Headache

Published by John Wiley & Sons, Inc.
doi: 10.1111/j.1526-4610.2011.01880.x

AMERICAN HEADACHE SOCIETY
www.AmericanHeadacheSociety.org

HEADACHE Toolbox

OnabotulinumtoxinA for the Treatment of Chronic Migraine

Chronic migraine is a common primary headache disorder that actively afflicts as many as 1 in 50 individuals and accounts for a disproportionate share of the financial cost, pain, and emotional suffering produced by migraine generally. "Chronic migraine" implies that one has an established history of migraine, has been experiencing headaches on at least 15 days of each month for at least 3 consecutive months, and the majority of those headaches each month either have had features characteristic of migraine or have been responsive to drugs which are relatively specific for migraine (examples: sumatriptan, rizatriptan, dihydroergotamine).

In October 2010 the Federal Drug Administration (FDA) approved onabotulinumtoxinA (onabotA; also commonly referred to as Botox, BotoxA, and botulinumtoxin-type A) injection therapy for the preventive treatment of chronic migraine; this established onabotA as the first (and only) therapy FDA-approved specifically for that indication. The FDA based its approval on the results from a large multicenter study, PREEMPT, that compared injections of onabotA to injections of placebo administered via a randomized, double-blind design (ie, neither the patient nor the physician investigator knew which the patient was receiving, placebo or active drug).

OnabotulinumtoxinA is a protein produced by a bacterium (*Clostridium botulinum*) that in high doses can cause diffuse muscular paralysis, inability to breathe, and death. Injected into specific muscles in tiny doses, however, onabotA has been demonstrated to be effective in treating various types of involuntary muscle contraction safely and effectively. OnabotA also is used for cosmetic purposes, relaxing facial muscles and so smoothing out facial wrinkles.

While evaluating onabotA administered for disorders involving muscle contraction, investigators discovered that the pain experienced by patients with those disorders tended to improve even before any meaningful reduction in muscle contraction occurred. In addition, patients with migraine who were receiving onabotA for cosmetic purposes frequently reported a significant improvement in their headaches following the injections. Those observations subsequently led to a series of clinical research studies designed to assess the value of onabotA therapy for headache prevention. To make a long story short, the results from those studies suggested that onabotA does not appear to be effective in

treating tension-type headache or patients with infrequent migraine attacks. The PREEMPT study, however, demonstrated onabotA to be both safe and effective for the treatment of chronic migraine.

In the PREEMPT study, between 155 and 195 units of onabotA were injected into 33 or more sites located over the forehead, temples, back of head, neck, and shoulders. The FDA has approved that same injection paradigm but recommends a fixed dose of 155 units. The entire injection procedure requires only 5 to 10 minutes, and most patients find it to be mildly uncomfortable at worst. Although it is, again, the only FDA-approved therapy for chronic migraine, insurers may require that a patient fail adequate trials of 1 or 2 oral medications commonly used for migraine prevention before authorizing coverage for onabotA.

When onabotA is administered for chronic migraine, side effects are rare. The most common side effects are bruising or swelling at the injection sites or a transient headache of mild intensity that resolves within 24 to 48 hours. On occasion patients may develop flu-like symptoms that typically resolve within a day or 2. Transient eye lid droop may occur as a side effect, and some patients may experience transient neck weakness with associated difficulty maintaining the head in an upright position. OnabotA will cause paralysis of the muscles into which it is injected, and patients may note associated smoothing of forehead wrinkles and some difficulty in voluntarily lifting the eyebrows; when present, these particular effects tend to vanish within 3 to 4 months.

In patients whose headaches diminish following initial onabotA injection therapy, the clinical improvement may not be apparent for 1 to 2 weeks following the procedure. Following the initial treatment, any improvement that occurs tends to persist for a period ranging from 2 weeks to 2 months or more. With subsequent treatments (typically administered every 3 months) some patients experience progressively greater and longer-lasting improvement in their headaches, with that improvement persisting for 4 to 6 months or longer.

Preliminary results indicate that when administered over a period of 2 years or more, onabotA is safe and continues to be effective in suppressing chronic migraine. Even better, a proportion of patients who respond to onabotA eventually may be able to cease injection therapy altogether and subsequently experience no increase in their headaches.

Injection of onabotA for migraine prevention is a short, simple procedure that is performed in the clinic or office, and it is extremely unusual for a patient to suffer any significant side effects following the treatment; patients typically are able to drive and otherwise function normally immediately after the injections. Because its effects on a developing fetus are unknown, women who are pregnant or intend soon to become pregnant should not receive onabotA. It is not yet known whether onabotA is safe and effective for patients under the age of 18.

In summary, onabotA appears to be a safe and effective therapy for many patients with chronic migraine, a common headache disorder which heretofore has proven to be notoriously refractory to treatment.

John F. Rothrock, MD
Editor-in-Chief, *Headache*
University of Alabama School of Medicine,
Birmingham, AL, USA