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Therapeutic Options

CGRP MONOCLONAL ANTIBODIES IN THE MANAGEMENT OF MIGRAINE HEADACHE

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Migraine is a common disorder, occurring in up to 12–15% of the general population, with an expected lifetime prevalence of 43% in women and 18% in men.[1,2] Although not considered life-threatening, migraine has been reported as a major cause of disability, with international studies citing negative impacts on patients' physical and mental health, economic circumstances and overall quality of life.[1,3] Given these widespread consequences, there is an unmet demand for more effective therapeutic options both in the prevention and treatment of episodic and chronic migraine. This article will review migraine pathophysiology and its management, focusing primarily on the use of the new calcitonin gene-related peptide (CGRP) monoclonal antibodies (mABs).

HEADACHE CLASSIFICATION, DIAGNOSIS AND PATHOPHYSIOLOGY

Headache is one of the most prevalent disorders reported by patients and may occur either on its own (primary disorder) or due to other underlying conditions (secondary).[4] Primary headache disorders include tension-type, cluster or migraine headache. Secondary headaches occurring as a result of head trauma, brain tumour or cerebrovascular causes will not be discussed in this report. Each type of primary headache can be further classified based on duration of symptoms.[1,4] Episodic headaches are often described as occurring on a periodic basis with a defined symptom-free interval; while chronic headaches tend to occur either continuously or with minimal symptom-free intervals between occurrences (see Table 1).

The diagnosis of primary headache type requires a thorough patient history, focusing on the presence/absence of symptoms (specifically evaluating quality, site and radiating propensity), intensity, frequency and duration of the headache. Most patients presenting with primary headache will have completely normal physical and neurological examinations and do not require imaging, assuming potential red-flag symptoms are absent. Although there may be an overlap of symptoms between the various subtypes of headache disorders, specific features can be used to differentiate between them; for example, pericranial muscle tenderness is often present in tension-type headaches. Migraine headaches exhibit more symptoms related to neuronal sensitization such as hyperalgesia or allodynia, while symptoms related to autonomic activation (e.g., facial sweating, nasal congestion, lacrimation) occur more frequently in cluster headaches.[5]

While tension-type headache may be the most common type of primary headache identified in population-based studies, migraine headaches account for the greatest number of physician visits.[5] Migraine headaches consist of recurrent attacks with typically unilateral, throbbing, headache pain. These headaches may worsen with physical activity and may be accompanied by photophobia, phonophobia, nausea, vomiting and/or cutaneous allodynia.[5,6] A migraine is thought to result from a cascade of events, developing over hours or even days. A typical migraine attack will progress through four stages:

1. A prodrome, occurring in up to 77% of patients, approximately 24–48 hours prior to a headache and involving symptoms such as yawning, irritability, food cravings etc.[1,2]
2. An aura phase, occurring in approximately 25% of patients; the onset of reversible symptoms is gradual, usually lasting no longer than an hour. Current data suggest this phase occurs *with* the headache rather than preceding it.
3. A headache, described as throbbing or pulsing pain, primarily unilateral and lasting for a period of four hours to several days, if untreated.
4. A postdrome, the transient period following resolution of the throbbing headache pain, when sudden head movements can produce pain in the area of the original headache.[1]

Historically, the pathophysiology of migraine headaches was thought to be due to vascular dilatation, with vasoconstriction causing the aura development. It is now recognized that an alternative theory of neuronal dysfunction is more likely responsible for the series of intra- and extracranial changes that produce the above-mentioned phases of migraine.[1] *Cortical spreading depression*, a self-propagating wave of neuronal depolarization, moves over the cerebral cortex and is thought to cause visual aura symptoms, activate trigeminal nerve afferents and increase permeability of the blood-brain barrier.[1,2] These effects produce a cascade response whereby inflammatory

Table 1: Classification of Primary Headache[1,3,5,6,15,16,17,18]

Type	Prevalence and Risk Factors	Characteristics	Comments
Cluster	• Prevalence in general population: <1% • Typically results in significant disability; the intensity of pain causes most people to seek medical attention	• Always unilateral, frequently occurs near or around the eye or temporally • Pain: described as severe intensity, excruciating, deep, continuous, overwhelming • Can be associated with ipsilateral lacrimation and redness of the eye, congestion, rhinorrhea, pallor, sweating, restlessness, or agitation • Onset: fast, may peak in minutes • Duration: 15 minutes to 3 hours	• Classified as episodic or chronic • Episodic: headaches occurring in clusters of 7 days to 1 year, with pain-free periods of ≥ 3 months • Chronic: headaches continuing over a year without a break of at least 3 months
Migraine	• Higher incidence in females (17% vs 6% of males yearly) • Impacts all ages, with peak prevalence between 25 – 55 years • Most common triggers include stress, menstruation, fasting, weather, and sleep disturbances • Menses can trigger migraine in 60% of women due to a drop in estrogen levels prior to menstruation	• Presents as unilateral in 60-70% cases, and bifrontal or global in 30% • Pain: pulsating or throbbing, moderate to severe in intensity • May be accompanied by nausea (60-95%), vomiting (50-62%), photophobia, phonophobia and/or may have aura (usually visual) • Can be aggravated or worsened by routine physical activity; patient often prefers quiet, dark setting • Onset: often gradual, in a crescendo pattern • Duration: 4-72 hours	• Several subtypes (e.g., with brainstem aura, hemiplegic, retinal, vestibular, menstrual, chronic) • Chronic migraine: the occurrence of headache >15 days per month for a duration of >3 months • 25% of patients will experience reversible "aura" (focal neurological symptoms). Symptom(s) include one or more of: visual (scintillations, loss of vision), sensory (numbness, "pins and needles"), verbal, (aphasia, dysarthria), motor weakness (on one side of body or face), brainstem (vertigo, tinnitus, ataxia etc.) • Migraine associated with menstruation may be more severe, longer-lasting, and harder to treat than other types • One report indicated that on average, patients with migraines lose the equivalent of 12 workdays per year (considering both absenteeism and reduced effectiveness at work)
Tension-type	• Most frequent headache type in population-based studies	• Bilateral or circumferential presentation • Pain: described as pressure or tightness; non-pulsating quality, mild to moderate in intensity • Can wax and wane • Not affected by routine physical activity • May be accompanied by one of photophobia or phonophobia (not both); mild nausea may be present in chronic cases • Duration: 30 minutes to 7 days or unremitting	• Episodic: headaches occur >1 day but <15 days per month • Chronic: headaches occur >15 days per month for >3 months • Preventative measures are typically non-pharmacological for mild headaches

changes at the meninges produce headache pain via central/peripheral reflex mechanisms. Activation of the trigeminovascular system involves the release of vasoactive neuropeptides including substance P, calcitonin gene-related peptides (CGRPs) and neurokinin A. These neuropeptides lead to neurogenic inflammation, which may prolong and intensify migraine pain. Finally, sensitization of the neurons (a heightened response to nociceptive and non-nociceptive stimulation) is thought to be associated with the clinical signs of migraine, such as throbbing pain and hyperalgesia.[1]

THERAPEUTIC MANAGEMENT

The course of migraine headaches can vary between patients and even within individuals over time. For this reason, a management plan should be individualized. Having patients record the frequency and intensity of headaches experienced per month, often referred to as "monthly migraine days" (MMD) and "monthly headache days" (MHD), as well as triggering factors can help characterize the migraine type and ultimately determine treatment choices. Episodic migraines can be described as fewer than 15 MMD or MHD, while over 15 MHD with a minimum of 8 MMD suggests chronic migraine. A stepwise approach to treatment based on symptom severity (mild, moderate, severe attack), concomitant symptoms (presence of nausea) and response to previous therapies is often used to dictate treatment of choice.[6]

Acute treatment options are used to rapidly reduce pain and other symptoms associated with a migraine attack and allow the patient to resume daily functioning while minimizing adverse reactions. Prophylactic measures are recommended for patients who experience ≥ 4 MMD, especially when attacks significantly interfere with daily routines or quality of life, despite acute treatment.[6] Recommendations for preventive or acute treatment of migraine are fairly consistent among published clinical guidelines and are briefly outlined in Table 2. This report will focus on CGRP mAB therapy, including how and where these agents may fit into the current treatment algorithm.

The expression of CGRP plays an important role in migraine pathogenesis, as it causes cerebral vessel vasodilation, neurogenic inflammation and neuronal sensitization. The efficacy of triptans, one of the most common classes of drugs used to treat migraine, may be in part due to their ability to decrease the release of CGRP.[2,7] Currently, two new pharmacological options utilize this pathway. Oral small molecule CGRP receptor antagonists (known as "gepants") are not yet approved in Canada but have been used in the acute migraine setting in the U.S. with studies also demonstrating efficacy in prevention. The second group, injectable

CGRP mABs, directly target the CGRP receptor or ligand binding site, thereby preventing trigeminal nociceptive signalling.[6] These larger molecules do not penetrate the CNS and act in peripheral tissue only. Like other mABs, these agents are not eliminated via hepatic, biliary or renal routes, potentially increasing their safety profile.[2] Currently, four CGRP mABs are available in Canada: erenumab, eptinezumab, fremanezumab and galcanezumab. All are injectable medications approved for use in the preventive treatment of migraine. All are usually dosed on a monthly basis subcutaneously, except for eptinezumab which is given intravenously every three months.[8,9,10,11] For a comparison of these CGRP mABs, see Table 3.

In the prevention of migraine headaches, a meta-analysis of 21 studies evaluated the use of CGRP mABs in patients with either episodic or chronic migraine. Compared to placebo, CGRP mABs resulted in 1.5 fewer MMDs in patients with episodic migraine and 2.23 fewer MMDs in patients with chronic migraines.[12] In general, these agents appear to prevent one or more episodic migraines per month (compared to placebo) and reduce MMD by at least 50% in approximately 25% of patients.[13] The CGRP mABs achieve efficacy benefit over days to weeks following the first dose, although evidence has demonstrated that a significant number of patients may not respond until after a second or even a third dose.[6] Most studies were done in patients who had failed or did not respond to standard preventative therapy. One of the agents, eptinezumab, has also demonstrated potential efficacy in shortening time to headache resolution when given during a migraine attack, as evidenced by a higher number of patients being headache-free at two hours, a reduced need for rescue medications within 48 hours, and a longer interval to the next migraine, compared to placebo in one trial.[14] In addition to migraine prevention, galcanezumab has also been approved for use in patients with episodic cluster headaches.[11]

Many treatment options exist for the management of migraine, both in the acute setting and as prophylaxis; however, the disorder continues to significantly reduce the quality of life for those afflicted. CGRP mABs offer another solution for management, particularly in those patients who may be refractory or intolerant to conventional treatment. Given the limited availability of comparative data as well as their prohibitive costs, CGRP mABs are currently reserved for use as second- or third-line therapies after multiple therapies have been optimally tried.

Table 2: Therapeutic Options for Acute Treatment or Prophylaxis of Migraine[4,6,15,19]

The following table includes recommendations based on the most recent available guidelines in Canada, the U.S. and Europe. When variation existed in the approved order of use, Canadian guidelines were given preference.[4,6,15,19] Only agents currently marketed in Canada have been included. Detailed guidelines should be consulted to determine if a particular agent is appropriate and safe for a patient.

Acute Migraine Treatment	
1st line	• NSAIDs • Acetaminophen
2nd line	• Triptans* (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan) +/- antiemetics (domperidone, metoclopramide) prn for nausea
3rd line	• NSAIDs + triptan**
Preventive Migraine Treatment	
1st line	• Beta-blockers (propranolol, metoprolol, nadolol) • Tricyclic antidepressants (amitriptyline, nortriptyline)
2nd line	• Topiramate • Candesartan • Lisinopril • Gabapentin
3rd line	• Divalproex sodium • Pizotifen • Onabotulinum toxin A • Flunarizine • Venlafaxine • CGRP mABs (erenumab, fremanezumab, galcanezumab, eptinezumab)

NSAIDs=non-steroidal anti-inflammatories; prn=when needed

* Triptans are available in the following formats: oral, orally-dissolving tablet or wafer, subcutaneous injection or nasal spray; choice is determined by patient preference, presence of nausea/vomiting and duration/severity of symptoms.

** The best-studied combination has been sumatriptan and naproxen, with studies demonstrating greater efficacy with the combination compared to either agent alone.[7]

Table 3: Comparison of CGRP Receptor Antagonists[6,8,9,10,11,13,14,18,20]

	CGRP Monoclonal Antibodies			
Generic Name (Brand)	**Erenumab (Aimovig®)**	**Eptinezumab (Vyepti®)**	**Fremanezumab (Ajovy®)**	**Galcanezumab (Emgality®)**
Approved Indication(s)	Prevention of migraine in adults with at least 4 MMD	Prevention of migraine in adults with at least 4 MMD	Prevention of migraine in adults with at least 4 MMD	Prevention of migraine in adults with at least 4 MMD The reduction in the frequency of episodic cluster headaches in patients with cluster headache periods lasting ≥ 6 weeks and are refractory to or intolerant of conventional preventive treatments
Dose	70 mg or 140 mg SC** once monthly No need for gradual dose escalation; either dose may be used as a starting dose	100 mg or 300 mg IV every 3 months	225 mg SC** once monthly OR 675 mg (3 consecutive injections of 225 mg) SC** every 3 months	Migraine: 240 mg SC given as a loading dose (2 consecutive injections of 120 mg) then 120 mg SC** once monthly Episodic cluster headache:[a] 300 mg SC** once monthly at the beginning of the cluster period
Available Dosage forms	Prefilled syringe (70 mg/mL) or Auto-injector (70 mg/mL)	100 mg/mL solution in a single-use vial	Prefilled syringe 225 mg/1.5 mL	Prefilled syringe (120 mg/mL or 100 mg/mL) or pen (120 mg/mL)
Cost	Approximately $575/month	N/A	Approximately $600/month	Approximately $675/month
Precautions / Contraindications / Drug Interactions	• Evidence for use in special populations (pediatric, elderly, pregnant or lactating patients) still very limited. • Use with caution in patients with history of recent cardiovascular or cerebrovascular ischemic events. Studies to date have not demonstrated cardiovascular adverse drug reactions but most studies with CGRP mAbs have excluded patients with underlying cardiac issues. • Presence of dry natural rubber in the needle cover of the Aimovig® injectable product can lead to allergic reactions in latex-sensitive patients.			
Adverse Drug Reactions	• Injection-site reactions • Hypersensitivity reactions, ranging from within minutes of administration to >1 week or even one month after treatment • Nasal congestion, sore throat, URTI and fatigue with eptinezumab • Constipation, muscle spasms, pruritus with erenumab • New onset or worsening hypertension reported with erenumab			
Comments	• Advantages of the injectable CGRP mAbs can include fixed dosing (i.e., little need to dose titrate), the rapid onset of therapeutic benefit in some patients and favourable tolerability profiles • Reduced dosing schedule may be helpful for patients with compliance issues • Efficacy should be assessed over 3-6 months • All injectable CGRP mAbs require refrigeration prior to use; stability at room temperature differs between agents: fremanezumab, 24 hours; galcanezumab, 7 days; erenumab, 14 days; eptinezumab, 8 hours after dilution • High cost and lack of insurance approval may limit use • To qualify for use, patients must have failed or been intolerant of multiple first-line migraine therapies			

CGRP=calcitonin-gene related peptide; IV=intravenously; mAbs=monoclonal antibodies; MMD=monthly migraine days; N/A=not available; SC=subcutaneously; URTI=upper respiratory tract infection

** Patients may self-administer doses after appropriate training. SC administration recommended into abdomen, thigh or upper arm. For galcanezumab, SC administration may also be into the buttocks.

[a] Galcanezumab should not be administered during remission time or after completion of a cluster period.

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