LETTER TO THE EDITOR

Reply: OnabotulinumtoxinA should be considered in medication overuse withdrawal in patients with chronic migraine

Judith A. Pijpers, Michel D. Ferrari and Gisela M. Terwindt

Department of Neurology, Leiden University Medical Centre (LUMC), Leiden, The Netherlands

Correspondence to: Gisela M. Terwindt
Department of Neurology, Leiden University Medical Centre (LUMC), Leiden, The Netherlands
E-mail: g.m.terwindt@lumc.nl

Sir,

We thank Prof. Dressler for his interest in our study and his honesty to report that he is shareholder of Allergan, the manufacturer of the drug tested in our trial, and that he holds patents on botulinum toxin and botulinum toxin therapy (Dressler, 2019).

His letter offers us the opportunity to correct some misconceptions with respect to the perceived efficacy of botulinum toxin A (BTA) in chronic migraine with medication overuse (CM + MO). It also enables us to correct some apparent misunderstandings with respect to the study design and to present new additional evidence, further supporting the conclusion that BTA does not afford any additional clinical benefit over withdrawal in patients with CM + MO.

Professor Dressler suggests that BTA is an effective treatment for chronic migraine. We would like to put this claim into perspective. While statistically significant, the greater reduction in headache days with BTA versus placebo was clinically hardly relevant: 1.8 days from 19.9 days at baseline (10%) (Aurora et al., 2010; Diener et al., 2010; Dodick et al., 2010; May and Schulte, 2016). Moreover, unblinding due to BTA-induced removal of facial wrinkling might well have biased outcome. Up to 90% of participants had correctly guessed their treatment in similar trials, mainly because of the cosmetic effect (Australian Government, 2011; Wollmer et al., 2012). In a recent Cochrane review, the efficacy of BTA was disputed because of the large and unexplained heterogeneity in the studies (Herd et al., 2018).

To avoid unblinding, we administered 17.5 units of BTA in the forehead of participants in the placebo group. This is very low compared to the 155 units used in the PREEMPT studies (Aurora et al., 2010; Diener et al., 2010). We are not aware of any published evidence that such low doses may afford clinically relevant improvement. In fact, 17.5 units is significantly lower than the lowest dose ever reported for headache (Jackson et al., 2012; Herd et al., 2018), psychiatric disorders (Wollmer et al., 2012), peripheral neuropathy (Attal et al., 2016), or regular cosmetic purposes (Durand et al., 2016). In animal studies, low doses were clearly less effective (Zhang et al., 2016) or not effective at all (Antonucci et al., 2008; Lawrence et al., 2012) on putative therapeutic modes of action. In conclusion, there is no evidence that seven injections with in total 17.5 units BTA in the forehead might have caused a clinically relevant reduction in headache days. Moreover, if such low doses were indeed effective, why then should we continue to treat patients with 31 injections totalling a 9-fold higher dose?

In his letter, Professor Dressler seems also mistaken with the study design and patient number. To clarify, all 179 participants were advised to stop all headache medication and were randomly allocated (1:1) to receive BTA (n = 90; 31 injections; in total 155 units) or placebo (n = 89; seven injections with a total of 17.5 units BTA in the forehead and 24 injections with saline elsewhere). Importantly, blinding was well kept. BTA did not afford any additional clinical benefit over withdrawal alone (Pijpers et al., 2019).

The effect of withdrawal in our study was similar to that in other studies, showing similar proportions of patients reverting from chronic to episodic headache (Rossi et al., 2006; Munksgaard et al., 2012) or with at least 50% reduction in headache days (Zeeberg et al., 2006; Rossi et al., 2011; Munksgaard et al., 2012). In a recent randomized,
controlled, clinical trial, patients with mainly CM + MO had 6.7 fewer migraine days after withdrawal (Carlsen et al., 2018). In a recent review, it was recommended to implement withdrawal in the care of patients with CM + MO (Diener et al., 2019). In summary, withdrawal is now recognized as a highly cost-effective therapy (Jellestad et al., 2019) leading to substantial reduction of headache days in most patients (Munksgaard et al., 2012; Pijpers et al., 2016; Carlsen et al., 2018; Diener et al., 2019; Jellestad et al., 2019).

Data availability

The trial is registered at the Netherlands trial registry, #3440, www.trialregister.nl. The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Support from the Netherlands Organisation for Scientific Research (NWO), VIDI 91711319 and the Dutch Brain Foundation for the submitted work. No author has financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. No other relationships or activities that could appear to have influenced the submitted work.

References

Antonucci F, Rossi C, Gianfranceschi L, Rossetto O, Caleo M. Long-distance retrograde effects of botulinum neurotoxin A. J Neurosci 2008; 28: 3689–96.
Atal N, de Andrade DC, Adam F, Ranoux D, Teixeira MJ, Galhardoni R, et al. Safety and efficacy of repeated injections of botulinum toxin A in peripheral neuropathic pain (BOTNEP): A randomised, double-blind, placebo-controlled trial. Lancet Neurol 2016; 15: 555–65.
Aurora SK, Dodick DW, Turkel CC, DeGryse RE, Silberstein SD, Lipton RB, 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: 804–14.
Australian Government. Australian Public Assessment Report for Botulinum toxin Type A Proprietary Product Name: Botox [Internet]. 2011. Available from: https://www.tga.gov.au/sites/default/files/auspar-botox.pdf.
Carlsen LN, Munksgaard SB, Jensen RH, Bendsen L. Complete detoxification is the most effective treatment of medication-overuse headache: a randomized controlled open-label trial. Cephalalgia 2018; 38: 225–36.
Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGryse RE, Lipton RB, 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: 804–14.

diener H-C, Dodick D, Evers S, Holle D, Jensen RH, Lipton RB, et al. Pathophysiology, prevention, and treatment of medication overuse headache. Lancet Neurol 2019; 4422: 1–12.
Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache J Head Face Pain 2010; 50: 921–36.
Dressler D. OnabotulinumtoxinA should be considered in medication overuse withdrawal in patients with chronic migraine. Brain 2020; 143: e5.
Durand PD, Couto RA, Isakov R, Yoo DB, Azizzadeh B, Guyuron B, et al. Botulinum toxin and muscle atrophy: a wanted or unwanted effect. Aesthetic Surg J 2016; 36: 482–7.
Herd CP, Tomlinson CL, Rick C, Scotton WJ, Edwards J, Ives N, et al. Botulinum toxins for the prevention of migraine in adults. Cochrane Syst Rev 2018; 6: CD011616.
Jackson JL, Kuriyama A, Hayashino Y, et al. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. JAMA 2012; 307: 1736–45.
Jellestad PL, Carlsen LN, Westergaard ML, Munksgaard SB, Bendsen L, Lainez M, et al. Economic benefits of treating medication-overuse headache–results from the multicenter COMOESTAS project. Cephalalgia 2019; 39: 274–85.
Lawrence GW, Osypeian S V., Wang J, Aoki KR, Dolly JO. Extravesicular intraneuronal migration of internalized botulinum neurotoxins without detectable inhibition of distal neurotransmission. Biochem J 2012; 441: 443–452.
May A, Schulte LH. Chronic migraine: risk factors, mechanisms and treatment. Nat Rev Neurol 2016; 12: 455–64.
Munksgaard SB, Bendsen L, Jensen RH. Detoxification of medication-overuse headache by a multidisciplinary treatment programme is highly effective: a comparison of two consecutive treatment methods in an open-label design. Cephalalgia 2012; 32: 834–44.
Pijpers JA, Kies DA, Louter MA, van Zwet EW, Ferrari MD, Terwindt GM. Acute withdrawal and botulinum toxin A in chronic migraine with medication overuse: a double-blind randomized controlled trial Brain 2019; 142: 1203–14.
Pijpers JA, Louter MA, De Bruin ME, Van Zwet EW, Zitman FG, Ferrari MD, et al. Detoxification in medication-overuse headache, a retrospective controlled follow-up study: does care by a headache nurse lead to cure? Cephalalgia 2016; 36: 122–30.
Rossi P, Di Lorenzo C, Faroni J, Cesarino F, Nappi G. Advice alone vs. structured detoxification programmes for medication overuse headache: a prospective, randomised, open-label trial in transformed migraine patients with low medical needs. Cephalalgia 2006; 26: 1097–105.
Rossi P, Faroni JV., Nappi G. Short-term effectiveness of simple advice as a withdrawal strategy in simple and complicated medication overuse headache. Eur J Neurol 2011; 18: 396–401.
Wollmer MA, De Boer C, Kalak N, Beck J, Götz T, Schmidt T, et al. Facing depression with botulinum toxin: a randomized controlled trial. J Psychiatr Res 2012; 46: 574–81.
Zeeberg P, Olesen J, Jensen R. Discontinuation of medication overuse in headache patients: recovery of therapeutic responsiveness. Cephalalgia 2006; 26: 1192–8.
Zhang X, Strassman AM, Novack V, Brin MF, Burstein R. Extracranial injections of botulinum neurotoxin type A inhibit intracranial meningeal nociceptors responses to stimulation of TRPV1 and TRPA1 channels: are we getting closer to solving this puzzle? Cephalalgia 2016; 36: 875–86.