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Botulinum toxin for chronic migraine: Clinical trials and technical aspects

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ABSTRACT

OnabotulinumtoxinA has been approved for the prophylaxis of chronic migraine following the demonstration of efficacy in two large controlled trials. Data collected from pragmatic studies in the real-life setting have contributed important additional information useful for the management of this group of extremely disabled and challenging patients. The main findings from these studies are presented and discussed.

1. Introduction

OnabotulinumtoxinA has recently been approved for the prophylaxis of chronic migraine (CM) in the US and in several European countries. CM is an aggressive type of migraine characterized by attacks of headache recurring ≥15 days/month for at least 3 months with 'migraine' features for at least 8 days/month (Headache Classification Committee of the International Headache Society, 2013). CM is a common condition as it affects up to 5% of the general population (Allena et al., 2015; Ayzenber et al., 2012; Katsarava et al., 2009). Specific data on the disability associated to CM are lacking, but the condition is one of the most disabling of the migraine spectrum. When considering that migraine has been rated as the sixth highest cause of disability worldwide, when disability is measured in years of life lost to disability (Global Burden of Disease Study, 2013 Collaborators, 2015).

CM is the most common type of primary daily headache seen in headache specialty centers in the USA and Europe (Bigal et al., 2008; Natoli et al., 2010; Pascual et al., 2001). It represents a challenge for the specialist because, in most cases, patients seeking help have already tried and failed several types of therapies. Indeed, the typical CM patient has been suffering from severe, disabling migraines for years with a poor or progressively waning effect of acute treatments, which are nonetheless used or overused in most cases (Bigal et al., 2004). A limited number of drugs have been tested for the prophylactic treatment of CM. Several trials have confirmed the efficacy of topiramate in CM, but they also underpinned a poor tolerability profile associated to quite a high discontinuation rate (Mathew and Jaffri, 2009). Indeed, persistence to oral prophylactic treatments (amitriptyline, gabapentin, nortriptyline, beta-blockers and topiramate) in CM is very low: 25% at six months and 14% at 12 months, with a sharp decline of patients discontinuing observed as early as 30 days (Hepp et al., 2017). The most commonly cited reasons for discontinuation in randomized trials on CM are adverse events, patient choice, and loss to follow-up (Hepp et al., 2014).

Many CM patients also bear a relevant load of comorbidities (anxiety, depression, obesity) (Lau et al., 2015; Minen et al., 2016; Yoon et al., 2013). CM is an underdiagnosed and undertreated condition: it is estimated that less than 5% of CM sufferers receive the correct diagnosis and the correct treatment approach consisting in acute medications associated to preventatives (Dodick et al., 2016).

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2. OnabotulinumtoxinA in the treatment of chronic migraine: from exploratory trials to pragmatic studies

Exploratory trials investigating the efficacy of onabotulinumtoxinA in episodic migraine, chronic tension-type headache, and chronic daily headache have yielded inconclusive results, partly because of methodological limitations regarding the injection paradigm and the dose (Aurora et al., 2007; Freitag et al., 2008; Gibson and Turkel, 2005; Silberstein et al., 2000, 2005, 2006). The efficacy of onabotulinumtoxinA in CM has instead been demonstrated in the clinical programme called REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) (Aurora et al., 2010; Diener et al., 2010; Dodick et al., 2010). In the two phase III trials of the PREEMPT programme (PREEMPT1 and 2) the injection paradigm consisted in the administration of onabotulinumtoxinA in 31 sites across 7 head and neck muscles using a 5-U dose per injection site. Eight additional injection sites with 5 U of onabotulinumtoxinA across 3 head and neck muscles were also allowed according to a follow-the-pain approach. The minimum dose was 155 U, the maximum 195U (Fig. 1).

The PREEMPT1 and 2 studies had a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week open-label phase and enrolled 1384 CM patients. The pooled analysis of results showed that onabotulinumtoxinA treatment significantly reduced the frequency of headache days when compared to placebo (- 8.4 onabotulinumtoxinA, - 6.6 placebo; $P < 0.001$). Several other secondary efficacy variables showed significant between-group differences favoring onabotulinumtoxinA. Notably, 45% of patients were responders (i.e. experienced a decrease in headache day $\geq$50% at the end of the double-blind phase and >60% of patients entering the open-label study were responders at the end of the evaluation. The PREEMPT results showed highly significant improvements in multiple headache symptom measures and demonstrated improvement in patients' quality of life. It is noteworthy that the long duration of the PREEMPT trials (24 + 32 weeks) allowed to observe a progressive improvement over time of several indicators of efficacy: headache days, migraine days, acute headache medications intake (Dodick et al., 2010). Another interesting information about the effects of onabotulinumtoxinA derived from the PREEMPT studies is that a relevant portion of patients (>20% of the entire baseline cohort) that did not improve after the first cycle, could become responders at the second or third cycle (Silberstein et al., 2015).

Controlled trials are extremely important to test and evaluate interventions. They adopt comprehensive designs to control for several sources of bias: randomization, blinding, allocation concealment, etc. A lengthy list of inclusion and exclusion criteria is used to identify a clearly defined and homogeneous population group to be investigated. Controlled trials are likely to lead to statistically credible results (i.e. they possess a high internal validity), however the applicability of these results to real life practice may be questionable. Indeed, the strict criteria used in controlled trials to select patients may weaken the possibility to generalize their findings to the clinical setting (low external validity) (Patsopoulos, 2013). This seems particularly relevant when dealing with CM patients who, in the real practice, show a wide variability of symptom severity and frequency along with multiple comorbidities. Furthermore, CM patients require long-lasting prophylactic cycles and several of the prophylactic drugs approved for migraine are burdened by common side effects, which may affect efficacy - when they prevent the possibility to reach the adequate dosing scheme – or undermine patients' adherence to lengthy cycles.

For the above reasons, pragmatic studies, aimed at addressing the question 'how does onabotulinumtoxinA works in CM in real life' have gained momentum. These pragmatic studies have provided a multitude of information on the long-term outcomes of patients and on the issues that need to be faced and addressed in the everyday practice. Thus far, several "real-life" studies on the effectiveness of onabotulinumtoxinA in CM have been published (Aicua-Rapun et al., 2016; Boudreau et al., 2015; Butera et al., 2016; Cernuda-Morollón et al., 2015; Demiryurek et al., 2016; Grazzi and Usai, 2015; Guerzoni et al., 2015; Khalil et al., 2014; Kollewe et al., 2016; Negro et al., 2015a, 2015b; Pedraza et al., 2015). The largest "real-life" study with onabotulinumtoxinA is a prospective post-

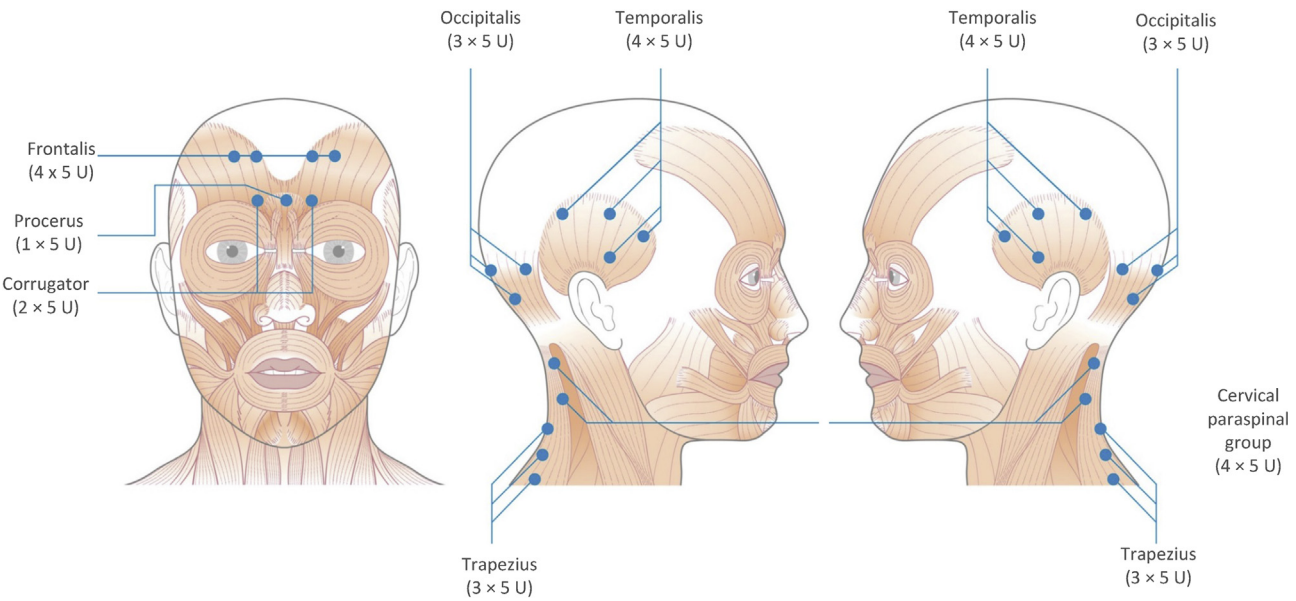

Fig. 1. The PREEMPT fixed-site fixed-dose injection paradigm. A total of 31 injections across seven specific head and neck muscles, with a dose of 155 U of onabotulinumtoxinA injected per patient. In the follow-the-pain paradigm, 8 additional injections (40 U) are administered: 2 in the temporalis muscle, 2 in the occipitalis muscle and 4 in the trapezium. (Modified from Blumenfeld et al. Headache 2010;50:1406–18).

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marketing analysis conducted in the UK in 254 CM sufferers (Khalil et al., 2014). Khalil et al. showed that onabotulinumtoxinA was effective in reducing headache and migraine days by at least 50%, simultaneously increasing the number of headache free days. The authors also reported a clinically meaningful and statistically significant improvement in quality of life (HIT-6 score) after with onabotulinumtoxinA. The effectiveness of onabotulinumtoxinA in CM has been confirmed in several small open-label studies. Grazzi and Usai (2015) treated 20 CM for 5 consecutive cycles and reported a significant decrease in headache days, from 21.7 ± 6.8 to 15.6 ± 8.7, $p < 0.005$), associated with a 50% decrease in migraine-related disability. Boudreau et al. (2015) reported the effect of two cycles of treatment in 32 patients with CM. When comparing the data obtained in the last month of observation versus baseline, the Authors found an increase in headache/migraine-free days (+8.2 ± 5.8, $p < 0.0001$)per 30-day period, together with a significant improvement in migraine-related disability: Headache Impact Test scores (−6.3, $p = 0.0001$) and Migraine Disability Assessment scores (−44.2, $p = 0.0058$). One interesting finding in this study was the demonstration of a significant improvement in depression and anxiety; Beck Depression Inventory-II (−7.9, $p < 0.0001$), Patient Health Questionnaire depression module (−4.3, $p < 0.0001$), and Generalized Anxiety Disorder questionnaire (−3.5, $p = 0.0002$) scores. Pedraza et al. (2015) found a reduction ranging from 46.5 to 58.1% in the number of headache days, migraine days and days of acute medication or triptan intake in 52 CM subjects after a single treatment cycle. The reduction in the same parameters in the 39 subjects who underwent a second treatment cycle ranged from 36.3 to 73.1%.

OnabotulinumtoxinA proved effective also in a small group (n. 44) of subjects with CM and medication overuse that were refractory to 3 classes of prophylactic drugs (Butera et al., 2016). These subjects were not detoxified from overuse medications, nor did they receive any instructions to withdraw their anti-migraine medications. Though limited by some methodological flaws and by a high rate of drop-outs (approximately 20%), the study has found a progressive increase in the effectiveness of onabotulinumtoxinA over 3 subsequent cycles also in this very difficult population of CM subjects. Indeed, the number of days with headache decreased from 25.1 ± 6.3 at baseline to 15.9 ± 7.6 in the last observation period. Similarly, migraine-related disability, score with the MIDAS tool, abated from 117.3 ± 94.8 (baseline) to 59.5 ± 90.9 (final observation period).

Interestingly, in a real-life study that evaluated the performance of onabotulinumtoxinA over a single cycle of treatment in 60 CM subjects, Demiryurek et al. (2016) reported evidence of improvement in the majority of outcome measures (headache days, number of attacks, duration of attacks, number of accesses to emergency services and the number of analgesics) during the first month after treatment. The positive effect was still evident at the third month, but it showed a tendency to wane. This temporal pattern may, of course, reflect a placebo component in the early effect, but it also points to the importance of adhering to the 12-week inter-injection program to avoid fluctuations and/or relapses into a chronic pattern.

Several of the real-life studies on onabotulinumtoxinA in CM patients evaluated the long-term effect of the drug. Cernuda-Morollón et al. (2015) followed quite a large group (N = 132) of CM patients who received a mean of 7.7 cycles of injection (range 2–29) (35). A total of 108 patients (81.8%) showed a response during the first year. In the first-year responders, the authors decided to extend the inter-injection interval to 4 months during the second year. Of these, 49 (45.4%) worsened prior to the next treatment, which called for a return to quarterly injections. Injections were stopped in 14 subjects: in 10 (9.3%) due to a lack of response and in 4 due to the disappearance of attacks. In responders, after an average of two years of treatment, consumption of any acute medication was reduced by 53% (62.5% in triptan overusers) and emergency visits decreased by 61%.

Negro et al. (2015a) prospectively evaluated 132 CM subjects with medication overuse who had previously failed multiple preventive therapies. Patients were treated with onabotulinumtoxinA at the dose of 155 U every 12 weeks for 2 years. A significant improvement was observed in headache days, migraine days, acute pain medication intake days and Headache Impact Test 6 score already after the first injection. Subsequently it progressively increased during the 2-year treatment, reaching an impressive level: headache days/month, baseline 22.3 ± 4.1, final observation period post 7.3 ± 2.1; $p < 0.001$; migraine days per month, baseline 21.4 ± 4.3, final observation period post 6.8 ± 2.3; $p < 0.001$; medication intake days/month, baseline 20.8 ± 4.5, final observation period 5.3 ± 1.7; $p < 0.001$.

In a subsequent study, Negro et al. (2015b) evaluated 143 patients with CM and medication overuse who were treated with onabotulinumtoxinA at the dose of 195 UI for 2 years. Once again, they reported a dramatic improvement in the outcome measures, which was significantly more marked than the improvement that they had previously observed in the population of CM patients who were treated with the dose of 155 U.A similar effect was obtained by Kollewe et al. (2016) in a small group of CM subjects who

Table 1
Long-term studies on the effectiveness of onabotulinumtoxinA in chronic migraine.

Ref.	N. of subjects	Duration of observations	Effectiveness
Cernuda-Morollón et al., 2015	132, refractory, 41% with MOH	More than 4 years	81.8% were 50%- responders at 1y 74.2% were 50%-responders at 2y
Negro et al., 2015a	132, refractory, 100% with medication overuse Dose: 155 UI	2 years	Headache days: pre −22.3 ± 4.1, final 7.3 ± 2.1; Migraine days: pre 21.4 ± 4.3, final 6.8 ± 2.3; Medication intake days/month: pre 20.8 ± 4.5, final 5.3 ± 1.7
Aicua-Rapun et al., 2016	115, refractory to > 2 prophylactic treatments, 80% with medication overuse	7.5 cycles	68.7% reverted to an episodic pattern
Negro et al., 2015b	143, all refractory to treatments, 100% with with medication overuse Dose: 195 UI	2 years	Headache days: pre 22.2 ± 4.9, final 4.1 ± 1.0 Migraine days: pre 21.6 ± 4.8, final 3.8 ± 1.0 Medication intake days/month: pre 21.0 ± 5.1, final 3.7 ± 1.3
Guerzoni et al., 2015	57, 100% with MOH	18 months	Percent reduction in headache days: - 34% Percent reduction in days of intake of acute medications: - 67%

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underwent 6.5 ± 2.9 cycles (min 4, max 13) of onabotulinumtoxinA injections according to the PREEMPT paradigm.

A Spanish group (Aicua-Rapun et al., 2016) treated 115 CM patients with onabotulinumtoxinA for a mean of 7.6 ± 2.3 cycles. In 42 cases (36.5%) the Authors needed to increase the dose form 155 U to 195 U, mostly because the response time was shorter than 3 months. They reported a favorable response to the treatment in 79 patients (68.7%), characterized by the reversal of the chronic pattern to the episodic one. Ninety-two of the CM subjects overused medication, but 57 (61.9%) discontinued overuse. Because of the good clinical response after the third cycle of injection, the authors increased the inter-injection interval of onabotulinumtoxinA to 4 or 5 months in 22 patients (19.1%).

In a retrospective study conducted on a sample of 66 patients with CM associated with medication overuse that received at least 7 cycles of treatment with onabotulinumtoxinA, Guerzoni et al. (2015) reported a decrease of 34% in the headache days, together with a decrease of 67% in the days of intake of acute drugs. The authors also noted an improvement in the quality of life, and a reduction in anxiety and depression. What is worth noting in the study, is the fact that 9 patients were forced to discontinue the treatment due to regulatory reasons. These patients experienced a general worsening of their condition in terms of quality of life (see Table 1).

3. Conclusions

OnabotulinumtoxinA has proved effective in the treatment of CM in controlled clinical studies. In order to maximize efficacy, it is important to follow the PREEMPT injection protocols, fixed-site/fixed dose or follow-the-pain, which requires the correct identification of injection sites and the careful implementation of the advised injection techniques (Blumenfeld et al., 2017). A thorough knowledge of the anatomy and a careful assessment of the patient before treatment is useful to minimize injection-related AEs (neck pain, muscular weakness, ptosis and headache).

Several prospective and retrospective “real-life” studies have shed some light on the issues that physicians encounter in their everyday practice. In this frame, data from the “real-life” studies have prompted extremely useful findings. They have confirmed that the effect of onabotulinumtoxinA tends to persist over time and to become progressively more marked. They also point to the need to adhere strictly to the PREEMPT protocol in terms of inter-injection interval, even more so in the initial cycles, when a stable improvement must be first sought and then consolidated. In some studies, indeed, the effect of onabotulinumtoxinA was more marked in the first month post-injection, while it tended to wane during the 3rd month, at least after the first cycle of injections. Only in those subjects who are stable responders to onabotulinumtoxinA for at least one year, the extension of the inter-injection interval may be a reasonable strategy to verify whether the improvement associated to repeated cycles with onabotulinumtoxinA is actually a long-lasting remission of the disease or just a drug-related temporary attenuation of symptoms. If the latter is the case, a new cycle of injections should be made ready available to patients. In the case of patients not responding to the first cycle of treatment, adoption of the follow-the-pain variant of the PREEMPT paradigm seem useful to increase the chances of response.

Other aspects remain to be illuminated by real life data coming from the experience of expert physicians. In this frame, useful details are provided by a survey recently conducted on Italian physicians with a substantial experience in the use of onabotulinumtoxinA for the treatment of migraine (Tassorelli et al., 2017). It is also important to assess and consider the patients' point of view.

Disclosures

CT has participated in advisory boards for Allergan and ElectroCore; she has lectured at symposia sponsored by Allergan; she is PI or collaborator in clinical trials sponsored by Alder, electroCore, Eli-Lilly and Teva. She has received grants from the European Commission (EC contract number 215366), the Italian Ministry of Health and the Italian Ministry of University (PRIN 2009).

Transparency document

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