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PERSPECTIVE

Combination CGRP monoclonal antibody and onabotulinumtoxinA treatment for preventive treatment in chronic migraine

OnabotulinumtoxinA, an approved preventive chronic migraine (CM) treatment, is well tolerated with demonstrated efficacy across multiple clinical trials. When injected into specific head and neck muscles, onabotulinumtoxinA impacts peripheral sensory nerve endings with cell bodies located in the trigeminal-occipital and cervical complex. OnabotulinumtoxinA blocks the fusion of synaptic vesicles within the nerve cytoplasm, preventing neurotransmitter and neuropeptide release and insertion of receptors and ion channels into the nociceptive nerve terminals. The effectiveness of onabotulinumtoxinA in CM is mediated at multiple points in pain activation pathways, including downregulating receptors on nociceptive neurons and reducing the availability of released neurotransmitters and neuropeptides for activating migraine-related pathways.

Directly inhibiting calcitonin gene-related peptide (CGRP) pathways has emerged as a targeted approach for preventing migraine. Four CGRP-targeted monoclonal antibodies (mAbs) are approved for preventing migraine, including one directed against the CGRP receptor (erenumab) and three directed against the CGRP ligand (galcanezumab, fremanezumab, and eptinezumab). All four CGRP monoclonal antibodies have established efficacy in preventing migraine with few systemic side effects.

Migraine is a polygenic disease involving multiple pathways, neurotransmitters, neuropeptides, and receptors. As a result, preventive treatments that focus on a single mechanism of action may not meet the aspirational goal of achieving migraine freedom. Response rates for preventive migraine treatments are generally <50%, so for people who continue to experience migraine and disability after using single-agent preventives, a layered approach targeting different pathways involved in migraine pathophysiology is used in practice.[1–4] We propose that combination therapy should be considered for people with CM who have continued disability after the use of a single preventive agent, based on the availability of data supporting their use.[5] Preclinical data suggest that combination CGRP mAb and onabotulinumtoxinA treatment is likely additive and could have a combined effect greater than the sum of separate effects (i.e., synergistic), as they have distinct mechanisms of action.[6,7] Specifically, CGRP-targeted mAbs prevent sustained trigeminal firing by preventing activation of CGRP receptors on thinly myelinated Aδ-fiber nociceptors, whereas onabotulinumtoxinA reduces sustained firing of unmyelinated C-fiber nociceptors.

The 2021 American Headache Society (AHS) consensus statement[5] states that CGRP mAb treatment may be added to ≥1 established preventive treatment, based on clinical judgment, in adults who meet International Classification of Headache Disorders, 3rd edition[8] criteria for the following conditions:

1. Migraine with/without aura (4–7 monthly migraine days [MMDs]) with at least *moderate disability* (Migraine Disability Assessment ≥11 or 6-item Headache Impact Test >50) and failure of an 8-week trial of ≥2 preventive treatments with established efficacy (e.g., topiramate, divalproex sodium, beta-blocker, tricyclic antidepressant, and others).
2. Migraine with/without aura (8–14 MMDs) and failure of an 8-week trial of ≥2 established preventive treatments.
3. CM (≥15 MMDs) with any level of disability and *either* failure of an 8-week trial of ≥2 established preventive treatments *or* inadequate tolerability or response to onabotulinumtoxinA for two quarterly injections.

The risk of the drug–mAb interactions is considered to be minimal or nonexistent according to the AHS[2,5]; thus, CGRP-targeted mAbs can be added to existing preventive treatments without making other regimen changes until mAb effectiveness is determined.

The recently updated AHS consensus statement suggests that the combination of CGRP-targeted mAbs and onabotulinumtoxinA in people with migraine is probably effective.[5] If we consider the preventive treatments with the best evidence in people with CM, these include topiramate, CGRP mAbs, and onabotulinumtoxinA. In our experience, combination preventive therapy should be considered in those with continued migraine and disability on a single preventive treatment. Consistent with the AHS consensus on initiating CGRP mAbs,[5] disability occurs when patients are experiencing ≥4 MMDs and have at least moderate disability (Migraine Disability Assessment ≥11, Headache Impact Test >50) or have ≥8 MMDs. We

Abbreviations: AHS, American Headache Society; CGRP, calcitonin gene-related peptide; CM, chronic migraine; mAb, monoclonal antibody; MMD, monthly migraine day.

propose that these criteria may be an indicator when deciding to combine therapies, whether it be adding a CGRP mAb to onabotulinumtoxinA or adding an oral preventive to any other preventive therapy. However, combinations have not been evaluated in high-quality controlled trials, and topiramate use may be hindered by systemic safety concerns (e.g., teratogenicity) and tolerability issues.[3] When deciding which treatments to combine, it may be beneficial to select treatments that target different mechanisms of action and increase the potential for synergistic/additive effects; thus, combining a CGRP mAb with onabotulinumtoxinA is logical. Following the approval of CGRP mAbs, a growing population of patients with CM has initiated preventive CGRP mAb treatment without having previously received onabotulinumtoxinA. Thus, we also propose that patients with CM continuing to experience ≥15 MMDs while receiving CGRP mAbs may benefit from adding onabotulinumtoxinA.

Recently, there have been several clinical reports of adding CGRP mAbs to onabotulinumtoxinA in real-world settings (Table S1). Most of the available data reflect combining with erenumab, the first Food and Drug Administration-approved CGRP mAb (May 2018); some emerging data support combination use with more recently approved mAbs (e.g., galcanezumab and fremanezumab). Only two reports have undergone full peer review and publication,[9,10] but available data suggest that our proposed criteria for introducing combination therapy are consistent with how experts treat patients in practice. Many of these initial reports support a potential synergistic effect of combination treatment. Results of one study suggest that CGRP mAbs may serve as an effective add-on therapy for patients with CM experiencing a "wear-off" of onabotulinumtoxinA effect in the period immediately before the next onabotulinumtoxinA treatment.[10] Although few studies reported safety data, no new safety signals have been identified, and available safety profiles appear consistent with those reported for each individual treatment in clinical trials.

In conclusion, clinicians currently add CGRP mAbs to onabotulinumtoxinA, which are the only approved treatments for the prevention of CM, in their practices, and this use is now supported by the updated AHS consensus statement. Data on the safety and efficacy of combination use are limited and have not been fully peer-reviewed. However, currently available real-world data suggest that this combination is well tolerated and associated with clinically meaningful benefits, including reductions in headache frequency. Additional controlled and real-world studies are needed to improve understanding of the risks and benefits of this combination therapy in CM.

KEYWORDS

botulinum toxins type A, episodic migraine, headache, prevention

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CONFLICT OF INTEREST

Jessica Ailani, MD, has served as a consultant for AbbVie, Amgen, Axsome, Aeon, CtrlM, Eli Lilly and Company, Lundbeck, Impel, Satsuma, Theranica, Teva, GlaxoSmithKline, and Nesos; has served as a speaker for Allergan/AbbVie, Amgen, Eli Lilly and Company, Lundbeck, and Teva; has received honoraria from Medscape; and has provided editorial services to *Current Pain and Headache Reports*, NeurologyLive, and *SELF* magazine. Her institute has received clinical trial support from Allergan/AbbVie, the American Migraine Foundation, Biohaven, Eli Lilly and Company, Satsuma, and Zosano. Andrew M. Blumenfeld, MD, has served on advisory boards for AbbVie, Aeon, Amgen, Alder, Axsome, Biohaven, Revance, Lundbeck, Novartis, Teva, Supernus, Promius, Egalet, Eli Lilly and Company, and Zosano; and has received funding for speaking from AbbVie, Amgen, Pernix, Supernus, Depomed, Avanir, Promius, Teva, and Eli Lilly and Company.

AUTHOR CONTRIBUTIONS

Study concept and design: Jessica Ailani, Andrew M. Blumenfeld. *Acquisition of data*: Jessica Ailani, Andrew M. Blumenfeld. *Analysis and interpretation of data*: Jessica Ailani, Andrew M. Blumenfeld. *Drafting of the manuscript*: Jessica Ailani, Andrew M. Blumenfeld. *Revising it for intellectual content*: Jessica Ailani, Andrew M. Blumenfeld. *Final approval of the completed manuscript*: Jessica Ailani, Andrew M. Blumenfeld.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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