries.

developed, it was the most commonly used triptan in direct head-to-head comparison trials with other triptans, was widely prescribed and consequently had a large clinical database.

Table I summarizes the results from the meta-analysis. Although all of the triptans included in the analysis were more efficacious than placebo, the meta-analysis demonstrated that three triptans, almotriptan 12.5 mg, eletriptan 80 mg, and rizatriptan 10 mg were associated with the highest likelihood of treatment success. In comparison with sumatriptan 100 mg, almotriptan 12.5 mg was associated with similar 2-h pain-relief rates, greater SPF rates, better consistency, and much better tolerability. Rizatriptan 10 mg was shown to have higher SPF rates and more consistency of effect. Eletriptan 80 mg exhibited better 2-h pain relief and SPF rates but inferior tolerability.

5. Early Intervention With Triptans

The protocols for registration trials for triptans stipulated that patients were not to use study medications until headache pain was moderate to severe in intensity. The reasons for requiring patients to delay treatment were to adhere to International Headache Society guidelines, to ensure that patients were treating migraines and not other headache types (e.g. tension-type headache), to minimize the placebo response, and to enable comparisons with other agents evaluated using the same treatment protocol.

Triptans have been shown to be significantly more efficacious than placebo for treating migraine headache when taken during moderate-to-severe pain. However, the meta-analysis of triptan trials by Ferrari et al.[17] found that response rates associated with dosing during moderate-to-severe headache pain, median rates from pooled mean estimates for 2-h pain free of 29% (excluding frovatriptan and naratriptan; range 23–40%) and 20% (range 11–26%) for SPF, showed room for improvement.

Data from a number of retrospective analyses and prospective studies demonstrated that higher 2-h pain-free and SPF rates were obtained when patients treated their migraine headache when the pain was mild.[18] For example, a retrospective analysis of two clinical trials of sumatriptan 100 mg reported 2-h pain-free rates of 69 and 73% when patients treated mild pain compared with 39 and 48% when patients treated moderate-to-severe pain.[19] Similar findings were seen in a prospective, randomized, double-blind early intervention trial in which eletriptan 40 mg treatment resulted in 2-h pain-free rates of 68% in patients treating mild pain compared with 39% in patients treating moderate or severe pain.[20] Post-hoc analyses of data from patients who treated with almotriptan 12.5 mg during mild migraine headache pain compared with those who treated during moderate-to-severe pain in 6-month and 12-month open-label studies observed significantly higher 2-h pain-free rates for treatment during mild pain (76.9 versus 43.9%, $P < 0.001$ for the 6-month trial; 84 versus 53%, $P < 0.001$ for the 12-month trial; figure 3).[21,22] The SPF rate in the 6-month trial was also significantly greater for patients treating mild pain compared with those treating moderate-to-severe pain (66.6 versus 36.6%, $P < 0.001$; figure 3a).[21] Treatment

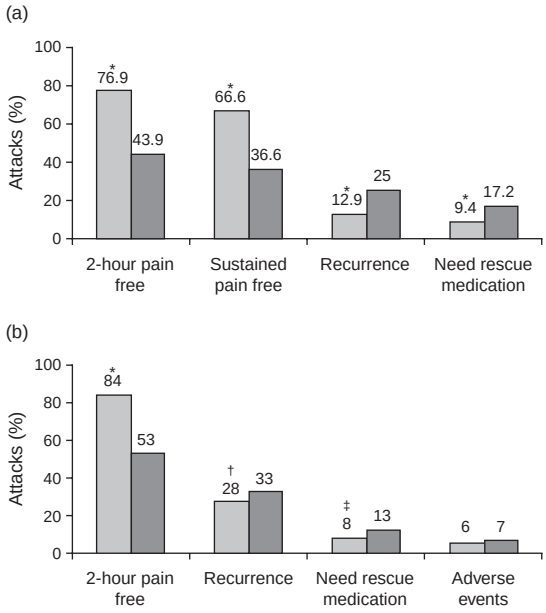

Fig. 3. Early migraine intervention with almotriptan 12.5 mg. (a) A 6-month open-label trial involving 582 patients and 10 645 attacks, $^{*}P < 0.001$.[21] □ = Mild; ■ = moderate/severe. (b) A 12-month open-label trial involving 118 patients and 708 attacks, $^{*}P < 0.001$; $^{\dagger}P = 0.01$; $^{\ddagger}P < 0.01$.[22]

started during mild pain was also associated with significantly lower headache recurrence rates and the use of rescue medication compared with therapy initiated during moderate-to-severe pain. Several other post-hoc analyses and prospective triptan trials have shown greater efficacy with early triptan intervention compared with delayed therapy.[23–27]

These early intervention studies used different definitions of 'early'; some compared treating mild pain compared with treating moderate-to-severe pain, whereas others assessed treatment within a fixed time from pain onset (e.g. one hour) compared with delayed treatment. It should be noted, however, that treating mild pain is not always equivalent to treating early because the timing of the progression of a migraine attack is variable. A recent study reported that treatment with eletriptan within 30 min of migraine pain onset but during moderate-to-severe pain was not

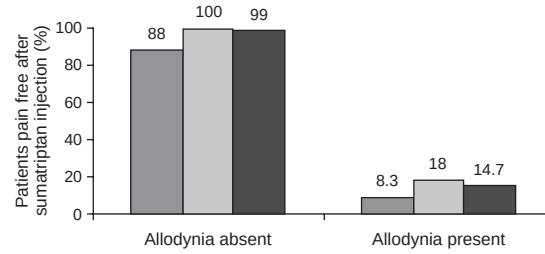

Fig. 4. Pain-free rates with triptan treatment in 34 attacks associated with cutaneous allodynia at the time of dosing with sumatriptan by injection and 27 attacks not associated with cutaneous allodynia at the time of dosing.[30] □ = 1 Hour; ▨ = 4 hours; ■ = all.

as effective as treatment during mild pain regardless of the timing of drug intake, suggesting that headache pain intensity at the time of treatment is more important than time to treatment.[20]

Early intervention with triptans is supported by our understanding of the pathophysiology of migraine. The early phase of migraine is characterized by the peripheral sensitization of trigeminovascular neurons and the development of headache pain. The progression of a migraine attack involves central sensitization of trigeminovascular neurons with increasing severity of headache pain and the development of cutaneous allodynia.[28,29] In a study by Burstein et al.,[30] intervention with a triptan before the development of cutaneous allodynia was associated with greater treatment response rates compared with treatment after the development of cutaneous allodynia (figure 4). There are, however, some brief reports in the literature of early intervention trials in which the presence of allodynia-associated symptoms at the time of treatment did not have an effect on treatment response.[31,32]

Physicians may hesitate recommending early intervention because of concerns over medication overuse; however, effective communication between physician and patient and patient education (see Edmeads article in this supplement) can help reduce this risk. Patients may hesitate to treat their migraines during the early phase for a number of reasons (table II). Whereas some patients delay treatment to be sure that their headache is

Table II. Barriers to early treatment of migraine

Barrier	Overcoming the barrier
Risk of headache from medication overuse	Improve patient/physician communication
Headache may not be migraine	The majority of headaches experienced by migraineurs are migraines[28] Most migraineurs can distinguish migraine from other types of headache
Headache may not progress from mild to moderate–severe	Most migraine headaches progress to severe pain[16]
Patient concerns over increased cost	Early intervention can reduce cost: fewer pills consumed, less medical resource utilization, less time lost[29]
Patient concerns regarding side-effects	Use triptan with good tolerability profile

a migraine, it has been reported that most headaches experienced by migraineurs are indeed migraines.[33] Some patients may delay treatment to ensure that they will progress to severe pain; however, most migraines progress to moderate-to-severe pain and thus will require treatment.[16] For patients concerned about cost, early intervention has been associated with less drug use overall, lower medical resource utilization, and a reduction in time lost because of migraine-associated disability.[34] A large proportion of patients, 67%, delay or avoid taking acute migraine medications because of concerns over side-effects.[35] Such patients should be advised about triptans, such as almotriptan, with placebo-like tolerability profiles.

6. Conclusions

Clinical endpoints such as 2-h pain free and SPF are difficult to achieve but reflect what patients seek from acute medical treatment for migraine. The stratified-care approach, in which patients receive treatment according to the severity of their migraines and the disability associated with the attacks, offers greater chances for treatment success than step care (starting with non-specific agents and delaying the use of specific agents until the former agents are shown to be ineffective). Triptans should be chosen on the basis of their treatment attributes, which then are to be matched to patients' individual treatment goals. Early intervention, before the development of moderate-to-severe pain and cutaneous allodynia, provides the greatest likelihood of treatment response.

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