The Effect of Adding Calcitonin Gene-Related Peptide Monoclonal Antibodies to Onabotulinum Toxin A Therapy on Headache Burden: A Retrospective Observational Study

Seniha Ozudogru
University of Utah Hospital
Jared Bartell (jared.bartell@hsc.utah.edu)
University of Utah https://orcid.org/0000-0002-0498-0830
Heidi Yuan
University of Utah Hospital
Kathleen Digre
University of Utah Hospital
Susan Baggaley
University of Utah Hospital

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Abstract

Background

The calcitonin gene-related peptide monoclonal antibody medications represent a novel and effective group of treatment options that can be added on to existing regimens such as onabotulinum toxin A injections for the treatment of refractory chronic migraine. Mechanistically, calcitonin gene-related peptide antibodies have been shown to inhibit Aδ fibers while onabotulinum toxin A modulates C fibers. Due to the differing loci of effect and anecdotal observations, a synergistic effect between these therapies is a theoretical possibility. The aim of this study was to investigate this relationship.

Methods

Patients from the University of Utah Headache Clinic having received at least two rounds of injections of onabotulinum toxin A who responded partially but not completely to therapy were started on a calcitonin gene-related peptide antibody medication. The patients' responses to a brief headache burden questionnaire prior to their onabotulinum toxin A administration at the time of each visit were collected. Parameters we monitored included the number of headaches experienced while receiving onabotulinum toxin A therapy, the initial timing of the of the wear off period, and the number of headaches after that the wear off period began.

Results

Half of the 36 patients included in the study demonstrated an improvement in their headache burden based on at least one parameter from their questionnaire. These 18 patients reported an average increase of 2.0 additional weeks for the beneficial effects of the onabotulinum toxin A to wear off. Twelve patients reported no change in onabotulinum toxin A efficacy while 6 patients showed greater headache burden or lower onabotulinum toxin A treatment efficacy following the initiation of one of the monoclonal antibodies.

Conclusions

Our study highlights the potential of calcitonin gene-related peptide monoclonal antibodies to serve as an effective add-on therapy for chronic migraine patients receiving onabotulinum toxin A injections, especially those designated "responders" but still experiencing the drug wear off prior to the next round of injections. Larger sample sizes and more frequent at-home questionnaire data are needed to corroborate these results.

Background:

Migraine is a complex neurological disorder which is associated with significant morbidity in patients and their families.[1] The generally accepted pathophysiology is that migraine involves activation and sensitization of trigeminovascular pathways.[2] Trigeminal nerve branches, mainly the ophthalmic nerve,

but also the maxillary and mandibular nerves, innervate meningeal vasculature by primary afferent nociceptive unmyelinated C fibers and thinly myelinated Aδ fibers.[3]

Onabotulinum toxin A has been an effective treatment for chronic migraine. Even though the mechanism of effect has not been fully elucidated, in 2014 Dr. Rami Burstein and colleagues showed that onabotulinum toxin A selectively inhibits the mechanical sensitivity of C type meningeal nociceptors.[4]

An analysis of pooled PREEMPT data showed that among 688 patients who received onabotulinum toxin A, 54.2% of patients reported at least a 50% reduction after the first cycle, with an additional 11.3% and 10.3% of patients showing their first response to onabotulinum toxin A after the 2nd and 3rd cycles, respectively.[5] Onabotulinum toxin A treatment at week 24 decreased the number of headache days by 9 and the change from baseline in HIT-6 score was 5.[6] For patients with chronic migraine and almost daily headaches there is still a significant impact from headaches in their lives even with a response to onabotulinum toxin A treatment.

Onabotulinum toxin A therapy is given every 12 weeks. In our clinical experience, benefit from onabotulinum toxin A wears off between weeks 9 and 12. Three recent studies have looked at the wear-off effect of onabotulinum toxin A.[7–9] The number of rescue medications used, emergency room visits, and number of moderate to severe migraine days increased after week 8.[9]

Anti-Calcitonin Gene-Related Peptide (CGRP) monoclonal antibodies represent a new therapeutic approach to episodic and chronic migraine treatment. CGRP monoclonal antibodies are large molecules that do not cross the blood brain barrier. The trigeminovascular system is one of the sites of action of monoclonal antibodies and recently the monoclonal antibody, fremanezumab, was shown to selectively inhibit Aδ meningeal nociceptors.[10]

The mechanisms of onabotulinum toxin A and CGRP monoclonal antibodies on different nociceptors could be complementary and may show improved efficacy of combination treatment.

Methods:

This retrospective chart review received approval from the University of Utah Institutional Review Board and was conducted in accordance with the Declaration of Helsinki. Patients included in the study were those with a diagnosis of chronic migraine made by ICHD-3 criteria and queried using ICD-10 coding, received at least two onabotulinum toxin A treatments, the last of which was after June, 2018, and who were currently prescribed any available monoclonal antibody preventative treatment, namely erenumab, fremanezumab, or galcanezumab.

Onabotulinum toxin A injection notes at each visit included a pre-procedure questionnaire to determine each patient's response to treatment based on three parameters: 1. the number of headache days while the onabotulinum toxin A was in effect; 2. the number of weeks until the benefit from injections started to wear off; and 3. the number of headache days after the benefit from the injections wore off. Patient

charts were examined to determine the perceived therapeutic efficacy of onabotulinum toxin A before and after monoclonal antibody administration as defined by patients' responses to their pre-procedure questionnaires.

Patients whose diagnosis did not meet criteria for chronic migraine based on the ICHD-3 beta definition, had not received or started monoclonal antibody treatment as per chart notes, and had not provided answers to all three questions in the procedure notes were excluded.

Results:

A total of 108 patients were identified as recipients of both onabotulinum toxin A and a CGRP antibody medication. There were 36 patients who met the inclusion criteria. The majority of the patients excluded did not have pre-procedure questionnaire data for either one or both of the before and after CGRP antibody introduction time points. Each of the patients (92% female, n = 33) had been diagnosed with intractable chronic migraine. All reported at least 50% improvement in their migraine burden with onabotulinum toxin A before adding monoclonal antibody treatments. Comorbidities included depression (n = 11), anxiety (n = 9), insomnia (n = 9), autoimmune disorder (n = 3), fibromyalgia (n = 2), and concussion (n = 3).

The average chronicity of migraines was 9.91 years and all patients had been refractory to a wide range of standard migraine therapies even before the initiation of onabotulinum toxin A treatment. The average number of onabotulinum toxin A treatments patients received prior to combination treatment was 10.14 (range 2 to 24). Each patient received onabotulium toxin A from the same provider over at least 2 cycles. The duration of combination therapies ranged from 91 to 335 days and averaged 113.5 days.

Fifty percent (n = 18) of the patients included in the study demonstrated an improvement in their headache burden after the addition of a CGRP antibody medication. Improvement in headache burden was defined by the report of a more favorable value in any of the parameters elicited from the pre-procedure questionnaire. These 18 patients reported an average increase of 2.0 weeks taken for onabotulinum toxin A to wear off during combination therapies. This was supported by qualitative reports of headaches being less frequent and intense while onabotulinum toxin A was still in effect.

Of the other 18 patients who did not experience any change in any of the parameters, 6 patients reported a greater headache burden or lower onabotulinum toxin A efficacy.

Discussion:

While onabotulinum toxin A is an effective treatment for chronic migraine, many patients experience an inadequate treatment response and continue to have disabling headaches which negatively impact the quality of their lives. In our clinical experience and from studies that have looked into the wear off phenomenon, the benefits received from onabotulinum toxin A appear to fade after approximately the 8th week.[7–9]

This retrospective chart review has many limitations and potential sources of bias. Answers to the pre-procedure questionnaire were based on the patients' own recollection of events during the injection visit and were therefore subject to potential recall bias from the preceding 2–4 weeks of increased headache burden. Lastly, the study is limited by the small number of patients who met inclusion criteria for the study.

Conclusion:

Our study highlights the potential of monoclonal antibodies to serve as an effective adjunctive therapy for chronic migraine patients receiving onabotulinum toxin A injections, especially those designated "responders" but still experiencing wear off prior to the next round of injections. These results suggest the potential for CGRP monoclonal antibody medications to maintain the therapeutic benefit of onabotulinum toxin A and delay the wear off effect by an average of two weeks.

We believe that future prospective studies with larger sample sizes, more comprehensive questionnaire data, and daily headache diaries will be necessary to more definitively evaluate whether the combination of CGRP monoclonal antibody therapy with onabotulinum toxin A is safe and efficacious at improving headache burden and patients' quality of life.

Declarations

Ethics Approval and Consent to Participate:

This retrospective chart review received approval from the University of Utah Institutional Review Board and was conducted in accordance with the Declaration of Helsinki.

Consent for Publication:

Not applicable.

Availability of Data and Materials:

Not applicable.

Competing Interests:

The authors declare that they have no competing interests or financial disclosures.

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SB, KD, HY, and SO contributed to the conception, design, and analysis of the data. KD, JB, and SO contributed to drafting the manuscript and revising it. All authors contributed to and approved of the completion of the manuscript.

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