

IncobotulinumtoxinA (Xeomin®) and OnabotulinumtoxinA (Botox®) for Chronic Migraine Headache: Experience with Higher Doses and Changes to the Injection Technique

Gabriel Salazar*, Marta Fragoso, Antoni Rey, Lourdes Sánchez and Manuela Gonzalez Navarro

Department of Neurology, Terrassa CST Hospital, Terrassa, Spain

*Corresponding author: Gabriel Salazar, C/Torrebonica S/N cp 08227 Terrassa, Barcelona, Spain, Tel: 34-607471876; Fax: 34-938745402; E-mail: gsalaz64@gmail.com

Rec date: Jul 23, 2014, Acc date: Nov 20, 2014, Pub date: Nov 22, 2014

Copyright: © 2014 Salazar G, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Background: OnabotulinumtoxinA has proven efficacious as a preventive treatment in patients with chronic migraine. However, non-response and tolerability problems were reported for some patients. This open-label study investigated long-term treatment with incobotulinumtoxinA in chronic migraine patients who were non-responsive to onabotulinumtoxinA injections.

Methods: Patients received pericranial injections of 200 U incobotulinumtoxinA (fixed dose) into 20 injection sites (10 U/site) using a dilution of 10 U/0.1 ml saline every three months for 18 months. They were subsequently switched back to onabotulinumtoxinA (200 U fixed dose into 20 injection sites with 10 U/site every 3 months) and were followed for another six months (length of study 24 months). The primary efficacy endpoints were monthly migraine episodes, pain intensity, the impact of migraine on functioning in daily life and consumption of pain relief drugs.

Results: Twenty-six patients (mean age 32 ± 4 years, 84.6% female) were included. IncobotulinumtoxinA significantly reduced mean monthly frequency of migraine episodes from 17.2 ± 2.1 to 4.3 ± 1.0 ($p < 0.05$), pain intensity during these episodes from 9.3 ± 0.8 to 6.3 ± 0.9 ($p < 0.05$) and consumption of acute pain medication from 32 ± 2 tablets to 5 ± 0.9 tablets after 18 months of treatment (all $p < 0.05$). Patients' daily functioning improved from severe (29 ± 3 points) to mild disability (8.2 ± 1.2 ; $p < 0.05$). Six months after switching back to onabotulinumtoxinA, the frequency of monthly migraine episodes was 4.1 ± 1.0 ($p < 0.05$), pain intensity 5.8 ± 0.9 ($p < 0.05$), and consumption of acute pain medication 4 ± 0.9 tablets ($p < 0.05$). Patients' daily functioning was 8.2 ± 1.2 points ($p < 0.05$; all p vs. baseline). Five mild adverse events were reported in the incobotulinumtoxinA treatment period.

Conclusions: Both botulinum toxin type A preparations were administered at a higher total dose at fewer injection sites in higher concentrations (10 U/0.1 ml) than previously described. This treatment regimen resulted in long-term benefits in incobotulinumtoxinA treated chronic migraine patients who were non-responsive to previous onabotulinumtoxinA injections. These improvements could be sustained after switching back to onabotulinumtoxinA. Treatment was well tolerated.

Keywords: Botulinum toxin; IncobotulinumtoxinA; Refractory chronic migraine headache; Headache prophylaxis; Injection technique

Abbreviations:

BoNT/A: Botulinum Toxin Type A; HADS: Hospital Anxiety and Depression Scale; MIDAS: Migraine Disability Assessment Questionnaire; NSAIDs: Nonsteroidal Anti-inflammatory Drugs; PREEMPT: Phase III Research Evaluating Migraine Prophylaxis Therapy

Background

Chronic migraine is the most debilitating type of migraine with patients experiencing significantly more severe disability, lower health-related quality of life, and higher levels of anxiety and depression than those suffering from episodic migraine [1]. Preventive treatment is

often required. Statistically significant efficacy in the treatment of chronic migraine compared with placebo was shown for the antiepileptic topiramate [2], and improvements were also observed with the botulinum toxin type A (BoNT/A) onabotulinumtoxinA (Botox®, Allergan Inc., Irvine, CA) [3,4]. Recently, efficacy, safety and tolerability of onabotulinumtoxinA in the treatment of chronic migraine compared with placebo was investigated in the PREEMPT (Phase III Research Evaluating Migraine Prophylaxis Therapy) trials (PREEMPT 1 and PREEMPT 2) consisting of a 24-week, controlled, double-blind phase followed by a 32-week open-label phase [5-8]. Apart from significant reductions in the frequency of headache days (primary study endpoint), these studies also showed a significant improvement on scales related to quality of life and the impact of chronic headaches [9,10]. Based on these trials, U.S. and European health authorities (FDA and EMA) approved onabotulinumtoxinA for the preventive treatment of headaches in patients with chronic migraines.

In the PREEMPT clinical program, 155 U of onabotulinumtoxinA or placebo were administered every 12 weeks in 31 fixed-dose injections of 5 U (solution 5 U/0.1 ml) across the pre-defined muscle locations corrugator, procerus, frontalis, temporalis, occipitalis, cervical paraspinal, and trapezius. An additional 40 U could be administered in the temporal, occipital or trapezius area. OnabotulinumtoxinA doses thus ranged from 155-195 U, with the higher doses injected into patients with additional pain sites, especially at occipital level [11]. Some authors have suggested that higher onabotulinumtoxinA doses than those used in PREEMPT may be more effective in patients with chronic migraine [3], although other authors associated this with higher probabilities of adverse effects such as neck pain and ptosis [12].

In the PREEMPT studies, adverse events occurred in 62.4% of onabotulinumtoxinA patients and 51.7% of placebo patients. Most were mild to moderate in severity and only a few patients discontinued prematurely (onabotulinumtoxinA 3.8%; placebo 1.2%) due to adverse events [7]. We hypothesized that most of the reported adverse events might be associated with toxin concentration and the number of injection sites causing toxin spread to undesirable muscles groups. We therefore decided to investigate a different injection regimen to the PREEMPT studies [5-8].

Almost all studies published to date on migraine headache prophylaxis were conducted with the BoNT/A onabotulinumtoxinA. We observed in our clinical practice that some of the chronic migraine patients in our headache unit who were non-responsive to onabotulinumtoxinA injections, reported improvement of migraine headache after incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals, Germany) injections.

Our prospective, open-label study therefore evaluated the efficacy and safety of incobotulinumtoxinA in chronic migraine in patients who were non-responders to onabotulinumtoxinA. Over an 18-month period, patients were treated with fixed-dose injections of incobotulinumtoxinA using a different injection regimen to the PREEMPT studies [5-8]. Patients were subsequently switched back to onabotulinumtoxinA using the same injection regimen as for incobotulinumtoxinA.

Materials and Methods

This prospective, open-label, controlled study was conducted at our neurology department at Terrassa Hospital, Barcelona, Spain from June 2012 to June 2014 over a total study period of 24 months. Adult patients with chronic migraine headache according to the International Headache Society classification [13] and non-responders to onabotulinumtoxinA injections were included. Patients were considered non-responders to onabotulinumtoxinA if they had at least 15 migraine headache episodes per month with a mean pain intensity of more than 7 points (0-10) on a visual analogue scale (0=no pain to 10=worst imaginable pain) and less than 20% improvement on the Migraine Disability Assessment scale (MIDAS [14]) after the three previous onabotulinumtoxinA injection sessions. Patients with a contraindication for botulinum toxin therapy could not participate. Our local ethics committee approved the study protocol; written informed patient consent was obtained before inclusion into the study. Previous migraine treatment could be continued maintaining stable doses for the duration of the study. If required, patients were permitted to use nonsteroidal anti-inflammatory drugs (NSAIDs) or triptans.

This study consisted of two parts. At first, patients received incobotulinumtoxinA injections at a fixed-dose of 200 U (dilution 10 U/0.1 ml saline) every 3 months for 18 months at pericranial and frontal regions. The 20 injection sites (10 U incobotulinumtoxinA/site) included the frontal area (frontal belly of the bilateral and midline epicranial muscle), pericranial area (frontalis, parietalis, and occipitalis), temporal area, and cervical area (occipital insertion of both trapezoids) and are shown in Figure 1. In the second part of the study, patients were switched back to onabotulinumtoxinA using the novel injection regimen described above (20 injection sites and 10 U/0.1 ml saline dilution) for six months.

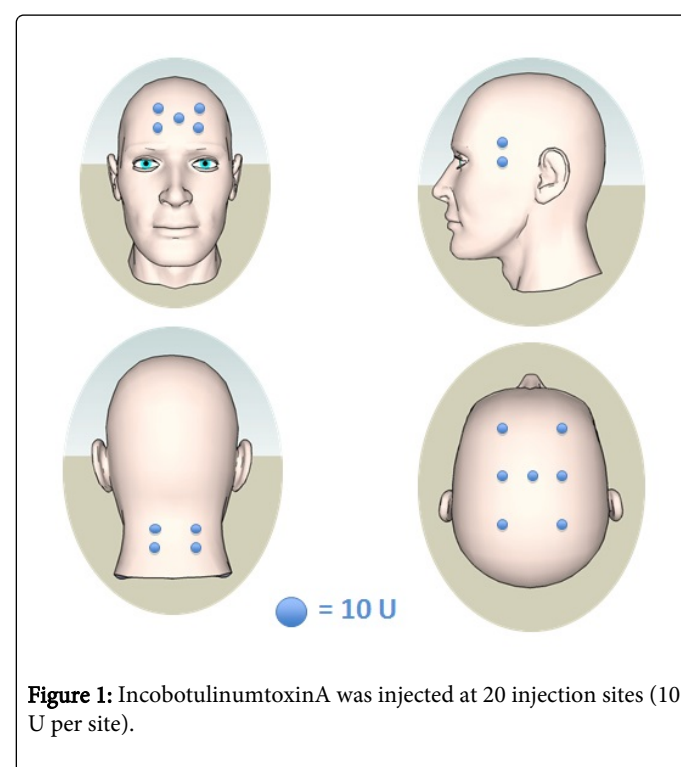


Figure 1: IncobotulinumtoxinA was injected at 20 injection sites (10 U per site).

Efficacy was assessed with several rating tools every three months. Patients were asked to document their migraine headache episodes in a diary and to rate pain during an episode on the visual analogue scale. They also rated the impact of their migraine headaches on functioning in daily life over the previous 3 months with the MIDAS scale [14]. Scores 0-5 indicate little or no disability (grade I), 6-10 mild disability (grade II), 11-20 moderate disability (grade III), and scores over 20 indicate severe disability (grade IV). Physicians additionally assessed patients' anxiety and depression levels on the Hospital Anxiety and Depression Scale (HADS [15]). Sum scores of 1-7 indicate not affected, of 8-10 indicate mildly affected, and of 11-21 moderately to severely affected patients. Furthermore, the use of NSAIDs and/or triptans was reported.

Tolerability was assessed by adverse events documentation.

Data were collected on case report forms and entered into the hospital's electronic medical records. Patients were followed over a period of 24 months. Data analysis was descriptive and performed after 18 and 24 months. The data showed normal distribution and $p < 0.05$.

Results

A total of 30 patients were included in the study; four discontinued after the first injection (one owing to a needle phobia; reasons unknown for the other three patients). Baseline demographic and clinical characteristics of the 26 patients with data for the 24-month observation period are listed in Table 1. The patient population was mainly female (84.6%); all had previously not responded effectively to preventive headache treatment. All 26 patients maintained their previous preventive treatment at baseline evaluation, the most common medications were topiramate (65%), valproic acid (25%) and amitriptyline (10%). After 24 months, 18 patients (69%) had discontinued all preventive previous prophylactic treatment, and the other 31% showed a mean reduction of 69% in total dose of preventive therapy. Patients had been previously injected for at least three treatment cycles with onabotulinumtoxinA following the conventional injection sites described for PREEMPT [5,6]; the last mean onabotulinumtoxinA dose was 170 ± 10 U.

Gender	
a) Female	22 (84.6%)
b) Male	4 (14.4%)
Age (years)	32 ± 4
Monthly headache episodes	17.2 ± 2.1
Pain intensity during episodes	9.3 ± 0.8
Accompanying migraine	12 (46%)
Allodynia	11 (42.3%)
MIDAS score	29 ± 3
Previous preventive headache treatment	26 (100%)

Table 1: Baseline demographic and clinical characteristics of the study population (n=26).

At study entry, patients presented with a mean 17.2 ± 2.1 monthly migraine headache episodes, which were significantly reduced under incobotulinumtoxinA to a mean 4.3 ± 1.0 episodes after 6 injection cycles (Figure 2A). Pain during these episodes was severe at baseline (9.3 ± 0.8) but decreased significantly during incobotulinumtoxinA treatment (Figure 2B) and was accompanied by a lower intake of acute pain medication (NSAIDs and/or triptans; Figure 2C). At baseline, all 26 patients reported taking NSAIDs and 22 were taking triptans; 58% of the tablet intakes were NSAIDs and 42% triptans. This proportion changed to 63%/37% at 6 months, and 76%/24% at 12 and 18 months, respectively. At the 18 months evaluation only 11 patients out of 26 were taking acute medication for pain relief (average of improvement 57.3% from baseline evaluation). In addition, functioning in daily life significantly improved over the treatment period: patients had presented with severe disability at baseline (MIDAS grade IV; 29 ± 3), which was reduced to mild disability (grade II) at all 3 observation time points (Figure 2D). Patients presented with mild anxiety/depression (mean HADS score 11 ± 2), which was reduced to 7 ± 1.4 at end of observation.

Three patients reported mild side effects with 3 incidences of pain in the occipital injection site lasting 10 to 12 days and 2 reports of a feeling of "heaviness of the head" without objectifiable weakness in the

cervical musculature. None of our patients showed ptosis or facial weakness after incobotulinumtoxinA injection.

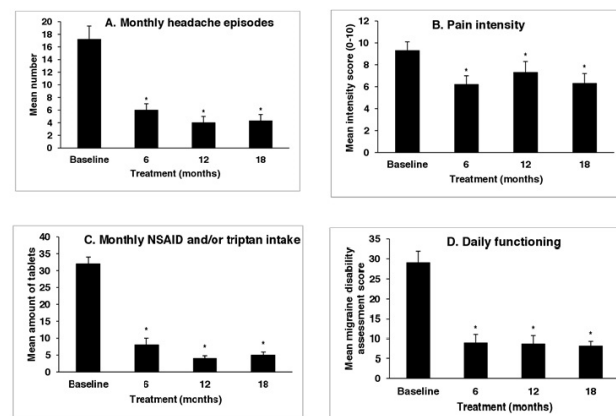


Figure 2: (A, B, C, D) Change from baseline in different efficacy parameters over the 18-month treatment period with incobotulinumtoxinA (n=26; 6 injection cycles). Data are mean + SD. *p<0.05 compared to baseline. NSAID=nonsteroidal anti-inflammatory drug.

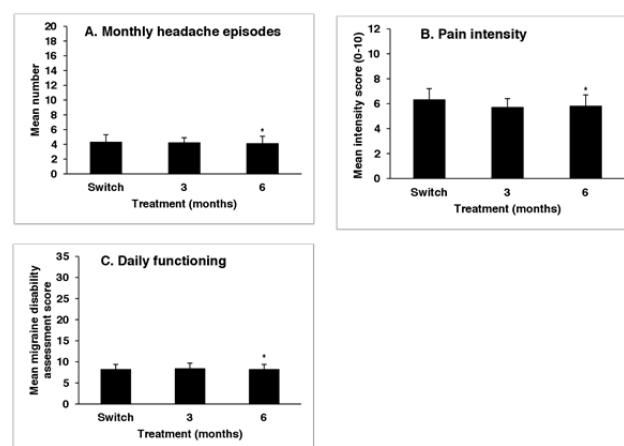


Figure 3: (A, B, C) Mean changes in different efficacy parameters after the switch to onabotulinumtoxinA (n=26; 2 injection cycles). *p<0.05 compared to baseline.

Following 18-month incobotulinumtoxinA treatment, patients were switched back to onabotulinumtoxinA. After six months of treatment with onabotulinumtoxinA, patients continued to show important improvements compared to baseline data with mean monthly migraine headache episodes of 4.1 ± 1.0 (p<0.05) (Figure 3A). Mean pain intensity during episodes was 5.8 ± 0.9 (p<0.05; Figure 3B), consumption of acute pain medication 4.0 ± 0.9 tablets (p<0.05), and mean functioning in daily life (MIDAS scale) 8.2 ± 1.2 points (p<0.05; mild disability; Figure 3C). Patients reported moderate anxiety/depression (mean 12 ± 2 on the HADS scale). Eleven patients out of twenty-six were taking medication for pain relief at the 6-month evaluation; 6 reported taking NSAIDs and 5 were taking triptans

(average improvement of 57.3% compared to the baseline). The number of patients still on pain relief was the same as at the end of incobotulinumtoxinA treatment.

None of the patients reported adverse events after onabotulinumtoxinA pericranial injections.

Discussion

The chronic migraine sufferers participating in this study experienced frequent and severe monthly headache migraine episodes at study entry and were markedly impaired in their daily functioning. None benefitted from previous prophylactic headache treatment and all were non-responders to onabotulinumtoxinA using the conventional injection regimen described in PREEMPT [5-8]. Pericranial injections of fixed-dose incobotulinumtoxinA over a period of 18 months resulted in significant improvements: mean frequency and severity of monthly migraine headache episodes were reduced by 75% and 32.3%, respectively. This was accompanied by an improvement of at least 68.9% in patients' daily functioning, and a lower consumption of acute pain medication and prophylactic treatment. Comparable results were observed in an open study with onabotulinumtoxinA: patients with refractory migraine (most of whom showed analgesic overuse) experienced a decrease in severe, disabling headache episodes, in the consumption of triptans, and in the number of emergency hospital visits over a median 4 treatment cycles [16]. After patients were switched back to onabotulinumtoxinA, the improvement achieved with incobotulinumtoxinA could be sustained during a further six months of evaluation.

The improvements seen in our study were still significant compared to baseline after six treatment cycles suggesting a sustained benefit with long-term incobotulinumtoxinA treatment in this patient group. Long-term BoNT/A benefit with onabotulinumtoxinA was also observed in clinical practice over a 5-year period in the treatment of chronic daily headache [17]. The authors reported a maximum reduction in monthly headache frequency after 12 months of treatment but improvements were still observed thereafter. An additional subgroup analysis of the PREEMPT clinical trials comparing patients who had received 5 treatment cycles with onabotulinumtoxinA with those patients who had received only 3 cycles found greater improvements for the former group in a number of headache symptom measures [18] indicating better outcomes with earlier treatment initiation for repeated BoNT/A treatment.

In the PREEMPT clinical program, onabotulinumtoxinA was administered in 31 fixed-dose injections of 5 U (dilution 5 U/0.1 ml saline) across pre-defined sites: corrugator (10 U, two sites), procerus (5 U, one site), frontalis (20 U, four sites), temporalis (40 U, eight sites), occipitalis (30 U, six sites), cervical paraspinal (20 U, four sites), and trapezius (30 U, 6 sites); the permitted dose range was 155-195 U [5-8]. None of our patients showed ptosis or facial weakness after BoNT/A injection. In our opinion, the more concentrated BoNT/A solution (10 U/0.1 ml) used in this study might explain the low rate of this type of adverse effects because this dilution avoids toxin spread to other facial muscles (Orbicularis oculis and eyelid levator). We would like to point out the sustained benefit that our patients experienced after switching back to onabotulinumtoxinA using the same injection regimen as for incobotulinumtoxinA treatment. We hypothesize that a higher BoNT/A concentration and fewer injection sites might be more effective and might reduce the incidence of adverse events in chronic migraine patients, as reported previously [19].

Although the patients in this study were initially non-responders to onabotulinumtoxinA (conventional regimen: 155-195 U, dilution 5 U/0.1 ml, 35-30 injection sites), onabotulinumtoxinA was well tolerated and effective in all assessments during the six months after being switched back from incobotulinumtoxinA at a higher fixed-dose (200 U), a higher concentration (10 U/0.1 ml) and fewer injection sites (20). Temporary muscle atrophy, weakness of neck extensors, or eyelid ptosis as previously shown [5,6] did not occur.

Study limitations include the lack of a control group and the small sample size. Better-designed studies with a larger sample size are needed to confirm our results. We think that not all patients tolerate the same BoNT/A dose and not all patients tolerate the same high-dose injections. Future parallel-group studies including a placebo arm should compare our treatment regimen to lower dose BoNT/A regimens and also to non-pharmacological modalities.

Conclusions

Although our study is limited by its open-label character, long-term treatment with incobotulinumtoxinA was well tolerated and showed sustained benefits for patients with chronic refractory migraine who were non-responders to onabotulinumtoxinA by reducing the frequency and severity of monthly headache episodes. This was accompanied by improvements in daily functioning and a lower consumption of acute pain medication. Subsequent switching back to onabotulinumtoxinA using the same injection regimen as for incobotulinumtoxinA sustained these benefits for a further six months. Higher concentrated BoNT/A solutions and fewer injection sites might reduce the incidence of adverse events while providing the same efficacy as reported in previous studies.

Competing Interests

GS has received honoraria from Novartis, Medtronic, Kirka, Juste, Esteve, Eisai, Biogen, Merz, Allergan, Arquimede, Italfarmaco, and UCB. MF has received honoraria from Novartis, UCB, Abbvie, Arquimede, and Biogen. AR has received honoraria from Novartis, Esteve, Eisai, and UCB. AF has received honoraria from Bayer, Esteve, Eisai, and UCB. MN and LS have not received honoraria.

Authors' Contributions

GS participated in the study design, injection procedure and critically reviewed the manuscript. MF wrote the first draft of the manuscript. MG, AR and LS participated in pre/post injection assessments. All authors read and approved the final manuscript.

References

1. Blumenfeld AM, Varon SF, Wilcox TK, Buse DC, Kawata AK, et al. (2011) Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). *Cephalalgia* 31: 301-315.
2. Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, et al. (2007) Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 47:170-180.
3. Silberstein SD, Stark SR, Lucas SM, Christie SN, Degryse RE, et al. (2005) Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 80: 1126-1137.

4. Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, et al. (2005) Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Headache* 45: 293-307.
5. Aurora SK, Dodick DW, Turkel CC, DeGryse RE, Silberstein SD, et al. (2010) OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia* 30: 793-803.
6. Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGryse RE, et al. (2010) OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia* 30: 804-814.
7. Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, et al. (2010) OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache* 50: 921-936.
8. Aurora SK, Winner P, Freeman MC, Spierings EL, Heiring JO, et al. (2011) OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. *Headache* 51: 1358-1373.
9. Silberstein SD, Blumenfeld AM, Cady RK, Turner IM, Lipton RB, et al. (2013) OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. *J Neurol Sci* 331: 48-56.
10. Lipton RB, Varon SF, Grosberg B, McAllister PJ, Freitag F, et al. (2011) OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. *Neurology* 77: 1465-1472.
11. Blumenfeld A, Silberstein SD, Dodick DW, Aurora SK, Turkel CC, et al. (2010) Method of injection of onabotulinumtoxinA for chronic migraine: a safe, well-tolerated, and effective treatment paradigm based on the PREEMPT clinical program. *Headache* 50: 1406-1418.
12. Blumenfeld A, Evans RW (2012) OnabotulinumtoxinA for chronic migraine. *Headache* 52: 142-148.
13. International Headache Society Classification Subcommittee. International classification of headache disorders (2004) 2nd edition. *Cephalalgia* 24(suppl 1): 1-160.
14. Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J (1999) Reliability of the migraine disability assessment score in a population-based sample of headache sufferers. *Cephalalgia* 19: 107-114.
15. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. *Acta Psychiatr Scand* 67: 361-370.
16. Oterino A, Ramón C, Pascual J (2011) Experience with onabotulinumtoxinA (BOTOX) in chronic refractory migraine: focus on severe attacks. *J Headache Pain* 12: 235-238.
17. Farinelli I, Coloprisco G, De Filippis S, Martelletti P (2006) Long-term benefits of botulinum toxin type A (BOTOX) in chronic daily headache: a five-year long experience. *J Headache Pain* 7: 407-412.
18. Aurora SK, Dodick DW, Diener HC, DeGryse RE, Turkel CC, et al. (2014) OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. *Acta Neurol Scand* 129: 61-70.
19. Ramirez-Castaneda J, Jankovic J, Comella C, Dashtipour K, Fernandez HH, et al. (2013) Diffusion, spread, and migration of botulinum toxin. *Mov Disord* 28: 1775-1783.