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ORIGINAL ARTICLE

A single-center retrospective study of onabotulinumtoxinA for treatment of 245 chronic migraine patients: survey results of a real-world experience

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Abstract
Preventive treatment in migraine is associated with poor adherence and persistence. In this observational study, our first aim was to evaluate the perceived effectiveness of onabotulinumtoxinA based on our chronic migraine (CM) patients' treatment experience. The second purpose of this study was to determine the compliance with onabotulinumtoxinA treatment in our cohort. Third, we assessed the reasons for withdrawal from treatment in our CM patients. A total of 245 consecutive patients with CM (40.43 ± 10.15 years; 214 females, 31 males) were treated with at least one onabotulinumtoxinA. Data were collected by a standardized interview over the telephone. One-hundred and eighty patients were willing to answer questions about: (1) perceived effectiveness of onabotulinumtoxinA based on their treatment experience; (2) the current continuity of the treatment; (3) their current migraine-related disability; and (4) their current medication usage. The mean number of onabotulinumtoxinA cycles of all patients and the participants were 2.58 and 2.90, respectively. Of the 180 participants, 149 patients (82.8%) thought that onabotulinumtoxinA was effective in controlling their headaches. The mean score for perceived effectiveness of onabotulinumtoxinA treatment given by the participants was as 6.94 ± 2.4 (on a scale from 0 to 10). Of the 245 treated subjects, 31 (12.6%) were treated for 12 months. Compliance rates with onabotulinumtoxinA were very low in our population. However, even CM patients who did not complete five cycles of the treatment showed marked improvement of their current migraine-related disability and reduction of their medication intake as compared to baseline.

Keywords Migraine · MIDAS · OnabotulinumtoxinA · Compliance · Chronic migraine

Introduction

Published studies about long-term experience with onabotulinumtoxinA in the treatment of chronic migraine (CM) have clearly demonstrated a significant reduction of monthly headache days, headache intensity, headache-related disability, and symptomatic medication consumption even after the first treatment session, together with improved health-related quality of life [1–16]. However, little research has been devoted to patients' compliance with onabotulinumtoxinA and the reasons for withdrawal from treatment in CM.

Chronic migraine is a significantly disabling and burdensome disorder; however, both episodic migraine and CM are mostly underdiagnosed and undertreated [17–20]. An American Migraine Prevalence and Prevention (AMPP) Study showed that almost all migraine patients were using acute treatments, while only 12% of 162,576 participants were currently taking preventive medication at the time of the survey [21]. The AMPP Advisory Group reported that 43.3% of migraine patients have never used preventive therapies as part of their treatment [22]. Not only use, but also perseverance with preventive medication for the recommended period of time would seem to be problematic issues in migraine. In this observational study, our first aim was to evaluate the perceived effectiveness of onabotulinumtoxinA based on our patients' treatment experience. The second purpose of this study was to determine the compliance with onabotulinumtoxinA treatment in our cohort. Third, we assessed the reasons for withdrawal from treatment in our CM patients.

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Methods

Study population and data collected at baseline visit

A total of 245 consecutive patients with CM [mean age ± standard deviation (SD): 40.43 ± 10.15] (214 females, 87.3%; 31 males, 12.7%) were treated with onabotulinumtoxinA as per the PREEMPT Protocol between May 2012 and May 2017. Chronic migraine and medication overuse headache (MOH) were diagnosed using clinical interview and neurological examination of the patients by three neurologists with expertise in the treatment of headache disorders, according to the criteria of the International Classification of Headache Disorders, third edition [23]. OnabotulinumtoxinA was initiated in CM patients who had not responded positively to at least two or more prophylactic migraine medications. We verified that these drugs were administered at adequate doses and enough time to be effective. We did not have any patients who were previously treated with onabotulinumtoxinA.

Data on patient demographics (age, gender), duration of migraine (years), family history of migraine, and previous migraine treatment history were collected during the baseline visit. A headache frequency, symptomatic medication intake per a month and Migraine Disability Assessment (MIDAS) were also recorded during the first onabotulinumtoxinA treatment of the patients. After the baseline visit (visit 1), the patients were requested to continue with four consecutive onabotulinumtoxinA cycles. Patients received onabotulinumtoxinA treatment quarterly during the first year. All patients received a minimum of one treatment. We followed the PREEMPT protocol (155 onabotulinumtoxinA in 31 sites).

At each session, headache diaries of the patients were collected to evaluate for headache frequency and MIDAS and the number of symptomatic drugs used by the patients were also recorded. We did not exclude patients in those receiving any preventive treatment, as it was our aim that our cohort would reflect a real clinical setting as closely as possible. Patients were allowed to continue with preventive oral medication during the treatment cycles if they had started their preventative treatments at least 3 months ago. Patients were also allowed to discontinue oral prophylaxis during onabotulinumtoxinA treatment (no alternative oral headache prophylaxis can be added later).

Eligibility of onabotulinumtoxinA

In our center, onabotulinumtoxinA treatment is not covered by the government's healthcare system; thus, a patient must have private health insurance. The approximate cost of one cycle of onabotulinumtoxinA treatment for migraine (200 units) is 750 USD. The total cost of five cycles for CM treatment per a year is 3000 USD.

Migraine disability assessment scale (MIDAS)

MIDAS is a tool-assessing headache-related disability in daily activities [24, 25]. The MIDAS questionnaire diagnoses: little or no disability (0–5), mild disability (6–10), moderate disability (11–20), or severe disability (21 or higher) depending on the severity of the attacks. MIDAS-A evaluates headache frequency and MIDAS-B assesses pain intensity (0 = no pain-10 = very severe pain) over the previous 3 months.

Study design

Eligibility was confirmed by a protocol-specific checklist. Exclusion criteria for the use of onabotulinumtoxinA treatment were pregnancy or breast-feeding, the presence of active somatic or psychiatric diseases, or allergic experience with onabotulinumtoxinA.

Data were collected through a standardized telephone interview. We called 245 CM patients treated with onabotulinumtoxinA (Fig. 1). We reached 194 patients and were unable to contact 51 patients. Fourteen patients declined to participate in the study. One-hundred and eighty patients were willing to answer questions. The responders were asked to give the following information:

(a) whether the treatment was effective (a yes or no response); **(b)** the perceived effectiveness of onabotulinumtoxinA based on their treatment experience, evaluated by a number from 0 to 10 (0 indicating ineffective and 10 indicating very effective) (patients gave to 5 or more for the perceived effectiveness of onabotulinumtoxinA, we defined them as positive feedback respondents or patients gave to below 5 for the perceived effectiveness of onabotulinumtoxinA, we defined them as negative feedback respondents); and **(c)** the current continuity of the treatment (if they were still being treated with onabotulinumtoxinA or if they had quit the treatment):

(i) If they had discontinued the treatment, the patients were asked the reason for doing so, from the following options: (1) no further need/significant improvement of headache; (2) its ineffectiveness; (3) cost/economic reasons; (4) distance to hospital; (5) dislike of needles; (6) side effects/cosmetic reasons; or (7) too busy a schedule, despite wanting treatment.

(ii) If they were still being treated with onabotulinumtoxinA in a different center, we asked them why they had quit our center and chosen a different clinic. We

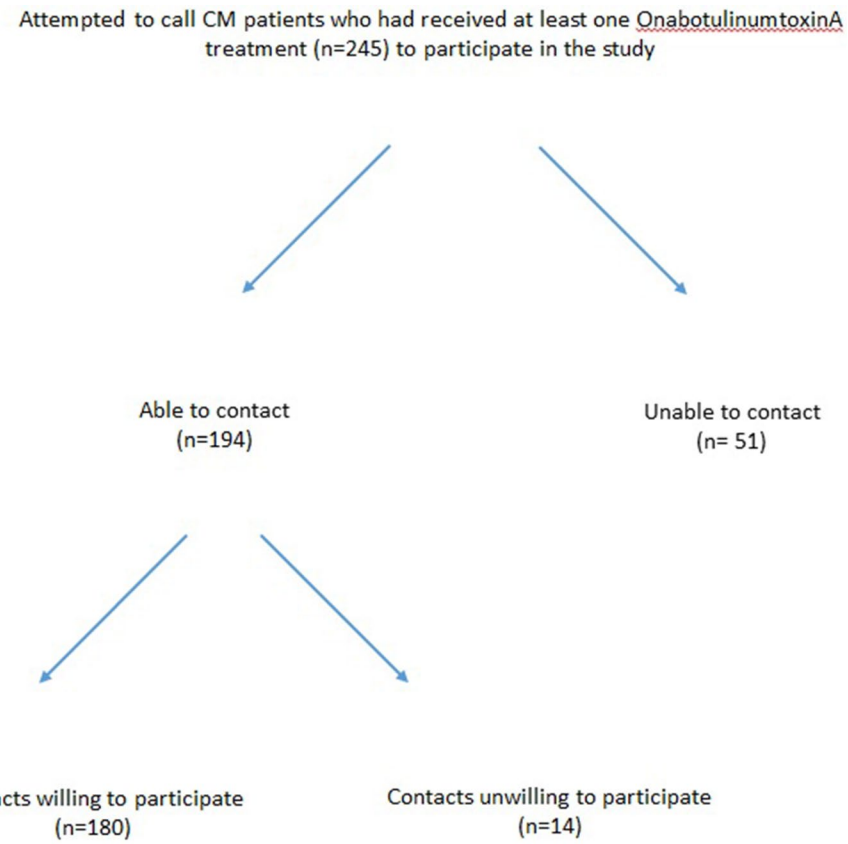

Fig. 1 Study design

gave them the following options: (1) cost/economic reasons; (2) distance to hospital; and (3) relationship with doctor.

We also asked them about

(d) their headache frequency per month;
(e) their current migraine-related disability (MIDAS, MIDAS-A, and MIDAS-B);
(f) their current use of medication.

The study protocol was conducted in accordance to the ethical principles stated in the "Helsinki Declaration" and approved by the Ethical Committee of Acıbadem University. Verbal informed constent was obtained from all the participants during the phone interviews before they enrolled on the study.

Statistical analysis

Data are expressed as mean ± SD. Data of categorical variables are shown as counts and percentages. Pearson's Chi square was used to compare the categorical variables between the study groups. Numeric variables were compared with the Kruskal–Wallis test and the Mann–Whitney *U* test. Given the small sample size for the comparison between baseline and post-treatment, the Wilcoxon rank test was used for paired data. All the statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 24.0 (SPSS Inc., Chicago, IL, USA, 2005). The level of significance was set at $p < 0.05$.

Results

Table 1 shows the demographic and clinical characteristics of all the patients and the study participants. The mean numbers of onabotulinumtoxinA cycles of all patients and the participants were 2.58 and 2.90, respectively. The mean numbers of symptomatic medications taken by all patients and the participants per month (nonsteroidal anti-inflammatory and triptan) were 27.38 and 25.80, respectively. The participants evaluated the perceived effectiveness of onabotulinumtoxinA for controlling their headaches as 6.94 (0–10) at the time of the interview. The baseline MIDAS scores showed that the two groups had suffered from severe headache-related disability (56.62 and 53.31). However, headache frequency, migraine-related disability and the mean number of symptomatic medications taken by the participants significantly decreased at the time of interview.

The previous migraine treatments of all CM patients ($n = 245$) were as follows: none ($n = 3$, 1.4%), antidepressant

Table 1 Demographic and clinical characteristics of all chronic migraine patients and participants

Variables	All patients ($n=245$)	The participants ($n=180$)
Gender	214 females (87.3%)	159 females (88.3%)
	31 males (21.7%)	21 males (11.7%)
Relatives with migraine		
+	95 (38.8%)	77 (42.8%)
−	150 (61.2%)	103 (57.2%)
CM	101 (41.2%)	105 (58.3%)
CM + MOH	144 (58.8%)	75 (41.7%)
	Mean (SD)	Mean (SD)
Age	40.43 (10.15)	40.4 (10.50)
Duration of migraine	10.06 (8.91)	12.00 (9.06)
Number of onabotulinumA cycle	2.58 (2.17)	2.90 (2.35)
Baseline number of symptomatic medication intake per month	27.38 (22.54)	25.80 (19.13)
Baseline headache days per month	18.80 (5.53)	18.86 (5.56)
Baseline MIDAS	56.62 (25.84)	53.31 (26.56)
Baseline MIDAS-A	56.76 (16.74)	56.98 (16.77)
Baseline MIDAS-B	7.89 (1.16)	7.92 (1.18)
Current headache days per month		7.68 (8.41)
Current MIDAS		19.22 (20.54)
Current MIDAS-A		23.10 (25.23)
Current MIDAS-B		6.43 (2.23)
Current number of symptomatic medication intake per month		11.23 (16.89)
Perceived effectiveness of onabotA (0–10)		6.94 (2.49)
Comparison of baseline and current values		*p*
Baseline vs current headache days per month		< 0.001*
Baseline vs current MIDAS		< 0.001*
Baseline vs current MIDAS-A		< 0.001*
Baseline vs current MIDAS-B		< 0.001*
Baseline vs current number of symptomatic medication intake per month		< 0.001*

N number of subjects, *SD* standard deviation, *CM* chronic migraine, *MOH* medication overuse headache, *MIDAS* migraine disability assessment scale, MIDAS-A evaluates headache frequency and MIDAS-B assesses pain intensity (0 = no pain, 10 = very severe pain) over the previous 3 months, $p < 0.05$

($n=129$, 61.4%), antiepileptic ($n=9$, 4.3%), antihypertensive ($n=5$, 2.4%), and multiple drugs ($n=64$, 30.5%). Participants responded as follows about their current prophylactic migraine treatments ($n=180$): none ($n=134$, 74.4%), antidepressant ($n=29$, 16.1%), antiepileptic ($n=11$, 6.1%), antihypertensive ($n=2$, 1.1%), and multiple drugs ($n=4$, 2.2%).

Table 2 shows baseline and consecutive headache frequency and MIDAS scores for every onabotulinumtoxinA cycle of 245 CM patients. The second headache frequency, MIDAS, MIDAS-A, and MIDAS-B scores of 245 CM patients statistically reduced compare to baseline values as follows: (18.8 vs 5.8 days; $p=0.001$), (53.62 vs 16.17; $p=0.001$), (56.76 vs 18.00; $p=0.001$), and (7.89 vs 6.35; $p=0.001$) (Fig. 2). Of the 245 treated subjects, 31 (12.6%) were treated for 12 months, 8 (3.2%) for 24 months, and 1 (0.04%) for 36 months. Forty-two percent of 245 subjects ($n=101$) discontinued treatment after only one onabotulinumtoxinA cycle. Sixty-four percent of 245 subjects ($n=159$) quit treatment after the second cycle.

Table 3 shows the current treatment status of the participants at the time of the interview. Eighty-four patients (46.7%) were continuing their treatments at the time of the interview. Ninety-six patients (53.3%) of 180 participants discontinued the treatment with onabotulinumtoxinA for different reasons. Three reasons for discontinuing treatment given by participants ($n=96$) were significant improvement of their headaches ($n=32$, 17.8%; mean number of onabotulinumA cycles was 3.2), ineffectiveness of treatment ($n=32$, 17.8%; mean number of onabotulinumA cycles was 1.4), and economic reasons ($n=19$, 10.6%; mean number of onabotulinumA cycles was 1.6). The side effects and

Table 2 Headache days per month and MIDAS scores of all chronic migraine patients for consecutive onabotulinumtoxinA cycles. OnabotulinumA treatment is associated with reduction in headache days per month and MIDAS scores, both with statistically significant differences between baseline and second cycle

Time point	Headache days per month, mean (SD)	MIDAS, mean (SD)	MIDAS-A, mean (SD)	MIDAS-B, mean (SD)
Baseline, $n=245$	**18.80 (5.53)**	**53.62 (24.84)**	**56.76 (16.74)**	**7.89 (1.16)**
Cycle 2, $n=144$	**5.77 (5.06)***	**16.17 (16.91)***	**18.00 (15.86)***	**6.35 (2.01)***
Cycle 3, $n=86$	5.56 (5.69)	14.37 (13.82)	16.24 (16.40)	5.94 (2.12)
Cycle 4, $n=49$	4.46 (5.38)	13.57 (15.69)	13.72 (15.95)	6.32 (1.76)
Cycle 5, $n=31$	4.0 (3.60)	14.19 (18.01)	12.83 (10.36)	6.32 (1.85)
Cycle 6, $n=21$	5.09 (6.41)	9.95 (7.36)	17.57 (21.87)	6.61 (1.32)
Cycle 7, $n=16$	4.56 (5.44)	11.56 (11.46)	15.56 (22.30)	6.37 (2.18)
Cycle 8, $n=12$	4.16 (3.27)	12.66 (16.79)	12.75 (10.09)	6.75 (1.21)
Cycle 9, $n=8$	1.87 (1.64)	6.50 (9.18)	6.12 (4.88)	6.88 (1.24)
Cycle 10, $n=4$	1.50 (2.12)	4.00 (4.83)	12.00 (12.56)	7.50 (1.0)
Cycle 11, $n=2$	7.0 (8.48)	15.00 (19.79)	20.50 (22.57)	8.50 (0.70)
Cycle 12, $n=2$	10.0	15.50 (20.50)	15.50 (20.50)	8.0
Cycle 13, $n=1$	3.00	10.0	10.0	7.0

N number of subject, *SD* standard deviation, *MIDAS* migraine disability assessment scale, MIDAS-A evaluates headache frequency and MIDAS-B assesses pain intensity (0 = no pain, 10 = very severe pain) over the past 3 months

Bold indicates statistical significance between baseline and cycle 2 of headache days per month and MIDAS scores

*$p<0.05$

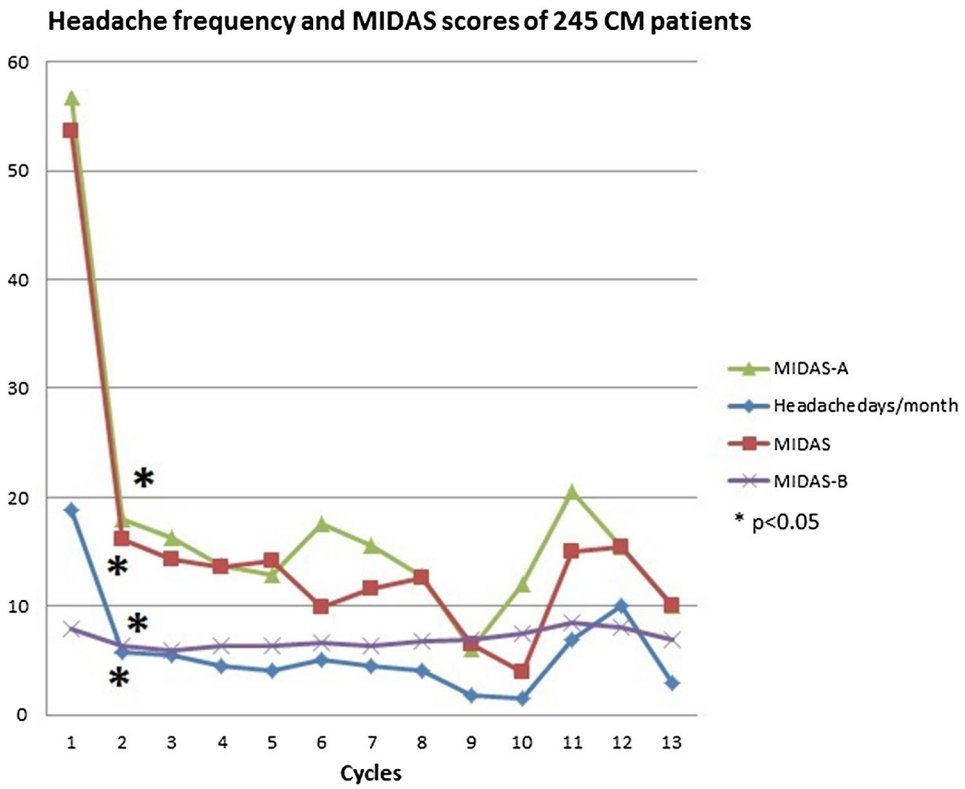

Fig. 2 Headache frequency and MIDAS scores of 245 chronic migraine patients

cosmetic reasons cited by the participants who discontinued the treatment included: neck/shoulder pain and stiffness ($n=2$), neck muscle weakness ($n=1$), and lateral eyebrow elevation ($n=2$). Four patients were treated with onabotulinumtoxinA at different centers due to the cost of the treatment ($n=3$) and the distance to hospital ($n=1$).

Table 3 Current onabotulinumtoxinA treatment status of the 180 participants at the time of the interview

Current status	*n*	%	Treatment cycles, mean (SD)
Participants who discontinued treatment ($n=96$, 53.3%)			
No further need/significant improvement of headache	32	17.8	3.2 (2.2)
Treatment ineffectiveness	32	17.8	1.4 (0.2)
Cost/economic reasons	19	10.6	1.6 (0.4)
Distance to hospital	2	1.1	0.7 (0.5)
Dislike of needles	2	1.1	3.0 (2.8)
Side effects/cosmetic reasons	5	2.8	0.9 (0.4)
Too busy a schedule despite wanting treatment	4	2.2	2.5 (1.0)
Participants who continued with treatment ($n=84$, 46.7%)			
Continued in our center	80	44.4	2.8 (0.3)
Continued in another center	4	2.2	1.3 (0.6)

N number of subjects, *SD* standard deviation

Table 4 shows the demographic and clinical characteristics of the participants. Of the 180 participants, 149 patients (82.8%) thought that onabotulinumtoxinA was effective in controlling their headaches (positive feedback), but 31 patients (17.2%) thought that it was ineffective (negative feedback). We found statistical differences between the positive and negative feedback respondents in terms of the duration of migraine (11.61 vs 14.06 years, $p=0.04$), concomitant MOH (55 vs 74.2%, $p=0.037$), the mean number of onabotulinumtoxinA cycles (3.11 vs 1.90, $p=0.003$), perceived effectiveness of the treatment (on a scale from 0 to 10) (7.87 vs 2.45, $p=0.001$), and the length of time since the last onabotulinumtoxinA treatment (12.98 vs 27.90 weeks, $p=0.01$).

Comparisons of the baseline and current headache frequency, migraine-related disability scores showed significant differences in the participants: for positive feedback respondents (18 vs 7 days for headache frequency, $p=0.001$), (53 vs 18 for MIDAS total, $p=0.001$), (57 vs 22 for MIDAS-A, $p=0.001$), (8 vs 6 for MIDAS-B, $p=0.001$), for negative feedback respondents (19 vs 8 days for headache frequency, $p=0.001$); (53 vs 22 for MIDAS total, $p=0.001$); (57 vs 30 for MIDAS-A, $p=0.01$); (8 vs 6 for MIDAS-B, $p=0.001$). Past vs current numbers of symptomatic medications used by the participants were also statistically different for the two groups: (25 vs 10 for positive respondents, $p=0.001$) and (30 vs 16 for negative respondents, $p=0.006$) (Table 4).

Discussion

Studies have shown that around 80% of CM patients respond to onabotulinumtoxinA during and after the first year of treatment [11, 12, 26]. In this observational study, a total of 82.8% of the participants thought that the treatment with onabotulinumtoxinA was effective for controlling their headaches and the mean score for perceived effectiveness of onabotulinumtoxinA treatment was reported by our CM patients as 6.94 (on a scale from 0 to 10). However, only 12.6% of the patients were treated for 12 months with five cycles. These findings indicate that even short-term compliance with onabotulinumtoxinA treatment was significantly low in our population.

Morollon et al. paid special attention to what happens to CM patients after 1 year of treatment [11]. Their study covers a total of 132 patients with CM. Only 20 patients (15%) with CM continued the treatment after more than 4 years. In the study by Russo et al., a total of 52 patients were treated with onabotulinumtoxinA and high rates of withdrawal from the initial sample were reported because of poor compliance [10]. Of the 52 treated subjects, 2 (3.8%) were treated for 15 months, 5 (9.6%) for 12 months, 7 (13.5%) for 9 months, 9 (17.3%) for 6 months, 14 (26.9%) for 3 months, and the remaining 15 (28.9%) underwent only one injection. Of the 28 patients who quit the treatment, 14 (50%) did so due to poor compliance, 10 (35.7%) because of its inefficacy, and 4 (14.3%) due to its poor tolerability. Vikelis et al. aimed to assess the efficacy and safety of onabotulinumtoxinA in Greek patients with CM. A total of 119 patients were initially enrolled in the study and only 81 (68.1%) of them continued for three cycles of onabotulinumtoxinA [13]. A study from Italy surveyed a total of 75 patients suffering from CM with MOH. Forty-six patients (61.3%) continued for three cycles and only 20 patients (26.6%) completed the first year of onabotulinumtoxinA treatment [4].

The participants in this study showed similar demographic and clinical features among all CM patients. At the time of the interview, the current headache-related disability and headache frequency of 180 participants were significantly reduced below their baseline values, despite

Table 4 Demographic and clinical characteristics of the positive and negative feedback respondents

Variables	Positive feedback respondents, *N* (%)	Negative feedback respondents, *N* (%)	*p*
Gender	131 F, 18 M	28 F, 3 M	0.690
CM	67 (45%)	8 (25.8%)	**0.037***
CM + MOH	82 (55%)	23 (74.2%)	
	Mean (SD)	Mean (SD)	
Age	40.08 (9.94)	41.90 (12.82)	0.460
Duration of migraine	**11.61 (9.20)**	**14.06 (8.23)**	**0.04***
Mean number of onabotulinumA cycles	**3.11 (2.45)**	**1.90 (1.46)**	**0.003***
Baseline headache days per month	18.25 (5.43)	19.06 (6.25)	0.440
Baseline MIDAS	53.37 (27.60)	53.03 (21.21)	0.778
Baseline MIDAS-A	56.91 (16.38)	57.35 (18.23)	0.092
Baseline MIDAS-B	7.86 (1.17)	8.22 (1.20)	0.736
Baseline number of symptomatic medication intakes/month	24.85 (18.52)	30.28 (21.58)	0.541
Perceived effectiveness of onabotulinumA	**7.87 (1.17)**	**2.45 (2.26)**	**< 0.001***
Last treatment interval (week)	**12.98 (14.39)**	**27.90 (15.52)**	**< 0.001***
Current headache days per month	7.20 (8.20)	7.96 (9.15)	0.97
Current MIDAS total	18.61 (21.14)	22.16 (17.74)	0.08
Current MIDAS-A	21.69 (24.61)	29.87 (27.46)	0.092
Current MIDAS-B	6.47 (2.17)	6.25 (2.52)	0.736
Current number of symptomatic medication intakes/month	10.18 (15.56)	16.25 (21.83)	0.541
Comparison of baseline and current MIDAS and number of symptomatic medication intakes			
Baseline vs current headache days month	**< 0.001***	**< 0.001***	
Baseline vs current MIDAS	**< 0.001***	**< 0.001***	
Baseline vs current MIDAS-A	**< 0.001***	**< 0.001***	
Baseline vs current MIDAS-B	**< 0.001***	**0.001***	
Baseline vs current number of symptomatic medication used by patients/month	**< 0.001***	**0.006***	

N number of subjects, *SD* standard deviation, *CM* chronic migraine, *MOH* medication overuse headache, *MIDAS* migraine disability assessment scale, MIDAS-A evaluates headache frequency and MIDAS-B assesses pain intensity (0 = no pain, 10 = very severe pain) over the previous 3 months, bold indicates statistical difference

*$p < 0.05$

insufficient onabotulinumtoxinA cycles [MIDAS 25.80 (current) vs 53.31 (baseline) and headache frequency 7.92 (current) vs 18.86 (baseline)]. Although the data showed a marked improvement in their MIDAS scores, the participants still had severe migraine-related disability and frequent headache days due to migraine at the time of the interview. Morollon et al. also report that around 90% of patients need to continue with onabotulinumtoxinA injections even after the first year's treatment to keep migraine frequency under reasonable control, probably due to the chronic nature of CM [11].

The headache frequency and migraine-related disability of the patients in the second cycle of onabotulinumtoxinA were reduced significantly compare to the baseline values (18.80 vs 5.77 days, $p = 0.001$) and (53.62 vs 16.17, $p = 0.001$). However, adherence with the treatment is low in our cohort. During consecutive cycles, the number of treated subjects with onabotulinumA gradually diminished. The patients who continued with onabotulinumtoxinA after five cycles had less frequent headache days and reduced migraine-related disability compare to their baseline values.

The three most common reasons for non-compliance given by participants who discontinued treatment were: improvement of headache, treatment ineffectiveness, and cost of onabotulinumtoxinA. One major difference between the patients with improvement and not improvement of their headache was mean number of onabotulinumtoxinA cycles (3.2 vs 1.4 cycles). Therefore, insufficient cycles of the patients with onabotulinumtoxinA need to be considered for treatment ineffectiveness. Besides a recent study showed that two treatment cycles might not be enough to evaluate ineffectiveness of onabotulinumtoxinA as suggested to PREMPT post hoc analysis [27, 28]. Our patients reported a low discontinuation rate (2.8%) because of adverse effects

compatible with a pooled analysis of the safety and tolerability of onabotulinumtoxinA in the treatment of CM (3.4%) [29]. One of the major reasons for discontinuing treatment was economic difficulty; 10% of the participants reported this challenge. In our center, the cost of onabotulinumtoxinA treatment is 3000 USD for a year, which generally speaking is expensive for a developing country such as Turkey. However, evidence from retrospective analysis of a United State-based insurance claims database revealed that headache-related emergency department visits and hospitalizations significantly declined after prophylactic treatment with onabotulinumtoxinA and notably increased after prophylactic treatment with oral migraine prophylactic medications [30].

The 82.8% of positive feedback respondents about onabotulinumtoxinA were statistically different from the negative respondents in terms of a lack of concomitant MOH, shorter duration of migraine, higher number of onabotulinumtoxinA cycles, perceived effectiveness of the treatment, and shorter length of time since the patient's last treatment. The concomitant MOH percentages for the positive and the negative feedback respondents were 55 and 74.2%, respectively. The mean number of onabotulinumtoxinA cycles was also different for the positive and for the negative feedback respondents (3.11 vs 1.90); this finding suggested that too few onabotulinumtoxinA cycles might be a significant factor in the negative feedback respondents' evaluation of the treatment as ineffective [27]. Moreover, one other potentially important factor for positive and negative feedback respondents could be the length of time between the last treatment and the interview (12.98 vs 27.90 weeks). Negative feedback respondents had a longer time interval between their last injections and the interview. We assume that the negative feedback respondents may have had a negative impression of the efficacy of the treatment, because onabotulinumtoxinA was no longer effective at the time of the interview. The current headache frequency of the positive and negative feedback respondents was reported as 7.2 and 8 days per month, respectively. In both groups, CM replaced to episodic migraine at the time of the interview. However, MIDAS scores of two groups showed difference. The positive feedback respondents suffered from moderate migraine-related disability, while the negative feedback respondents were still severely disabled because of migraine. The other explanation of the respondents who gave a negative feedback evaluation for onabotulinumtoxinA might be their higher MIDAS scores. Even for respondents who evaluated onabotulinumtoxinA as a negative way, the current migraine-related disability scores still significantly reduced below their baseline values.

There are a few limitations in this study. First, it comes from a single headache center, so our selected sample does not allow our results to be generalized. Second, we treated 245 CM patients with onabotulinumtoxinA in the course of 5 years, but we could not reach all these patients by phone; thus, the participants were only part of our cohort. If all our patients had been included in our study, the results could easily have been different. Third, we assessed headache days per month, symptomatic medication intake per month, and MIDAS scores on the basis of the respondents' memory and statements at the time of the interview. Fourth, in the interview, 10.6% of our patients cited the high cost of onabotulinumtoxinA as a reason for withdrawal from treatments; it was the reason why three patients were receiving treatment at other centers. Moreover, most of our patients had been finding it difficult to get adequate reimbursements for their onabotulinumtoxinA injections from insurance carriers. Therefore, the cost of the treatment seems to be a considerable factor in the discontinuation of this treatment, at least for some CM patients who might have responded well to it. If the national healthcare system had covered onabotulinumtoxinA treatment in our clinic or if onabotulinumtoxinA had cost less, the compliance rates of our population would probably have been different. Finally, as an observational study, this has no control group, so the above results must be interpreted with great caution.

Even the CM patients who did not complete five cycles of the treatment showed markedly improved migraine-related disability and reduced headache frequency and a reduction of medication intake below their baseline values. It may be hypothesized that onabotulinumtoxinA treatment is capable to a certain extent of interfering with the prolonged sensitization of the peripheral nociceptor even if patients do not receive five cycles of treatment. It might be extended to at least 1 year; cumulative effects of onabotulinumtoxinA might be reduced and remodeled peripheral sensitization directly and central sensitization indirectly. Our observational study highlights a low compliance with onabotulinumtoxinA. Achieving optimal outcomes in CM necessitates that continue to do so throughout persistence with treatment. Poor adherence to treatment was a major problem among patients with CM in real-life setting and might be as one of the main causes of failure to achieve adequate control of headache.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing of interests.

Ethical approval The study protocol was conducted in accordance to the ethical principles stated in the "Helsinki Declaration" and approved by the Ethical Committee of Acıbadem University.

Informed consent Verbal informed constent was obtained from all the participants during the phone interviews before they enrolled on the study.

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