Headache
© 2020 The Authors. *Headache: The Journal of Head and Face Pain* published by Wiley Periodicals LLC on behalf of American Headache Society
ISSN 0017-8748
doi: 10.1111/head.13996
Published by Wiley Periodicals, LLC.

Letter to the Editor

Response to "Modifications to the PREEMPT Protocol for OnabotulinumtoxinA Injections for Chronic Migraine in Clinical Practice"

The recent article "Modifications to the PREEMPT protocol for onabotulinumtoxinA injections for chronic migraine in clinical practice" by Begasse de Dhaem et al and published in *Headache*[1] reports findings from an online, anonymous survey of headache medicine clinicians in the United States on the use of the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) protocol of onabotulinumtoxinA injections for migraine prevention. The authors conclude that over two-thirds of surveyed clinicians are altering the PREEMPT protocol, which calls into question the standardized nature of the protocol and suggests the creation of evidence-based advisory statements to discuss the protocol rationale.[1] We thank the authors for highlighting this important issue but believe that further clarification is needed about the evidence-based guidance and follow-the-pain strategy described in previous PREEMPT injection protocol publications in *Headache*.[2,3]

The authors report that 141/182 (78%) clinicians who responded to the survey (out of 878 contacted) reported not always following the PREEMPT protocol. Modifications were primarily in the number of injections (70%) and the total volume injected (63%), with the rationale for these changes stated as a need to adapt to the patient's pain, anatomy, and preferences. While these findings are characterized by the study authors as deviations, they were actually performed in accordance with the original study protocol from the pivotal PREEMPT clinical trials.[4,5] In both PREEMPT studies, the clinician was given the discretion to inject up to 40 additional units of onabotulinumtoxinA (maximum of 195 U) with the administration in up to 8 additional sites (maximum of 39) to maximize treatment benefits.[4,5] Although the target dose in the PREEMPT trials was 155 U,[4-6] the trials were designed to allow clinicians the ability to adapt practice and maximize treatment benefits, and therefore approximately 40% of patients received a higher dose during treatment cycles. Additionally, in the Begasse de Dhaem et al study, there may have been confusion between the US label and PREEMPT protocol. The US label specifies 155 U at 31 injection sites,[7] while other labels are more consistent with the PREEMPT protocol recommendations and allow up to 195 U and 39 injection sites.[8,9]

In 2 prior publications on the PREEMPT injection paradigm,[2,3] we outlined the follow-the-pain injection approach to provide clinicians a guide to individualize treatment and maximize the benefits of onabotulinumtoxinA treatment. In the present study,[1] 36% of respondents indicated that they increased the number and sites of injections specifically based on follow-the-pain, which is in line with PREEMPT protocol

[Corrections added on November 20, 2020, after first online publication: the copyright has been changed.]

Conflict of Interest: Andrew M. Blumenfeld, MD: Has served on advisory boards for AbbVie, Amgen, Alder, Teva, Supernus, Promius, Eaglet, and Lilly; and has received funding for speaking from AbbVie, Amgen, Pernix, Supernus, Depomed, Avanir, Promius, Teva, and Eli Lilly and Company. Stephen D. Silberstein, MD: Consultant and/or advisory panel member for and has received honoraria from Alder Biopharmaceuticals, AbbVie, Amgen, Avanir, eNeura, ElectroCore Medical, Labrys Biologics, Medscape, Medtronic, Neuralieve, NINDS, Pfizer, and Teva. His employer receives research support from AbbVie, Amgen, Cumberland Pharmaceuticals, ElectroCore Medical, Labrys Biologics, Eli Lilly, Mars, and Troy Healthcare.

recommendations. We strongly support that clinicians use their judgment and adapt the protocol to best fit the needs and individual anatomy of their patients. Furthermore, over three-quarters of the respondents to this survey indicated that they had at least 3 years' experience with onabotulinumtoxinA injections.[1] We are encouraged to see that these experienced clinicians are following the evidence-based recommendations and are comfortable using their judgment to adapt the dose and number of injection sites to fit the needs of their patients. Rather than describing these as deviations, we believe that these results show that experienced clinicians are following the pain of their patients and, therefore, utilizing the PREEMPT injection protocol.

In the Discussion of their article, the authors suggest that the reduced clinician adherence to the PREEMPT protocol is because the rationale for a standardized approach is perceived as arbitrary, and the authors further suggest that published evidence supporting this approach is lacking.[1] However, the protocol used in the PREEMPT trials was based on evidence from multiple clinical studies in episodic migraine,[10] tension-type headache,[11] and phase 2 trials in chronic daily headache.[2,12] Specifically, these phase 2, exploratory, randomized, placebo-controlled trials recruited over 1000 patients, and provided critical insights into the optimal dose and injection protocol for onabotulinumtoxinA.[2,12,13] The protocol was then validated in the 2 randomized, placebo-controlled PREEMPT clinical trials to establish the efficacy and safety of onabotulinumtoxinA for adults with chronic migraine.[4-6,14] Since the publication of these 2 pivotal trials in chronic migraine, the efficacy, safety, and patient-reported satisfaction of the PREEMPT paradigm have been validated and substantiated in the 2-year COMPEL trial,[15] head-to-head FORWARD study,[16] and real-world REPOSE and CM-PASS trials.[17-19] These results demonstrate more than 10 years of robust efficacy, safety, and clinical and real-world effectiveness data supporting the use of onabotulinumtoxinA for the treatment of chronic migraine using the PREEMPT protocol. Although the authors pose the question "whether evidence-based advisory statements might be more helpful than a proscriptive protocol,"[1] we suggest that, in contrast, there is robust evidence to support the PREEMPT protocol and its specific instructions and flexibility in dosing and injection sites that allow clinicians to use their judgment and tailor treatment to their individual patients.

Finally, it is also important to clarify that the injection sites were not determined arbitrarily but were based on the understanding of the underlying mechanisms of action of onabotulinumtoxinA for chronic migraine. Specifically, neurons with sensory nerve endings with cell bodies located in trigeminal and cervical ganglia are distributed throughout the 7 injected muscles in the head and neck.[20] By inhibiting these sensory nerve endings, the mechanism of action for onabotulinumtoxinA in migraine is consistent with a reduction in the number of pain signals that travel along sensory nerves from the dura to the spinal trigeminal nucleus, which then indirectly prevents the development of hyperexcitability of spinal, brainstem, thalamic, and cortical neurons implicated in migraine pathophysiology.[20] This mechanism of action has been demonstrated in a preclinical model of migraine.[20-22]

In conclusion, we appreciate the publication of this important article. We support the approach that clinicians are using a validated, evidence-based, individualized approach to maximize the treatment benefits of onabotulinumtoxinA for their patients with chronic migraine. We encourage readers to review all of the published literature on the PREEMPT injection protocol and use their judgment to determine the best approach for each individual patient.

Andrew M. Blumenfeld, MD;
Stephen D. Silberstein, MD
The Headache Center of Southern California, The Neurology Center, Carlsbad, CA, USA (A.M. Blumenfeld); Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA (S.D. Silberstein)

REFERENCES

1. Begasse de Dhaem O, Gharedaghi MH, Rizzoli P. Modifications to the PREEMPT protocol for onabotulinumtoxinA injections for chronic migraine in clinical practice. *Headache*. 2020 Apr 25. doi:10.1111/head.13823. [Epub ahead of print]

2. Blumenfeld A, Silberstein SD, Dodick DW, Aurora SK, Turkel CC, Binder WJ. Method of injection of onabotulinumtoxinA for chronic migraine: A safe, well-tolerated, and effective treatment paradigm based on the PREEMPT clinical program. *Headache*. 2010;50:1406-1418.
3. Blumenfeld AM, Silberstein SD, Dodick DW, Aurora SK, Brin MF, Binder WJ. Insights into the functional anatomy behind the PREEMPT injection paradigm: Guidance on achieving optimal outcomes. *Headache*. 2017;57:766-777.
4. Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia*. 2010;30:793-803.
5. Diener HC, Dodick DW, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia*. 2010;30:804-814.
6. Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: Pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache*. 2010;50:921-936.
7. *Botox [package insert]*. Irvine, CA: Allergan, Inc.; 2019.
8. *Botox [summary of product characteristics]*. Marlow, Bucks, United Kingdom: Allergan Ltd.; 2017.
9. *Botox Australia [package insert]*. Gordon, NSW, Australia: Allergan Australia Pty Ltd; 2017.
10. Aurora SK, Gawel M, Brandes JL, Pokta S, Vandenburgh AM. Botulinum toxin type a prophylactic treatment of episodic migraine: A randomized, double-blind, placebo-controlled exploratory study. *Headache*. 2007;47:486-499.
11. Silberstein SD, Göbel H, Jensen R, et al. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: A multicentre, double-blind, randomized, placebo-controlled, parallel-group study. *Cephalalgia*. 2006;26:790-800.
12. Silberstein SD, Stark SR, Lucas SM, Christie SN, Degryse RE, Turkel CC. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: A randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc*. 2005;80:1126-1137.
13. Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C. Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: A randomized, double-blind, placebo-controlled trial. *Headache*. 2005;45:293-307.
14. Matharu M, Halker R, Pozo-Rosich P, DeGryse R, Manack Adams A, Aurora SK. The impact of onabotulinumtoxinA on severe headache days: PREEMPT 56-week pooled analysis. *J Headache Pain*. 2017;18:78.
15. Blumenfeld AM, Stark RJ, Freeman MC, Orejudos A, Manack Adams A. Long-term study of the efficacy and safety of OnabotulinumtoxinA for the prevention of chronic migraine: COMPEL study. *J Headache Pain*. 2018;19:13.
16. Rothrock JF, Manack Adams A, Lipton RB, et al. FORWARD study: Evaluating the comparative effectiveness of onabotulinumtoxinA and topiramate for headache prevention in adults with chronic migraine. *Headache*. 2019;59:1700-1713.
17. Ahmed F, Gaul C, Garcia-Monco JC, Sommer K, Martelletti P. An open-label prospective study of the real-life use of onabotulinumtoxinA for the treatment of chronic migraine: The REPOSE study. *J Headache Pain*. 2019;20:26.
18. Frampton JE, Silberstein S. OnabotulinumtoxinA: A review in the prevention of chronic migraine. *Drugs*. 2018;78:589-600.
19. Matharu M, Pascual J, Nilsson Remahl I, et al. Utilization and safety of onabotulinumtoxinA for the prophylactic treatment of chronic migraine from an observational study in Europe. *Cephalalgia*. 2017;37:1384-1397.
20. Burstein R, Blumenfeld AM, Silberstein SD, Manack Adams A, Brin MF. Mechanism of action of onabotulinumtoxinA in chronic migraine: A narrative review. *Headache*. 2020;60:1259-1272.
21. Melo-Carrillo A, Strassman AM, Schain AJ, et al. Exploring the effects of extracranial injections of botulinum toxin type A on prolonged intracranial meningeal nociceptors responses to cortical spreading depression in female rats. *Cephalalgia*. 2019;39:1358-1365.
22. Burstein R, Zhang X, Levy D, Aoki KR, Brin MF. Selective inhibition of meningeal nociceptors by botulinum neurotoxin type A: Therapeutic implications for migraine and other pains. *Cephalalgia*. 2014;34:853-869.