Neurol Sci (2015) 36 (Suppl 1):S33–S35
DOI 10.1007/s10072-015-2140-2

Onabotulinum toxin A (Botox) for chronic migraine treatment: an Italian experience

L. Grazzi · S. Usai

Abstract Chronic migraine is a common and debilitating headache syndrome. Botulinum neurotoxin, a potent toxin produced by the anaerobic bacterium clostridium botulinum, used largely for treatment of disorders associated with increased muscle tone and hyperhidrosis, is used for patients suffering from chronic migraine. In this study, a group of patients suffering from chronic migraine with medication overuse was treated with onabotulinum toxin A (Botox) to verify its efficacy for chronic migraine. The results confirmed the efficacy of onabotulinum toxin A (Botox) when used at the dosage of 155 UI according to the PREEMPT protocol. Although these results are preliminary, they led to intense efforts to evaluate the analgesic properties of onabotulinum toxin A (Botox) and to assess its use in clinical practice, in particular in migraine field.

Keywords Onabotulinum toxin A (Botox) · Chronic migraine (CM) with medication overuse (MO) · PREEMPT study

Introduction

Chronic migraine (CM) is a disabling syndrome which involves 2/3 % of the general population [1] with >15 or more days per month for >3 months, and often associated with medication overuse (MO). This category of patients is problematic and difficult to treat and only partial benefit is obtained from oral preventive medications.

L. Grazzi (✉) · S. Usai
Headache Center, Neurological Institute "C. Besta",
Via Celoria, 11, 20133 Milan, Italy
e-mail: grazzi.l@istituto-besta.it

Nowadays, onabotulinum toxin A (Botox) is considered an effective alternative to manage this condition as already evidenced by the PREEMPT study and other clinical experiences [2–4].

The rationale of the potent analgesic effect of the toxin is based on the results from animal and human studies indicating that Botox inhibits the release of nociceptive mediators as CGRP, glutamate and substance P. Blocking the release of these neurotransmitters inhibits neurogenic inflammation and consequently the peripheral sensitization of nociceptive nerve fibers. As a result, peripheral pain signals to the central nervous system are reduced and central sensitization is blocked [5–7].

The PREEMPT study confirmed the efficacy of Botox [2, 3] to reduce significantly days of headache per month and medication intake per month after 1 year of treatment. Moreover, HIT-6 values decreased too [2–4].

Concerning tolerability and safety of the treatment, the study confirmed low incidence of adverse events during the course of treatment and a good tolerability [2–4].

A shift from overuse to non overuse was observed after treatment in a significant proportion of patients [8].

The use of Botox for chronic migraine in Italy was indicated 2 years ago (January 2013) with the possibility of reimbursement for adults patients with a specific diagnosis of CM according to IHS criteria [9], and patients intolerant or unresponsive to pharmacological treatments.

Encouraged by preceding clinical experiences, Botox has been used to treat patients referring to our headache center, suffering from CM with MO, according to the PREEMPT study protocol schedule.

Aim of this study was to evaluate a group of patients treated with 155 UI of Botox to verify its efficacy for chronic migraine treatment.

Methods

A group of 75 adults patients suffering from CM with MO (diagnosis made according to the IHS criteria) [9] was studied.

Patients were treated by a withdrawal protocol in a day hospital regimen for 5 days to stop the overuse of symptomatic medications. After that, patients were treated by Botox injections, in multiple sites, according to the protocol of the PREEMPT study, at the dosage of 155 UI for 31 sites. Every session of local injection (155 UI per 31 sites; 5 UI per each site) was repeated every 3 months for a period of 1 year. Totally five injections of Botox were performed.

Clinical indexes as number of medication intake per month and days of headache per month, were recorded using an headache daily diary.

Questionnaires for disability and quality of life (MIDAS; HIT-6) were also performed at every session of treatment.

Forty-six patients achieved the 3rd session of treatment and 20 patients completed the period of treatment of 1 year with the five injections schedule.

Results

Data concerning the group of 46 patients who completed the 3rd session of treatment evidenced that days of headache/month decreased significantly during the period of treatment from the first to the third session of therapy, (pre 21.7 ± 6.8 post 15.6 ± 8.7 $p < 0.005$). Also medication intake decreased significantly (pre 20.3 ± 67.5 post 14.3 ± 8.4 $p < 0.0005$). The group of 20 patients who completed the treatment showed a significant decrease of number of migraine days per month and a decrease, although not significant, of medication intake per month (22.4 ± 6.5 vs 13.8 ± 7.4; 20.7 ± 7.2 vs 16.4 ± 18.6, respectively). MIDAS total score decreased significantly after treatment (63.1 ± 50.1 vs 31.4 ± 34.1); HIT-6 values decreased, but not significantly (65.4 ± 7.5 vs 59.9 ± 9.3).

Discussion

CM is a serious clinical condition for patients, very disabled and at risk of medication overuse; the partial response to treatment is so common for this category of patients, that the possibility to use new therapeutic options is crucial.

In the past decade, data from different studies were not conclusive about efficacy of Botox for CM, due to the erroneous selection of patients. On the other side, the most recent clinical trials have shown more positive results as more selective criteria for inclusion of patients were used.

The selection of patients is the key to the successful use of Botox in chronic migraine management [10].

Our results are preliminary, but they led to intense efforts to evaluate analgesic properties of Botox and to assess its clinical applicability and efficacy in a limited, but homogeneous group of patients.

The pharmacological profile of Botox makes it a good candidate for migraine prevention at the adequate dosage as proposed in the PREEMPT study. Its long duration of action (3 months) makes it particularly attractive for patients who are not compliant with the daily use of preventive medications, or if they cannot tolerate them or when they are refractory to preventive medications.

Although we did not assess it specifically, patients did not report any adverse event and the treatment was well tolerated. Patients did not miss any appointment and they did not ask for any supplemental visit between the sessions.

The problem concerning the cost of this innovative treatment was not evaluated specifically, even if a lower medication intake and a lower number of neurological visits in emergency departments were observed: these can be indexes of a decrease in medical costs as reported by Rothrock et al. [11] in a recent study.

In conclusion, data from recent studies show encouraging results: Botox seems to be effective for patients with CM, in particular the long duration of action and favorable adverse events make it a suitable therapeutic alternative for those patients not compliant with oral preventive medications. The application of Botox can be also indicated in the early stage of the disease and this may result in better treatment outcome [2, 3].

Future studies will be aimed to identify possible predictors of response for this innovative treatment and also to determine the best strategy to manage patients after 1 year of treatment: if more than one treatment can be performed and which could be the best interval of time for patients who need supplemental treatments; in fact it seems that supplemental treatments can enforce the efficacy of this approach by increasing the benefit obtained at the first cycle of treatment [12, 13].

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Diener HC, Limmroth V (2004) Medication-overuse headache: a worldwide problem. Lancet Neurol 3:475–483
2. Dodick D, Turkel C, De Gryse R et al (2010) Onabotulinum toxinA for treatment of chronic migraine: pooled results from double blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 50:921–936
3. Diener HC, Dodick D, Aurora S et al (2010) Onabotulinum toxinA for treatment of chronic migraine: results from the double

blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalagia 30:804–814
4. Blumenfeld A, Silberstein S, Dodick D, Aurora S, Turkel C, Binder W (2010) Method of injection of onabotulinum toxin A for chronic migraine : a safe, well-tolerated and effective treatment paradigm based on the PREEMPT clinical program. Headache 50:1406–1418
5. Ranoux D, Attal N, Morain F, Bouhasira D (2008) Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. Ann Neurol 64:274–283
6. Aoki KR (2005) Review of a proposed mechanisms for the antinociceptive action of botulinum toxin type A. Neurotoxicology 26:785–793
7. Aoki KR (2003) Evidence for antinociceptive activity of botulinum toxin type A in pain management. Headache 43(suppl):S9–S15
8. Silberstein S, Blumenfeld A, Cady R, Turner I, Lipton R, Diener HC, Aurora S, Sirimanne M, DeGryse R, Turkel C, Dodick D (2013) Onabotulinum toxin A for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci 15(331(1–2)):48–56
9. Headache Classification Committee of the International Headache Society (IHS) (2013) The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33:629–808
10. Ashkenazi A (2010) Botulinum toxin type A for chronic migraine. Curr Neurol Neurosci Rep 10:140–146
11. Rothrock J, Bloudek LM, Rothrock DA, Varon SF (2014) Real-world economic impact of onabotulinum toxin A in patients with chronic migraine. Headache 54:1565–1573
12. Cernuda-Morollon E, Ramon C, Larrosa D, Alvarez R, Riesco N, Pascual J (2014) Long-term experience with onabotulinumtoxinA in the treatment of chronic migraine: what happens after one -year? Cephalalgia. doi:10.1177/0333102414561873
13. Silberstein SD, Dodick WD, Aurora SK, Dienere H-C, DeGryse RE, Lipton RB, Turkel CC (2014) Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT. J Neurol Neurosurg Psychiatry. doi:10.1136/jnnp-2013-307149