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Expert Opinion

OnabotulinumtoxinA for Chronic Migraine

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In 1992, Binder, a facial plastic surgeon in Los Angeles, first noted migraine improvement in a patient he was injecting with onabotulinumtoxinA for wrinkles. At the American Headache Society meeting in 1998, Binder and colleagues presented the first poster on onabotulinumtoxinA treatment in patients with migraine. The author of this month's expert opinion, Blumenfeld, then started to treat migraine patients at Kaiser Permanente San Diego who were high utilizers of triptans. His preliminary findings of efficacy were published in 2002,[1] which also found paradoxical cost savings, were confirmed with a larger study of 271 patients.[2]

CLINICAL HISTORY

This is a 33-year-old female with a 5-year history of chronic migraine occurring 22 days per month not responsive to prevention with topiramate, amitriptyline, and β-blockers. She has received 155 units of onabotulinumtoxinA (Botox) in a fixed pattern according to the package insert. Two and one-half months after injection, the headaches are still occurring 19 days per month.

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Questions: What is the possible mechanism of action for onabotulinumtoxinA for preventing chronic migraines? (Additional questions and responses follow)

The potential targets for onabotulinumtoxinA in chronic migraine include the following:

1. Decreasing the afferent stimulation of the trigeminal nucleus caudalis by reducing input from trigeminal and cervical dermatomes with injections around the unmyelinated sensory C fibers of the trigeminal-cervical (occipital) afferents. OnabotulinumtoxinA is able to enter these unmyelinated C fibers along their peripheral course and decrease neurochemical release (eg, CGRP) from these nerve endings.
2. Direct effect on trigeminal meningeal nociceptives via extracranial connections with intracranial structures.[3]
3. Parasympathetic effects may occur following onabotulinumtoxinA injections for chronic migraine using the standard injection paradigm[4] by two mechanisms: distant spread to cholinergic sites or, more importantly, local diffusion along deep portions of temporalis muscle to the ptyergopalatine ganglion.
4. Downregulation of sensory and parasympathetic receptors: sequential benefit in migraine treatments supports this hypothesis. This has also been hypothesized to be part of onabotulinumtoxinA's effects in overactive bladder syndromes.[5] Extracranial effects are unlikely due to lack of documented muscle overactivity as part of migraine. In addition, masseter injections have been associated

with worsening outcomes in chronic migraine. Phase 2 onabotulinumtoxinA studies suggest this. Myofascial trigger-point injections with onabotulinumtoxinA have not shown convincing evidence of benefit in studies to date.[6]

After 24 weeks and 56 weeks, what percentage of chronic migraineurs respond to treatment, and what is the percentage reduction in headache days per month from baseline?

In the PREEMPT (phase 3 research evaluating migraine prophylaxis therapy) clinical program, a responder rate of ≥50% was used to determine the proportion of patients who responded to treatment. This rate exceeds the previously suggested clinically meaningful response rate of ≥30% in patients with chronic migraine.[7]

At 24 weeks, 47.1% of onabotulinumtoxinA-treated patients in PREEMPT had a ≥50% decrease from baseline in frequency of headache days (primary endpoint) compared with 35.1% of placebo-treated patients ($P < .001$). Significance favoring onabotulinumtoxinA compared with placebo in the proportion of patients who demonstrated ≥50% decrease from baseline was also shown at week 24 for other efficacy endpoints, such as frequency of migraine days (48.2% onabotulinumtoxinA, 36.4% placebo; $P < .001$), frequency of moderate/severe headache days (49.4% onabotulinumtoxinA, 37.5% placebo; $P < .001$), and total cumulative hours of headache on headache days (50.3% onabotulinumtoxinA, 38.9% placebo; $P < .001$).[8]

After all patients were treated with onabotulinumtoxinA in the open-label phase, approximately 68% of patients treated with onabotulinumtoxinA over the entire 56-week PREEMPT study experienced at least a 50% reduction in headache days ($P = .038$) and migraine days ($P = .018$) compared with those treated with placebo (approximately 61%) in the double-blind phase.[9]

At the 2011 International Headache Society (IHS) meeting in Berlin, Dr Dodick presented a subanalysis of the pooled PREEMPT data showing that onabotulinumtoxinA (n = 688) vs placebo (n = 696) demonstrated a statistically significant between-group difference favoring onabotulinumtoxinA in the proportion of patients who had a ≥75% reduction from baseline in headache days at week 24 (22.8% onabotulinumtoxinA, 15.5% placebo; $P = .002$).[10]

How does this compare with other preventive medications for chronic migraine?

Few clinical trials investigating prophylactic treatment in chronic migraine patients exist. Here, I 5 will discuss two double-blind, placebo-controlled clinical trials in patients with chronic migraine that directly compared topiramate (labeled for the prophylaxis of migraine but not for chronic migraine) with onabotulinumtoxinA (labeled for prophylaxis of headache in patients with chronic migraine) treatment.

Topiramate was compared with onabotulinumtoxinA treatment in 60 chronic migraine patients. The response to treatment was assessed using the Physician's Global Assessment scale at months 1, 3, 6, and 9. It was determined that onabotulinumtoxinA and topiramate had comparable efficacy, with between 68% and 83% of patients in both groups reporting at least a slight (25%) improvement in migraine. In both groups, headache/migraine days decreased, and Migraine Disability Assessment (MIDAS) scores and headache impact (Headache Impact Test [HIT]-6) improved. Fewer onabotulinumtoxinA-treated patients reported adverse events that required permanent discontinuation of study treatment (2.7% for onabotulinumtoxinA vs 24.1% for topiramate).[11]

The results from the second trial of 59 chronic migraine patients[12] were comparable with the first trial.[11] Both onabotulinumtoxinA and topiramate had similar efficacy at week 12, as measured by the Physician's Global Assessment scale; 70.8% of topiramate patients improved compared with 79.2% of onabotulinumtoxinA patients. At week 12, the mean number of headache days per month decreased by 12.4 days in the topiramate group and by 13.8 days in the onabotulinumtoxinA group. Similar results were also observed for MIDAS and HIT-6. Assessments of safety and tolerability were also similar across both treatment groups.[12]

In addition, a cross-study comparison of the magnitude of clinical effect of onabotulinumtoxinA

(PREEMPT pooled results)[13] and the largest topiramate study in chronic migraine[14] reveal the following 50% responder rate in reduction of migraine days from baseline: onabotulinumtoxinA 48%, placebo 36% ($P < .001$); topiramate 37%, placebo 26% $P = .012$). Thus, the number needed to treat (NNT) based on these results is 8 for onabotulinumtoxinA compared with 12.5 for topiramate. The magnitude of response is –8.2 days for onabotulinumtoxinA, with a between-group difference of 2 days, compared with –6.4 days for topiramate, with a between-group difference of 1.7 days. The discontinuation rate was 3.8% for onabotulinumtoxinA compared with 10.9% for topiramate.

Is there a difference in the response rate and response in those with and without medication overuse?

Because medication overuse often occurs in patients with chronic migraine, PREEMPT investigated headache prophylaxis using onabotulinumtoxinA treatment in the chronic migraine subpopulation with medication overuse at baseline. Patients enrolled into either PREEMPT study were stratified a priori using a predefined algorithm based on their frequency of acute headache medication use during the 28-day baseline screening period, as "medication overuse-yes" (MedO-Yes) or "medication overuse-no".[15,16] Medication overuse occurred in 65.3% (n = 904) of the pooled patients in the intent-to-treat population.[13]

There were significant differences favoring onabotulinumtoxinA-treated patients over placebo-treated patients in the MedO-Yes subgroup for the primary efficacy measure – mean change from baseline in the frequency of headache days. Differences were significant at every visit in the double-blind phase (weeks 4, 8, 20, and 24, $P < .001$; weeks 12 and 16, $P = .001$). Among the MedO-Yes subgroup, onabotulinumtoxinA treatment was also statistically superior to placebo for all secondary variables at the week 24 primary time point except acute headache medication intakes.[17] These results are comparable with the efficacy results observed in the total PREEMPT population that included patients with and without medication overuse.[13]

How many injection cycles should be performed before a patient is deemed a nonresponder, and what is the minimum response rate for a patient to be deemed a responder?

Although there is no current recommendation, subanalysis of the PREEMPT data demonstrated that among onabotulinumtoxinA-treated patients, 49.3% had a responder rate (improvement from baseline) of ≥50% in the frequency of headache days after treatment cycle 1. Additionally, the ≥50% responder rates in onabotulinumtoxinA-treated patients for moderate/severe headache days and cumulative hours of headache on headache days were 53.0% and 54.2%, respectively, and a ≥5-point improvement in HIT-6 was found in 56.3% of patients. After treatment cycle 2, an additional 11.3-14.5% of patients who did not respond to treatment cycle 1 became responders. With a third treatment, an additional 7.4-10.3% of patients became responders.[18]

These data suggest that certain onabotulinumtoxinA-treated patients who failed to respond (≥50% improvement) in the first treatment cycle did respond in the second and/or third treatment cycles.[18]

Why might the response improve with time, and is this seen with other preventive treatments?

The PREEMPT data show sequential benefit over five treatment cycles.[9] This matches clinical observations of improved outcomes with repeated injections.

I now view onabotulinumtoxinA for chronic migraine as a series of treatments rather than an individual treatment to be assessed equally after each administration. No other prophylactic migraine medication has been as well studied as onabotulinumtoxinA for chronic migraine; the PREEMPT study involved data collection for a 4-week baseline period and then 56 weeks of treatment, and thus comparisons with other medications such as topiramate are not possible. The topiramate chronic migraine studies were 16 weeks in duration. The mechanism of onabotulinumtoxinA in migraine is unknown but may include down regulation of receptors, particularly those involved with CGRP. If down regulation is a component of the mechanism of action, this would help to explain the sequential benefit.

In the two pivotal studies, was saline a placebo or a treatment, and would saline injections alone be effective?

The saline responses seen in all the onabotulinumtoxinA studies for migraine have been robust. In the pivotal studies, there was separation from the saline response at 4 weeks and at every time point thereafter for the majority of the outcome measures during the double-blind portion of the study. The saline-treated patients did not have a nocebo response, as they had improvement from baseline. The difficulty in designing this type of study requires that the only change in the active arm be the onabotulinumtoxinA, so the same syringes, needles, and diluent (ie, normal saline) are used in the placebo arm. Unfortunately, there is no simple answer to the question of whether saline injections alone would be effective, as the study design presumes that saline is inert and the effects seen have been attributed to a placebo response. The results for acupuncture in headache disorders have been mixed. Even if the PREEMPT study is considered as a comparator study with saline injections, onabotulinumtoxinA still achieved significantly superior results.

Has 155 units been proven superior to other total doses and injection patterns?

Yes, lower- and higher-dose (up to 260 units) protocols have been tested and did not show the same efficacy. Higher-dosage treatment groups had a greater incidence of side effects, particularly neck pain and ptosis.[19,20] The PREEMPT injection paradigm reduced the incidence of these adverse events; for a review of this topic, see Blumenfeld et al.[4]

Is injection into trigger points of any benefit?

In one well-designed study, no benefit was shown, although there are numerous case reports suggesting benefit; see Ferrante et al.[6]

Is there any evidence of benefit from combined therapy with a preventive medication that either has not been tried or was not effective previously?

This has not been formally studied, as other preventive medications were not allowed as part of the PREEMPT protocol. In my experience, the effectiveness of triptans is often improved after onabotulinumtoxinA treatments. I do use adjunctive medications in chronic migraine patients, particularly to treat comorbid psychosocial issues.

Have there been any deaths from treatment with onabotulinumtoxinA for migraine either in published studies, or reported to Allergan or to the FDA?

No deaths reported on the chronic migraine studies and no cases of distant spread of toxin effect were reported in this study population.[13] The cases of distant spread were mainly noted in adolescents treated for spasticity, although there are adult cases treated with cervical dystonia dosing (mean 236 units) who have had features of distant spread.[21] 6

What is the long-term efficacy and safety of onabotulinumtoxinA?

The safety and tolerability of onabotulinumtoxinA is well established across multiple studies.[22,23] No cases of death or distant spread of toxin effect have been reported in studies of chronic migraine patients.[9,13] However, temporal muscle atrophy has been reported in this journal.[24] The PREEMPT protocol avoids this issue by injecting the temporalis behind the hairline.[4]

How often does injection site pain occur following onabotulinumA injection, at what locations, and for what duration? What treatment for the pain do you recommend? Does the pain recur with subsequent injections?

Based upon the PREEMPT data,[9] approximately 14% have injection site pain. Headache post-injection has been non-specific in my experience with no fixed pattern. Migraine can be triggered by injections. The treatment depends on the timing of the symptoms. For example, pain immediately and over the first 48 hours is most likely secondary to the needle, and possible hematoma in muscle or periosteum. If the pain starts after 72 hours, it is more likely to be a direct effect of the neurotoxin with weakness. This can occur if the incorrect sites are injected. The trapezius and cervical paraspinal muscles are the most important in this regard, as small changes in location can result in neck weakness with neck pain and headache. The frequency of these symptoms is in part related to injector technique. If the cervical paraspinals are injected too inferiorly and the trapezius muscles are injected in the inferomedial section, then neck weakness with neck pain can occur. This can be worsened

by using high doses in the incorrect sites. In PREEMPT,[9] neck pain was present 9% of the time with doses ranging from 155 to 195 u. These symptoms resolve over a few weeks in most cases. Some patients develop headache every time they are injected, and in these cases, I anecdotally use a 3-day course of decadron (12 mg on day 1, 8 mg on day 2, and 4 mg on day 3) around the injection day.

In responders, after how long should you consider stopping injections, and is there any data on the relapse rate after discontinuation?

I treat sequentially until the patient is free of headache for 6 months and then gradually wean the patient off treatment by opening up the time of the treatment cycle to 4-6 months. I am in the process of retrospectively collecting these data.

Are there other headache types that respond to onabotulinumtoxinA other than chronic migraine?

Controlled studies of onabotulinumtoxinA in tension-type headache and episodic migraine have been negative. However, there are uncontrolled studies that suggest benefit with onabotulinumtoxinA in trigeminal neuralgia,[25] cluster headache,[26] hemicrania continua,[27] occipital neuralgia,[28] new daily persistent headache,[29] and nummular headache.[30]

A number of published observations and studies address the treatment of tension-type headache with botulinum toxin.[31] The results have been mixed.[32-41]

Harden et al evaluated the efficacy of botulinum toxin type A as a prophylactic treatment for chronic tension-type headache with myofascial trigger points producing referred head pain.[42] The results did not show significant benefit for botulinum toxin type A treated patients.

Naumann et al evaluated studies that described outcomes in patients with chronic tension-type headaches randomized to botulinum toxin or placebo injections.[43] Based on the results of these studies, botulinum toxin injection was assessed as being probably ineffective for patients with chronic tension-type headaches (level B).

There have been several reports of treatment of cluster headache with botulinum toxin. The results have been mixed. The spontaneous end of an episodic cluster period regardless of treatment makes interpretation of these studies problematic. Ginies et al reported botulinum toxin type A benefit in three of five cluster patients.[44] Freund and Schwartz reported that botulinum toxin type A shortened a cluster period in two patients.[45] Robbins reported on seven patients with chronic cluster headache treated with botulinum toxin type A or type B.[46] Some beneficial effect was seen in four of the seven patients. In addition, he reported on three patients with episodic cluster headache treated with botulinum toxin, and two of the three patients had some benefit. Smuts and Barnard reported positive responses to botulinum toxin treatment in two of four cluster patients.[37]

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