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Review article

Botulinum toxin for the treatment of headache: a promising path on a "dead end road"?

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Abstract

Available preventive treatments for primary headaches such as migraines and tension-type headaches have limited efficacy and often disabling side effects (Schoenen 2004, Schoenen 2000). There is thus room for new more effective and better tolerated therapeutic approaches as long as they can be proven superior to placebo. Based on pilot studies and open trials, botulinum toxin (BT) appeared in the headache armamentarium more than a decade ago and it remains widely used in North America since. The initial enthusiasm for BT was not confirmed by subsequent randomized controlled trials reviewed in this article, neither in tension-type headache, nor in episodic migraine and hence BT was considered a "dead end road" by certain headache experts. A promising "path" for BT may, however, exist. In two recent trials (PREEMPT 1 and 2), OnabotulinumtoxinA (Botox°) was found effective in chronic migraine. The therapeutic gain over placebo is modest (± 11%), but chronic migraine is most disabling, often drug resistant and a serious public health problem, as it affects 1-2% of people in the general population. Because the PREEMPT trials leave unsolved a number of clinically relevant questions, OnabotulinumtoxinA cannot become yet the pre-emptor of CM treatment. Although the path is promising, it seems wise, at this stage, to restrict its use to specialized headache centres where BT can be included in a multidisciplinary approach for chronic headache patients.

Key words: Botulinum toxin, OnabotulinumtoxinA, migraine, chronic migraine, chronic tension-type headache

Introduction

Since more than a decade, Botulinum Toxin (BT) injections have proven therapeutic efficacy in neurologic disorders like dystonias. Their application to headache therapy stems from case reports of pain improvement after cosmetic use. Consequently, on the sole basis of some positive open-label trials, BT became a most popular (and profitable) therapy for headache patients in North America. The initial enthusiasm was not confirmed by subsequent randomized controlled trials (RCT) neither in migraine nor in tension-type headache which led certain headache experts (Evers and Olesen 2006) to consider that BT in headache therapy was a "dead end road". There was evidence, however, from subanalyses of certain RCT and from clinical experience that subgroups of patients might benefit from BT, in particular those suffering from chronic migraine, the most disabling form of this disorder. Two recent large RCT (PREEMPT 1 and 2) confirm that OnabotulinumtoxinA (Botox°) is effective in chronic migraine patients with or without acute medication overuse, although its therapeutic gain over placebo is modest (Aurora *et al*., 2010, Diener *et al*., 2010). This could thus be a promising path for BT in migraine therapy, but a number of clinically relevant questions remain unsolved. In this article, we have done a critical review of the most published RCT with BT in headache.

Before getting to the clinical data, it must be reminded that there are several commercial preparations of BT known to interfere at the neuromuscular junction with the molecular mechanisms of storage and release of acetylcholine. There are several subtypes of BT (A, B, C). BT A is the one most frequently used in medical applications. There are also various preparations of Botulinum toxin type-A (BT A), which have recently be renamed: OnabotulinumtoxinA (Botox°) and AbobotulinumtoxinA (Dysport°). BT acts on the SNARE complex that is involved in vesicular transmitter release at the nerve ending. BT A splits the protein SNAP-25 and acts also on synaptobrevin. The result is muscle relaxation and weakness by reduction of acetylcholine release. Most of the studies were realized with botulinum toxin marketed by Allergan under the name of BOTOX °. In view of the muscle relaxant properties of BT, it is not surprising that it was first thought to have therapeutic potentials in tension-type

headache where myofascial factors may play a role. After some promising open-label studies, large multicenter RCT did not confirm the initial enthusiasm and migraineurs became a target for BT the more so that it was shown that the toxin could have analgesic properties in a rat model of inflammatory pain and was able to inhibit glutamate and CGRP release by nociceptive afferents in superficial laminae of the spinal cord dorsal horns (Cui *et al.,* 2004, Meng *et al.,* 2007).

We will synoptically review RCT performed with BT in migraine (Mig), in "chronic daily headaches" (CDH) which chiefly comprise chronic migraine and medication overuse headache, and in chronic tension-type headaches (CTTH).

The results of placebo-controlled trials are summarized in tables 1-3. Except one, all studies were performed with OnabotulinumtoxinA (Botox° - Allergan Inc). In all studies a parallel group design was used with a BT arm and a saline arm.

Chronic tension-type headaches.

The chronic form of tension-type headache is characterized by the occurrence of ≥ 15 days of headache per month. The headache has no migraine features. As mentioned above, some open-label studies suggested that BT could be effective in CTTH. Most of these studies were published in sponsored journal supplements and thus not peer-reviewed. This was the case for two small sample trials that showed positive results for BT in CTTH (Smuts *et al.,* 1999, Relja and Telarovic's 2004).

All subsequent RCT of BT in CTTH found no significant difference between BT and placebo (Table 1). Three negative studies were performed with abobotulinumtoxinA (Dysport°) (Rollnick *et al.,* 2000, Schulte-Mattler *et al.,* 2004, Straube *et al.,* 2008). The study by Rollnick *et al.,* (2000) is important because it shows that BT does not improve CTTH in spite of a clear reduction of EMG activity in the injected pericranial muscles. Schulte-Mattler *et al*'s study (2004) included 112 patients who, after an observational baseline phase of 1 month, were treated once with BT injections in multiple fixed sites (total dose 500 U) or placebo and followed for 3 months. The area under the curve (AUC) (duration × severity of headache) was analyzed, but also the number of headache days, of days with acute drug treatments and headache severity. The results showed no significant difference between BT (-8% AUC) and placebo (- 4%). Also, the comparison of 2 subgroups of patients differing by the degree of pericranial palpation tenderness disclosed no significant difference between the 2 treatment arms. In the last RCT performed with Dysport° (Straube *et al.,* 2008) 118 patients were included in the intention-to-treat analysis and injections of a total dose of 420U or 210U were performed at multiple head and neck sites. There was no difference between Dysport° and placebo for the primary outcome measure: change in the number of headache-free days at 4-8 weeks after injection compared with 4 weeks before injection. Treatment with 420 units was, however, associated with significant improvements compared with placebo for two secondary efficacy parameters: mean change in headache duration from baseline to weeks 8-12 ($P < 0.05$) and improved global physician and patient assessment scores ($P < 0.05$).

A large multicentre study included 279 patients randomized into 6 groups. 3 groups received respectively 50, 100 and 150 units of Botox° into 5 muscles; 2 other groups received 86 or 100 units of Botox° into 3 muscles and placebo in the 2 others; the last group had placebo injections in all 5 muscles (Silberstein *et al.,* 2006). The results for all efficacy measures were negative. For the primary outcome parameter, number of headache-free days, results were even significantly better for placebo compared to 150 U BT (Plac.+4.5 vs BT +2.8).

In two other RCT (Schmitt *et al.,* 2001, Padberg *et al.,* 2004), outcome was not significantly different between BT and placebo. By contrast, Kokoska *et al.,* (2004) in a study of 40 patients suffering from frontal tension-type headaches, found that an injection of 50 U BT in frontal muscles significantly decreased headache intensity compared to placebo, but had no effect on headache frequency.

Episodic migraine.

The first studies of BT in migraine prevention were carried out in patients suffering from 2 to 8 headache episodes per month. In the first placebo-controlled study the results were surprising in so far that there was a significant decrease in the number of migraine episodes with 25U administered as multiple, fixed, pericranial injections, but not with the 75U dose (Silberstein *et al.,* 2000) (Table 2).

The study by Barrientos et Chana (2003) is limited to 30 subjects, half of them injected with 50U of BT, the other half with placebo. After a 3 months follow-up, there was a significant reduction of monthly migraine attacks in the BT group (BT -3.14 vs Plac. -0.53) and of acute anti-migraine drug intake (BT 1.73 vs Plac. 5.60). The authors conclude therefore that BT is efficient in migraine prevention. This conclusion must be taken with reservation because of the small sample size and the quasi absence of placebo effect.

Table 1

Randomized, double-blind, placebo-controlled studies about chronic tension-type headache.

RCT and authors	Clinical parameters and number of patients	Doses and injection sites	Results
Rollnick *et al*. 2000	CTTH + ETC N = 21	200 U (Dysport°) (1×) Follow-up 3 months Multiple fixed sites	**Negative** (despite □ of EMG activity in injected muscles)
Schmitt *et al*. 2001	CTTH N = 60	20 U (Botox°) (1×) Follow-up 2 months Forehead and temples	**Negative** (no significant difference in responders: BT 54% vs plac. 38%)
Schulte-Mattler *et al*. 2004	CTTH N = 112	500 U (Dysport°) (1×) Follow up 3 months Multiple fixed sites	**Negative** (no significant □ of area under the curve)
Kokoska *et al*. 2004	CTTH (frontale) N = 40	50 U (Botox°) (1×) Multiple fixed sites	**Positive for intensity** (signif □ for BT) **Negative for frequency** (no signif difference)
Padberg *et al*. 2004	CTTH N = 40	1U/Kg max. 100 U (Botox°) (1×) Follow up 3 months Mode "Follow-The-Pain (FTP)"	**Negative** (no significant difference for headache intensity: VAS: BT + 10.6 vs Plac +7.1)
Silberstein *et al*. 2006	CTTH N = 279	50U/100U/150U (Botox°) 5 fixed sites (1×) OR 86U/100U + Plac. 3 + 2 fixed sites (1 ×) follow up 4 months	**Negative** (Plac > Botox° 150U for headache-free days/mth: +4.5 vs 2,8)
Straube *et al*. 2008	CTTH N = 118	420U/210U /saline (Dysport°) 18 fixed sites	**Negative** (headache-free days/mth: Plac = 1.93, 420U = 2.60, 210U = 2.87)

The study by Evers *et al.,* (2004) is the first negative study published for BT in migraine. This RCT was run for 11 months (1 month baseline, 1 month placebo treatment, followed by a 9 months double-blind phase with 1 BT injection every 3 months). Sixty patients suffering from migraine since at least 1 year were included and randomized into 3 groups. The first group received 100U BT in frontalis and neck muscles, the second 16U BT in frontalis and placebo in neck muscles, the third one only placebo. The primary outcome measure was the percentage of responders, i.e. patients with at least 50% reduction of monthly migraine attack frequency. Secondary efficacy parameters were decrease of attack frequency per month, number of days with migraine, number of days with moderate or severe migraine, associated symptoms and days with use of acute anti-migraine drugs. Differences between groups were not significant (30% of responders in the 2 BT groups; 25% in the placebo group) except for associated symptoms which were more attenuated in the 16U group. This study does therefore not argue in favour of an effect of BT in migraine prevention, but its statistical power could have been too weak.

The large European multicenter study had an observation period of 11 months (Relja *et al.,* 2007). It included 495 patients suffering from at least 3 migraine attacks per month, but less than 15 headache days per month. The mean monthly frequency of attacks before randomization was between 4.3 and 4.7. At the end of the baseline month, patients received a placebo injection to identify placebo responders. After 1 month, placebo responders (n = 173) and non-responders (n = 322) were randomized into 4 groups: placebo, 75 U BT, 150 U BT and 225 U BT injected in 7 predefined pericranial sites. The primary outcome measure was the decrease of monthly migraine attack frequency in placebo responders and non-responders. There were no significant differences between treatment groups for neither parameter, even not after control for age, sex or illness duration.

Similar negative results were obtained in two large North American trials (Aurora *et al.,* 2006, Elkind *et al.,* 2006) and in a smaller trial of drug-resistant migraine patients (Cady and Schreiber 2008), although the latter found improvement after BT in disability scales.

Table 2

Randomized, double-blind, placebo-controlled studies in episodic migraine.

RCT and, authors	Clinical parameters and number of patients	Doses and injection sites	Results
Silberstein *et al*. 2000	Migraine. (2-8 episodes/month) N = 42	25 U/ 75 U (Botox°) (1×) Multiple fixed sites Follow up 3 months	**Positive for 25 U** (□ 38% of days with acute treatments) **Negative** for 75U
Barrientos & Chana 2003	Migraine N = 30	50 U (Botox°) (1×) Follow up 3 months 6 fixed sites	**Positive** (signif. □ of frequency at day 90: BT -3.14 vs plac. -0.53)
Evers *et al*. 2004	Migraine (2-8 episodes/month) N = 60	16 U/ 100 U (Botox°) (1×) fixed sites forehead and neck Follow up 3 months	**Negative** (BT: 30% responders; Plac: 25%)
Relja *et al*. 2007	Migraine (≥ 3 episodes/month) N = 495 (n = 322 placebo non-responders)	225 U/ 150 U / 75U (Botox°) 1×/3months during 9 months Multiple fixed sites	**Negative** (no significant difference between 4 groups after 3 months
Aurora *et al*.2007	Migraine (≥ 4- ≤ 15 episodes/month) N = 369 (n = 203 placebo non-responders)	110-260U (Botox°) 1×/3months during 9 months Modified protocol Follow The Pain (FTP)	**Negative** (no difference with placebo, except for patients with ≥ 12 headaches/month : n = 88)
Elkind *et al*. 2006	Migraine (≥ 4- ≤ 8 episodes /month) N = 418	3 injections at 4-month intervals (Botox°) - 0U/7.5U/25U/50U - 25U/50U - 0U/25U/50U fixed sites forehead and temples	**Negative** (no difference with placebo; improvement with time in all groups)
Cady & Schreiber 2008	Migraine (HIT-6 ≥ 56) failing oral prophylactic treatment N = 61 (2 BT:1 pl.)	139 U (Botox°) (1×) Multiple fixed sites Follow up 3 months	**Negative** (no signif. difference for headache frequency or severity **Positive** Signif. difference of HIT-6 score, MIDAS and MIQ at month 3 in favour of BT

One may wonder if the outcome measures used in most RCT, i.e. frequency and intensity of attacks, are sensitive enough to disclose differences between BT and placebo. In a randomized study comparing the preventive anti-migraine effect of valproic acid and BT, both treatments had equal beneficial effects on headache frequency, but BT was clearly superior for quality of life measures and disability (Blumenfeld and Schim 2008). This difference must be verified in placebo-controlled trials again, but it may explain why BT continues to be used by certain practitioners despite the lack of scientific evidence for its efficiency.

Duration of illness might influence the response to BT treatment. This is suggested by a prospective, non-controlled study which evaluated 61 migraineurs and found that responders to BT (62%) differed from non-responders (38%) by illness duration (21.9 vs 31.4 years) (Eross *et al.,* 2005).

It has finally been suggested that episodic migraine patients with an "imploding" pattern of headache (external constriction) may respond to BT treatment contrary to those with an "exploding" (intracranial pressure) pattern (Jakubowski *et al.,* 2006).

Chronic daily headache.

The chronic daily headache (CDH) group is defined by a headache frequency of at least 15 days per month. It includes different types of primary headaches, but most often chronic migraine with and without medication overuse (Fumal *et al.,* 2006).

In the large North-American multicenter study (Mathew *et al.,* 2005) (table 3), 355 patients suffering from CDH were followed during 11 months. The

Table 3

Randomized, double-blind, placebo-controlled studies inchronic daily headache (CDH) and chronic migraine (CM).

RCT and authors	Diagnosis and number of patients	Doses and injection sites	Results
Ondo *et al*. 2004	CDH N = 60	200 U (Botox°) (1×) Follow up 3 mths Mode FTP	**Negative** (no significant decrease of headaches)
Mathew *et al*. 2005	CDH (± 50% with analgesic overuse) N = 355 (n = 279 placebo non-responders)	105-260 U (Botox°) 1×/3months during 9 months Mode FTP	**Negative** (1°param.) (no signif □ of headache-free days: BT 6,7 vs Plac 5,2) **Positive** (2°param.) (50% □ of headaches: BT 32,7% vs Plac 15%)
Dodick *et al*. 2005 (Mathew *et al*. sub-analysis)	CDH without prophylactic treatments (± 50% with analgesic overuse) N = 228 (out of 355)	105-260 U (Botox°) 1×/3months during 9 months Mode FTP	**Positive** (better □ headaches in BT -7,8 vs Plac-4,5; 50% □ of headache after 3 inj: BT 50% vs Plac 35%)
Silberstein *et al*. 2005	CDH N = 702	225U/150U/75U (Botox°)	**Negative** (1°param.) (no signif □ of headache-free days at day 180: 6/7,9/7,9/8 for BT225/BT150/BT75/Plac) **Positive** (2°param.) (signif □ headaches at day 240 for BT225-8,4 ; BT150-8,6 vs plac 6,4)
Freitag *et al*. 2008	CM (without analgesic overuse) N = 36	110U (Botox°) (1×) Follow up 4 mois Multiple fixed sites	**Positive** (□ of headache: BT 31% vs Plac 8,1%; responders 33% vs 16.7%)
Aurora *et al*. 2010 (PREEMPT 1)	CM N = 679	155U (up to 195U) (Botox°) (N = 341); placebo (N = 338) 31 fixed sites (5U/site) every 12 weeks 4 week baseline/ 24-week double blind/ 32-week open-label	**Negative 1° endpoint** Headache "episodes": no difference -0.5%) **Positive 2° endpoints** Significant BT effect for headache days (-6.7%), migraine days (-7.9%), headache hours (-10.4%), HIT-6 score (- 3.4%)
Diener *et al*. 2010 (PREEMPT 2)	CM N = 705	Same protocol BT (N = 347); placebo (N = 358)	**Positive 1° endpoint** Headache days (-11%) ($p < 0.001$) **Positive 2° endpoints** Migraine days (-11.3%), headache episodes (-8%), headache hours (-13.4), HIT-6 score (-3.8)

first period of 1 month was a baseline observational period. Thereafter, 279 subjects who did not improve during baseline, were included in the randomised phase. They received 3 BT injections separated by 3 months at a dose ranging from 105 U to 260 U or placebo in a "follow the pain" pattern meaning that the injections are made in tender points identified by palpation of pericranial and neck muscles. The primary outcome measure was the number of headache-free days per month. Secondary outcome measures were ≥ 50% decrease from baseline of headache days, number of acute headache medication used per month and quality of life. The primary endpoint was not reached. Indeed, there was no significant increase of headache free-days after BT injections (+6.7) by comparison with placebo (+5.2). The percentage of patients with a ≥ 50% decrease of headache days was, however, superior in the BT group (32.7% vs 15%). The authors speculated that the lack of efficacy of BT might be due to an overuse of acute headache medications and/or interference with concomitant preventive anti-migraine drugs. It must be pointed out that more than 50% of patients included in the BT arm overused analgesics com-

pared to ± 40% in the placebo arm. As it is well known that interruption of excessive analgesic intake can by itself improve headache frequency, the bias due to medication overuse, if any, would have been in favour of BT.

To verify the possible interaction with preventive anti-migraine treatments, Dodick *et al.,* (2005) analyzed a subgroup of patients coming from the Mathew *et al.,*'s study, i.e. those who did not receive any prophylactic treatment (n = 228/355). In this subgroup, BT induced a significant decrease in headache frequency with an improvement of ≥ 50% in 50% of subjects from day 150 onwards, i.e. after the 3rd injection compared to 30% in placebo-treated patients. A decrease in headache severity was evident from the second BT injection onwards. Improvement in quality of life was, however, not superior in the BT group.

Two other smaller studies are of interest (Table 3). The study by Ondo *et al.,* (2004) also failed to show a beneficial effect of BT. Freitag *et al.,* (2007) studied 36 chronic migraine patients without analgesic overuse and found evidence for the efficacy of BT. Because of the small sample size, this study cannot be taken as convincing evidence for the use of BT in chronic migraine.

Chronic migraine (the PREEMPT trials)

In 2006, broader diagnostic criteria for chronic migraine (CM) were proposed by an expert group of the International Headache Classification committee (CM-R A 1.5.1) (Olesen *et al.,* 2006). This facilitated the launch of 2 large multicentre studies of OnabotulinumtoxinA in patients diagnosed with chronic migraine, the PREEMPT trials. As shown in table 3, both studies undoubtedly do support efficacy in the patients studied and have demonstrated undisputable strengths. They were well-designed, performed by experienced investigators and included large numbers of patients with a long blinded follow-up of 24 weeks and a subsequent open label period of 32 weeks. OnabotulinumtoxinA was statistically superior to placebo in a range of outcome measures, including quality of life and disability scales. These results appear encouraging, especially since they concern a most disabled patient population. They were confirmed by the pooled data analysis of PREEMPT 1 and 2 (Dodick *et al.,* 2010) which also confirmed the excellent tolerability and safety of BT treatment. Adverse events, most of them mild to moderate in severity, occurred in 62.4% of onabotulinumtoxinA patients and 51.7% of placebo patients. Few patients discontinued treatment due to adverse events (onabotulinumtoxinA, 3.8%; placebo, 1.2%). No unexpected treatment-related adverse events were identified. The following considerations, however, may temper an excessive optimism.

One major concern is that both trials recruited a majority of patients (up to 65%) fulfilling criteria for medication overuse headache (MOH-R A 8.2) (Olesen *et al.,* 2006). Although this reflects real world life, it means that many patients may have been suffering from a secondary headache disorder and not, as stated in titles and methods section, from CM per se. Detoxification suffices in many patients to convert the chronic headache pattern into an episodic one and/or ineffective preventives to effective drugs. This may explain part of the beneficial effect, admittedly both in BT and placebo groups. Both groups had indeed an average decrease of ± 10 acute medication intakes at week 24, but there was a significantly greater decrease of triptan intake in OnabotulinumtoxinA-treated patients. It would have been informative to know whether the treatment response differed between patients with and without medication overuse.

Along the same line of patient selection, it comes as a surprise that up to 40% of enrolled patients never received a preventive treatment before, the more so as mean duration of CM in both trials was 20 years and mean age of participants ± 40 years! Although the reliability of the historical data on migraine pattern and previous treatments may be questioned, knowing if prophylaxis-naive patients respond differently is of practical interest. Unfortunately, this information is not provided.

A frequent question in RCTs concerns the clinical significance of statistical differences. There is no consensus on the minimal change in an outcome measure required to be considered clinically relevant and this minimum has to be balanced against the severity of the disorder. Because of the well-known high placebo response in headache trials using injections of drugs, in particular, of BT, the therapeutic gain of OnabotulinumtoxinA over placebo is not impressive in numerical terms: absolute gain of 6.7% and 11% for headache days and 7.9% and 11.3% for migraine days, respectively in PREEMPT 1 and 2 (see Table 3).

Looking at the absolute mean change in headache days, there is little doubt, however, that a substantial number of migraine patients switched from a chronic to an episodic pattern. According to data from the American Migraine Prevalence and Prevention Study, conversion from CM to EM occurs over a 3-year period in 26% of patients, whereas CM persists unchanged in only 22% (Manack *et al.,* 2009). Unfortunately, the percentage of patients who converted and the difference between treatment arms are not

given in the PREEMPT articles, nor are the respective percentages of responders with a 50% or 25% of reduction in headache days, so that a comparison with the natural history of the disorder is not possible. These missing data, as those on the proportion of patients who would choose to continue the treatment, would have been useful to further estimate the clinical relevance of the results.

The only other RCT performed in CM has studied topiramate (Silberstein *et al.,* 2009) and it is somewhat surprising that the PREEMPT authors, several of whom also participated in the topiramate trial, do not compare the results in the discussion. Although preventive treatment-naive patients were excluded in the topiramate trial contrary to PREEMPT 1 and 2, the effect size in the three studies seems to be similar, e.g. 10.2% absolute gain over placebo for migraine days in the topiramate trial compared to 11.3% in PREEMPT 2. OnabotulinumtoxinA was directly compared to topiramate in a small randomized double-blind single-centre trial (Mathew and Jaffri 2009). No statistical difference was found between the 2 treatment groups, but the results are not based on an intent-to-treat analysis. Adverse events, however, were more numerous and severe for topiramate.

The only question that really matters to patients and doctors is whether the PREEMPT 1-2 results are convincing enough to justify our present or change our future medical practice. The answer could be "Yes" with some reservations. OnabotulinumtoxinA was proven to be moderately superior to placebo, and probably to natural outcome, in a population of chronic migraine patients of whom the majority was overusing acute medication and a substantial proportion had never received preventive drugs. This is good news as CM is a most disabling disorder with a 1-2% prevalence in the general population in which even a small effect or an effect in a small percentage of patients can be of medical value. A major advantage of OnabotulinumtoxinA compared to other drug treatments is its excellent tolerance. Before it can become the pre-emptor of CM treatment, however, the abovementioned questions need to be addressed.

The mechanisms by which BT improves CM are speculative. As central sensitization in the trigeminal sensory systems may play a role in migraine chronification, one may hypothesize that this might be reduced by BT thanks to its capacity to attenuate glutamate and CGRP release by trigeminal afferents (Cui *et al.,* 2004; Kitamura *et al.,* 2009).

Phase IV studies should be able to provide answers to crucial open questions like "How to identify responders?" or "Is the treatment cost-effective?" For translational benefits, they should be paralleled by more research on the mode of action of OnabotulinumtoxinA in chronic migraine, which still remains a mystery.

Tolerance and safety of use.

All mentioned studies have assessed tolerance and safety of BT. The conclusion is that BT causes only few, non-disabling and transient side effects. As with its use in other disorders, the most frequent ones are muscular weakness, ptosis and neck pain. Because of the motor side effects, unblinding may be a problem in RCT of BT. Overall, tolerance seems to be superior to that of the most effective preventive antimigraine drugs such as the anticonvulsants valproate and topiramate.

Conclusions

Randomized placebo-controlled trials in primary headaches indicate convincingly that BT has no efficacy in chronic tension-type headache or in episodic migraine without aura.

These disappointing results of BT treatment may have several explanations. First, it is clear that in CTTH, pericranial muscle activity which is supposed to be reduced by the BT, does not play a major pathophysiological role contrary to central sensitization and dysfunction of endogenous pain control systems (see review by Schoenen 2005). Episodic migraine attacks, on the other hand, are associated with activation of the trigemino-vascular system, the visceral portion of the 1st division of the trigeminal nerve (V1), and with a transient and reversible sensitization of the 1st and 2nd order central trigeminal nociceptors. Subcutaneous injections of BT, by contrast, act on the somatic portion of V1. If BT is able to decrease the release of transmitters by somatic trigeminal afferents at the level of the spinal dorsal horns (Cui *et al.,* 2004), it might reduce cutaneous allodynia which accompanies up to 30% of migraine attacks without preventing the attacks themselves. To our knowledge this has not been investigated up to now.

Contrasting with the studies in CTTH and episodic migraine, those performed with BT in chronic migraine have provided evidence of efficacy. The evidence comes from subanalysis of chronic daily headache trials and, more convincingly, from the two recent PREEMPT trials. The Pro's and con's of these trials have been discussed. It seems of uttermost importance in future trials to develop methods which are able to better identify patients who may respond to BT.

Taken together, OnabotulinumtoxinA (Botox°) cannot be considered yet as a standard treatment for

CM. it seems wise at this stage to restrict its use to specialized headache centres where it can be included in the multidisciplinary armamentarium recommended in chronic headache patients and where the indispensable supplementary studies on its target patient population, basic mechanisms of action and pharmaco-economic profile can be conducted.

Thus, after several negative studies forecasting a "dead end road", the CM "path" for BT is promising, but needs to be more clearly delineated and clarified in clinical practice, before anyone can take it with confidence.

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