

Aurora S, Winner P, et al. Onabotulinumtoxin A for treatment of Chronic Migraine: Pooled Analysis of the 56-Week PREEMPT Clinical Program. Headache 2011;51:1358-1373.

Design: Randomized clinical trial followed by open-label study

Population/sample size/setting:

- 1384 patients (1198 women, 186 men, mean age 41) treated for migraine at 122 sites in 6 countries (Canada, Croatia, Germany, Switzerland, UK, and USA)
- Eligible participants were age 18 to 65 with chronic migraine
 - o Defined by 2004 International Classification of Headache Disorders (ICHD-II) criteria with the exception of “complicated migraine,” i.e., hemiplegic, basilar-type, ophthalmoplegic migraine, or migrainous infarction
 - o Headache occurred at least 15 days per month for each episode lasting at least 4 hours
- Exclusion criteria were any medical condition which would increase the risk of receiving onabotulinumtoxin A (BTX), diagnosis of any other primary or secondary headache disorder, use of any headache prophylactic medication in past 28 days, Beck Depression Inventory score >24, or previous exposure to any BTX serotype

Main outcome measures:

- All patients completed a 28-day baseline screening period
- The drug study was done in two phases: a 24 week double-blind phase and a 32 week open label phase
- During the double-blind phase, patients were randomized to BTX-A (n=688) or to placebo (n=696)
 - o Patients were stratified on whether or not they overused headache medication during the 28-day baseline, defined as taking simple analgesics on 15 or more days, or combination medications for 10 days or more
 - o BTX was administered at a dose of 155 U in fixed-site, fixed-dose injections, with 5 U at each of 31 sites in s head and neck muscle areas
 - o Injections were given at weeks 0, 12, 24, 36, and 48
 - o At the investigator’s discretion, an additional 40 U of BTX could be administered among 3 muscle groups, so that up to 195 U of BTX could be dosed during one treatment cycle
- 88.2% of BTX patients and 90.4% of placebo patients completed the 24-week double-blind phase of the study; 74.6% of BTX and 70.7% of placebo patients completed all 56 weeks of the study
- Primary outcome measure was the change in frequency of headache days per month at the end of the 24-week double blind phase of the study
 - o Mean frequency at baseline was 19.9 days/mo for BTX and 19.8 for placebo

- At 24 weeks, mean decrease in frequency was 8.4 days/mo for BTX and 6.6 days/mo for placebo, for a difference of 1.8 days/mo (95% confidence interval 1.13 to 2.52) in favor of BTX
- Numerous secondary outcomes were measured, one of which was the group difference in frequency of headache at 56 weeks, which was at the end of the 32-week open label phase in which all participants had BTX injections every 12 weeks
 - The group which had BTX during both the double-blind and the open-label phase had an advantage at the 56 week evaluation over the group which received placebo injections for 24 weeks and then BTX during the open-label phase
 - The BTX-BTX group had a decrease in headache frequency of 11.7 days/mo, and the placebo-BTX group had a decrease of 10.8 days/mo, for a group difference of 0.9 days/mo (95% CI, 0.14 to 1.53 days/mo)
- Another secondary outcome was the Headache Impact Test-6 (HIT-6), a measure of quality of life in relation to headache symptoms
 - At baseline, HIT-6 was severe in 93.5% of BTX patients and in 92.7% of placebo patients
 - At 24 weeks, HIT-6 was severe in 67.6% of BTX patients and in 78.2% of placebo patients; the 10.6% difference had a confidence interval from 5.9% to 15.2%
- The groups did not differ in change from baseline in frequency of acute headache medication intakes; the decline was 10.1% in the BTX and 9.4% in the placebo group
- Adverse effects were reported in the double-blind phase in 4.8% of BTX patients and 2.3% of placebo patients; neck pain and muscular weakness (facial paresis, eyelid ptosis, and muscle tightness) were rated as mild to moderate in severity
 - Over the 56-week course of the study, the rate of adverse events decreased with subsequent BTX injections

Authors' conclusions:

- BTX is a safe and effective long-term prophylaxis for chronic migraine
- Although the placebo response was high, the advantage of BTX was apparent across a variety of outcome measures
- Physical changes in the forehead of patients with BTX may have compromised blinding, but the doses used in the glabellar region were lower than the dose approved for cosmetic purposes

Comments:

- The current study is a pooled analyses of two separate licensing studies for FDA approval of BTX for chronic migraine: PREEMPT-1 (Aurora 2010) and PREEMPT-2 (Diener 2010)
- The enrollment criteria were the same in the two studies; PREEMPT-1 began on January 23,2006 and PREEMPT-2 on February 7,2006

- The primary endpoint in the PREEMPT-1 protocol (clinicaltrials.gov #NCT00156910) was frequency of headache episodes in the 24-week double blind phase
 - o This endpoint did not differ significantly from placebo, but the number of headache days did differ in favor of BTX when PREEMPT-1 ended on 7-76-2008
- PREEMPT-2 had the same primary outcome in its initial protocol (clinicaltrials.gov #NCT00168428) filed on 5-7-2007, but the primary outcome was changed on 9-29-2008 to number of headache days; PREEMPT-2 ended on 8-11-2008
- It appears that the primary outcome for PREEMPT-2 was changed after the same primary outcome was known for PREEMPT-1, and the “significantly different” outcome for PREEMPT-1 was substituted as the primary outcome of PREEMPT-2
- Although the substitution may have been done before the PREEMPT-2 data analyses were done, it may have been motivated by the results of PREEMPT-1
- The studies were large, and the “statistically significant” advantage of BTX over placebo (1.8 days/mo) may be of modest clinical significance
- It is difficult to judge how the injection dose and placement differ from that of BTX for cosmetic purposes, since the reader of PREEMPT-2 is referred to other studies (Mathew 2005 and Silberstein 2005), which were studies of BTX for chronic headache, and neither reported BTX significantly different from placebo
 - o Mathew 2005 injected 25 to 40 U of BTX into the frontal/glabellar muscles; Silberstein 2005 tested three different BTX doses (75, 150, and 225 U), with the 150 U dose (closest to the dose in PREEMPT) administering 20 U into 4 sites of the frontalis and 10 U at 2 sites of the corrugator
 - o The dose of BTX in Allergan’s package insert is 8 U in each corrugator and 4 U in the procerus for a total of 20 U
 - o It appears that PREEMPT may have been administering BTX in doses and locations similar to those used in cosmetic applications
 - o Therefore, there is a real possibility that blinding was compromised by the effect on the facial muscles
 - o Since there is no report of success of blinding (percent of patients in BTX and placebo groups who successfully guessed their treatment), an important source of bias was not adequately controlled
 - o Mathew 2005 did ask patients to guess their treatment assignment, and reported that after the first dose, 70% of patients correctly guessed their treatment
- Table 1 reports that 64.8% of BTX and 66.1% of placebo patients had overuse of acute headache medication at baseline
 - o The definition of chronic migraine was stated to be that of ICHD-II
 - o ICHD-II defines chronic migraine with primary headache disorders (1.5.1) as 15 or more days per month of migraine headache, but

excludes patients with medication overuse unless the headache pattern persists 2 months after medication has been withdrawn; otherwise, the diagnosis is medication overuse headache, which is classified with the secondary headache disorders (8.2)

- There is no separate reporting of results for the patients with and without medication overuse
- It is likely that 2/3 of the participants did not meet the ICHD-II definition of a primary headache disorder of chronic migraine, and may have had a different diagnosis
- In both PREEMPT-1 and PREEMPT-2, about 60-65% of patients at baseline had previously used one or more headache prophylaxis medications; this suggests that 35-40% had not used previous prophylactic medication, and an adequate trial of less invasive and expensive interventions had not been done
- The cumulative problems of a small effect size, potential compromise of blinding, and dubious enrollment of patients without separate reporting for medication overuse patients, collectively weaken the quality of the study results

Assessment: Inadequate for evidence that BTX is effective in the prophylaxis of chronic migraine

References:

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