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ORIGINAL ARTICLE

The wear-off phenomenon of repeated botulinum toxin injection for chronic migraine treatment: A retrospective study

Kronik migren tedavisinde tekrarlanan botulinum toksin enjeksiyonunun yıpranma payı (wear-off fenomeni): Retrospektif çalışma

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ABSTRACT

Objectives: This study aimed to evaluate the efficacy, predictors of response, clinical considerations, and analysis of patient-reported wear-off events during injection periods of onabotulinumtoxinA (Onabot-A).

Patients and methods: This retrospective study was conducted with 30 adult chronic migraine patients (26 females, 4 males; mean age: 37.9±9.3 years; range, 24 to 72 years) followed between January 2017 and December 2022. All patients received Onabot-A injections at different frequencies throughout their treatment and responded to Onabot-A. The duration between cycles was 3 months in 26 patients, and this period varied in four patients. The Visual Analog Scale scores were measured before and after the injection, all patients responded to Onabot-A.

Results: Nine patients stated that they experienced wear-off at least once during their treatment cycles. In some patients, the duration of action lasted less than 12 weeks, resulting in a wear-off phenomenon. Although sex and age were not significant variables in terms of the presence or absence of wear-off phenomenon, the number of Onabot-A injections (Onabot-A treatment cycles) among patients was found to be a statistically significant variable in terms of the presence of wear-off ($p<0.011$).

Conclusion: Repeated treatments using Onabot-A appear to be safe and well-tolerated, but the effectiveness of the drug appears to be affected by wear-off phases that may occur during long-term treatment with Onabot-A.

Keywords: Botulinum toxin, headache, migraine, Onabot-A, wear-off.

ÖZ

Amaç: Bu çalışmada, onabotulinumtoksinA (Onabot-A)'nın etkinliği, yanıtın belirleyicileri, klinik hususlar ve enjeksiyon periyotları sırasında hasta tarafından bildirilen yıpranma olaylarının analizi değerlendirildi.

Hastalar ve yöntemler: Bu retrospektif çalışma, Ocak 2017 - Aralık 2022 tarihleri arasında takip edilen 30 erişkin kronik migren hastası (26 kadın, 4 erkek; ort. yaş: 37,9±9,3 yıl; dağılım, 24-72 yıl) ile gerçekleştirildi. Tüm hastalara tedavileri boyunca farklı sıklıklarda Onabot-A enjeksiyonu uygulandı ve tüm hastalar Onabot-A'ya yanıt verdi. Döngüler arasındaki süre 26 hastada 3 ay, diğer dört hastada ise bu süre değişkenlik gösterdi. Görsel Analog Skala skorları uygulama öncesinde ve sonrasında ölçüldü, tüm hastalar Onabot-A'ya yanıt verdi.

Bulgular: Dokuz hasta tedavi döngüleri sırasında en az bir kez yıpranma etkisi yaşadığını belirtti. Bazı hastalarda etki süresi 12 haftadan kısa sürdü ve bu da yıpranma etkisine yol açtı. Cinsiyet ve yaş, yıpranma etkisinin varlığı veya yokluğu açısından anlamlı değişkenler olmasa da, hastalar arasında Onabot-A enjeksiyonu sayısı (Onabot-A tedavi döngüleri) yıpranma varlığı açısından istatistiksel olarak anlamlı bir değişken olarak bulundu ($p<0.011$).

Sonuç: Onabot-A kullanılarak tekrarlanan tedavilerin güvenli ve iyi tolere edildiği ancak ilacın etkinliğinin Onabot-A ile uzun süreli tedavi sırasında ortaya çıkabilecek yıpranma aşamalarından etkilendiği görülmektedir.

Anahtar sözcükler: Botulinum toksin, baş ağrısı, migren, Onabot-A, yıpranma.

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Migraine, a neurological condition characterized by disabling primary headaches, is a prevalent issue that impacted over one billion individuals worldwide in 2016. This condition resulted in 45.1 million years of life lived with disability.[1] Numerous epidemiological studies have highlighted its high prevalence and the significant socioeconomic and personal consequences it brings. According to the Global Burden of Disease Study 2010, migraine ranks as the third highest cause of disability globally among individuals under the age of 50 years, regardless of sex.[2,3] Annually, approximately 2.2 to 3.1% of patients with episodic migraine progress to chronic migraine.[4] Moreover, an estimated 1 to 4% of the population has been diagnosed with chronic migraine.[4] The diagnosis criteria for chronic migraine are determined by the International Classification of Headache Disorders criteria for migraine. To be diagnosed with chronic migraine, an individual must experience headaches occurring at least 15 days per month for more than three months; during at least eight days within those months, these headaches must exhibit features characteristic of a typical migraine episode.[5] One common factor that contributes to symptoms suggestive of chronic migraine is medication overuse.[6]

A definitive cure for chronic migraine treatment has not been found. The aim of treating chronic migraine is to reduce the frequency of attacks and alleviate the intensity of pain. Various groups of pharmacological drugs are commonly employed in managing migraine attacks, including analgesics, nonsteroidal anti-inflammatory drugs, triptans, ergot alkaloids, opioids, and antidepressants.[7] Preventing these attacks is crucial and mandatory for individuals suffering from migraine. For many patients with chronic migraine headaches, effective preventive treatments such as onabotulinumtoxinA (Onabot-A) and monoclonal antibody agents have shown positive results. In 2010, the effectiveness of Onabot-A in treating chronic migraine was confirmed through Phase 3 Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials.[5,6] Consequently, it received approval from both the European Medicines Agency and the USA Food and Drug Administration for prophylactic use against chronic migraine.[4,5] Many patients have found Onabot-A to be a successful treatment for chronic migraine, but it can still be challenging to determine how effective it will be for certain individuals.

The PREEMPT study revealed that administering injections of Onabot-A to the craniofacial-cervical regions of individuals with chronic migraine resulted in a significant improvement compared to placebo. In the treatment of chronic migraine, this therapy is typically administered in three to five cycles at intervals of three months.[4,5] The use of Onabot-A has been shown to significantly reduce both the frequency and severity of migraine attacks for a period lasting at least three months.[4,5] The degree to which these reductions occur can range from 50% up to 70-80%.[4,5] What sets Onabot-A apart from other prophylactic medications is its convenience; it does not require daily dosing and does not produce common cognitive side effects.[8]

Botulinum toxin, also known as Botox, is a highly potent substance found in nature. Botulinum toxin is produced by a specific type of bacteria called *Clostridium botulinum*.[9] The first documented use of botulinum toxin as a medical treatment came from the efforts of Scott[10] in treating strabismus, specifically crossed eyes. Botulinum toxin works by inducing flaccid paralysis within both skeletal muscle tissues and autonomic cholinergic nerve terminals.[11] One unique characteristic of botulinum toxin is its selective targeting within synaptic vesicles located on presynaptic membranes. This attribute contributes to both its lethality at high doses and its effectiveness when used therapeutically. Once inside these vesicles, the potent neurotoxin cleaves nine amino acids. Based on the process by which botulinum toxin affects nerve terminals, synaptic vesicles are unable to merge with the membrane of the nerve terminal, thereby blocking the release of neurotransmitters at the synapse and hindering the integration of receptors/ion channels into the membrane of the nerve terminal.

Many studies are showing that botulinum injection is safe and effective not only in migraine but also in cervical dystonia, various facial region disorders, blepharospasm, hemifacial spasm, and sialorrhea.[12-15] To date, many studies, including meta-analyses, have been conducted on migraine diagnosis and treatment. Placebo-controlled multicenter trials, the PREEMPT 1[6] and PREEMPT 2[5] clinical trials, consisted of a 24-week placebo-controlled phase followed by a 32-week open-label extension phase. OnabotulinumtoxinA was administered at 12-week intervals and injected in 31 sites (5 U per injection) with the possibility for eight additional injections according to a "follow-the-pain" strategy. The total dose of Onabot-A was 155 U to 195 U injected in 31 to 39 sites. This is hereafter referred to as the PREEMPT injection protocol.[16]

A Cochrane review conducted in 2018 analyzed 28 randomized control trials and concluded that Onabot-A resulted in a reduction of 3.1 migraine days (95% confidence interval 1.4-4.7) and 1.9 headache days (95% confidence interval 1.0-2.7) after six months.[17] The REPOSE (real-life use of botulinum toxin for the symptomatic treatment of adults with chronic migraine, measuring healthcare resource utilization, and patient-reported outcomes) study further examined the long-term effectiveness of Onabot-A in chronic migraine by conducting a 24-month open-label study involving 641 participants. The study found that the mean number of migraine-headache days decreased from an initial value of 20.6±6.6 to just 7.4±6.6 after two years, resulting in noticeable improvements in quality-of-life measures.[18] However, when it comes to migraine episodes, three separate meta-analyses have failed to find any evidence supporting the efficacy of Onabot-A.[17,19,20]

In the PREEMPT studies, individuals who experienced a decrease of at least 50% in the number of headache days per month were considered responders. On the other hand, according to the NICE (National Institute for Health and Care Excellence),[21] responders were defined as patients who had a minimum reduction of 30% in their monthly headache days. Like other chronic pain conditions, experts specializing in headaches view a 30% reduction in headache days as clinically significant for individuals with chronic migraine, a complex disorder that requires careful management.[22]

The term wear-off is utilized when the frequency and intensity of attacks commence before the completion of three months following more than five cycles of Onabot-A injections. Cases where attacks occur before the three-month mark after prolonged Onabot-A treatment (for instance, with a minimum of seven cycles) are known as the wear-off effect.[23,24] This study aimed to identify the potential causes for a decrease in response to Onabot-A injections in patients with chronic migraine, occurring after multiple injections.

PATIENTS AND METHODS

This retrospective study involved 30 adult patients (26 females, 4 males; mean age: 37.9±9.3 years; range, 24 to 72 years) at Altınbaş University Medical Park Bahçelievler Hospital Department of Neurology who underwent Onabot-A treatment for migraine between January 2017 and December 2022. The patients included in the study were those who had previously received irregular treatment such as triptans or ergotamine but did not receive an adequate response. The study had certain inclusion criteria, which included being diagnosed with migraine according to the ICD-10 (International Classification of Diseases 10th Revision), indicating Onabot-A treatment with five to six attacks per month and experiencing headaches for 10 to 12 days per month. Additionally, the patients had to be above the age of 18. The exclusion criteria were having primary or secondary headache disorders and other contraindications to Onabot-A treatment. To be classified as chronic migraine sufferers according to our definition in this study, it was necessary for individuals to experience at least 15 days of headaches per month or have between six to eight migraine attacks each month. However, some patients experienced only four to five attacks monthly that could last between two to three days each time. Despite not meeting the standard criteria for chronic migraine based on frequency alone, we decided to include these patients within the chronic migraine group. The patients were categorized into two groups based on Onabot-A treatment cycles: the first group (Group A), representing one to five cycles (n=18); the second group (Group B), representing 6 to 23 cycles (n=12).

The patients were administered Onabot-A injections (BOTOX; AbbVie Inc., North Chicago, IL, USA) after a careful examination. The Visual Analog Scale (VAS) scores were measured before and after the Onabot-A injection. There was no prophylactic medication use or analgesic overuse in our patients. In this study, patients were not given peripheral nerve blockade, intramuscular ketorolac injections, or intravenous/oral steroid drugs. However, some of them were started on selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors due to anxiety disorders. Duloxetin is a serotonin-noradrenaline reuptake inhibitor (SNRI). We used it in patients where necessary to both reduce the patient's fibromyalgia and the anxiety symptoms. The anticonvulsant topiramate was used only in few patients for migraine prophylaxis when needed (Table 1). The worsening of symptoms was defined as any explicit report made by a patient regarding an increase in headache intensity or neck pain during the four weeks (28 days) leading up to their scheduled Onabot-A reinjection session (Figure 1). The duration between cycles was three months in 26 patients, and this period varied in four patient as given in Table 2. The number of attacks before and after Onabot-A is also shown in Table 2 as descriptive data.

TABLE 1
Demographic data

	n	%	Mean±SD	Median	IQR 25th-75th percentile	Min-Max
Age (year)			37.9±9.3			24-72
Onabot-A cycle				5	3.00-8.25	
Sex						
Female	26	87				
Male	4	13				
Medical history						
HT, coronary artery disease	1	3				
Mild anxiety	9	30				

SD: Standard deviation; IQR: Interquartile range; HT: Hypertension.

Statistical analysis

Data were analyzed using IBM SPSS version 28.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were presented as frequency (n) and percentage (%). Quantitative variables were expressed as mean ± standard deviation (SD) (min-max). Checking the distribution of quantitative variables for normality was assessed by the Shapiro-Wilk test. If the variables did not distribute normally, the Mann-Whitney U test was used to compare two independent samples. For instance, between wear-off groups, the age was compared by the Mann-Whitney U test. Additionally, the number of Onabot-A treatment cycles was compared between wear-off groups by the Mann-Whitney U test (Table 3). Analysis of the VAS was performed by the Wilcoxon signed-rank test. A logistic regression test was performed for the evaluation of the effects of independent variables on wear-off status. Sex, age, and the number of Onabot-A treatment cycles were independent variables in the logistic regression model. Two dependent categorical groups were assessed by the McNemar test. A p-value <0.05 was considered statistically significant.

RESULTS

The majority of the patients were young female adults. The demographic data is presented in Table 1. There was a statistically significant difference between VAS scores before and after Onabot-A injection (p<0.001). After the injection of Onabot-A, there were no noticeable negative effects. Table 2 shows the number of attacks both before and after the injection, as well as any wear-off phenomenon that may have occurred. After Onabot-A treatment, a decrease in the number of migraine attacks was observed in all patients. Although each patient reported a different period, the frequency of migraine attacks was reduced in all patients (Table 2).

A linear regression equation was created as follows: Y=-14,245-18.264*(Sex)-0.035*(Age) + 0.88*(n). The number of Onabot-A treatment cycles,

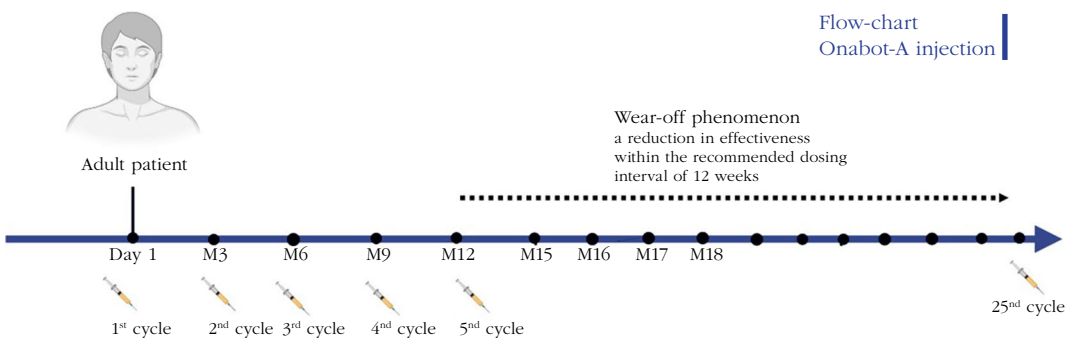

Figure 1. Onabot-A injection flow-chart.
M: Month; *(created with BioRender.com).*

TABLE 2
Descriptive data for Onabot-injection

	Patients who were treated with Onabot-A	
	n	%
Duration between injections (month)		
3	26	86.7
3 or 7	1	3.3
6	2	6.7
7	1	3.3
Frequency of migraine attacks before Onabot-A (month)		
3-6 per	1	3.3
4-6 per	5	16.7
5-6 per	7	23.3
5-7 per	6	20
6-7 per	9	30
7 per	1	3.3
7-8 per	1	3.3
Frequency of migraine attacks after Onabot-A (month)		
1 per 2	2	6.7
1 per 4-7	1	3.3
1 per 6	1	3.3
1 per	9	30
1 per year	3	10
1-2 per	5	16.7
1-3 per	1	3.3
2 per	2	6.7
2-3 per	1	3.3
No attack during 3rd months; 1 per month at 4th month	1	3.3
No attack during 4th months; and then 1-2 per month	1	3.3
No attack during 5th months; 1 attack at 6th month	1	3.3
No attack during 6th months; and then 1-2 per month	1	3.3
No attack in 1st year; 1 per month in 2nd year	1	3.3

TABLE 3
The relation between wear-off effect and treatment cycle (n)

	B	SE	Wald	df	*p* (Sig.)	Exp(B)	95% CI for Exp (B)	95% CI for Exp (B)
Sex	-18.264	19027.452	0.000	1	0.999	0.000	0.000	
Age	-0.035	0.076	0.211	1	0.646	0.966	0.833	1.120
Onabot-A treatment cycle (n)	0.880	0.347	6.450	1	0.011*	2.412	1.223	4.759
Constant	-14.245	9513.726	0.000	1	0.999	0.000		

B: Coefficient of variables; SE: Standard error; Wald: Wald Statistics; df: degree of freedom; *p*: Significance; Exp (B): OR (Odds ratio); CI: Confidence interval; * While sex and age did not affect whether wear off or not, the Onabot-A n (treatment cycle) variable had a significant effect on whether wear off or not (p=0.011).

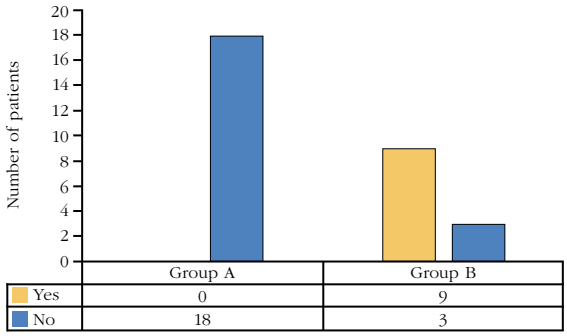

Figure 2. The number of patients who experienced wear-off during their treatment cycles is presented. Blue bars represent the number of patients who did not experience wear-off, and yellow bars represent the number of patients who experienced wear-off. The groups were categorized by the number of Onabot-A cycles: Group A) representing 1-5 cycles, patient n=18; Group B) representing 6-23 cycles, patient n=12.

one of the independent variables, was found to be statistically significant in predicting the dependent variable Y (p=0.011). The odds ratio for the number of treatment cycles variable was calculated as 2.412. The dependent variable Y represents the presence of wear-off. While sex and age were not significant variables for the presence of the wear-off phenomenon (Table 3), the number of Onabot-A injections was found to be a statistically significant variable for the presence of the wear-off phenomenon (p=0.011, Table 3). In Group B who received Onabot-A injection for more than 5 cycles, the number of patients reporting wear-off was recorded as 9 (Figure 2).

DISCUSSION

Onabot-A treatment has proven to be a successful therapeutic option for patients with chronic migraine who have previously shown little or no response to pharmacological treatments. Evaluating the response to migraine treatment is a complex process as it involves not only measuring the frequency but also considering the severity of headaches, patient tolerability towards the treatment, levels of disability, and patient preferences. It is preferred that patients have already tried two or three other migraine preventive medications before initiating Onabot-A therapy. Additionally, factors such as headache intensity, degree of disability experienced by patients, and their individual preferences should also be taken into account when evaluating treatment response. In this study group, some patients who received Onabot-A therapy were also using duloxetine or topiramate drugs due to coexisting conditions, such as anxiety disorder or fibromyalgia. After week 12, a group-level analysis showed both statistically significant and clinically relevant wear-off effects in terms of prevention provided by Onabot-A injections for chronic migraine. The findings from this study demonstrate clearly that there is indeed a wear-off effect associated with OnabotA after its initial efficacy wears off over time.

To monitor the response, we utilized the simplest measure known as the VAS score before and after the Onabot-A treatment, and there was a statistical difference, showing that the Onabot-A injection was effective. One of the inclusion criteria of the study was Onabot-A being effective in migraine treatment. When it comes to initial responders of Onabot-A, evaluating their response over time becomes complicated since the effect of the treatment diminishes after a certain period, usually around two to three months. A partial increase in the VAS score was observed in patients who developed wear-off. Therefore, it was important to evaluate wear-off effect time points. It would be beneficial for further studies to explore how Onabot-A interacts with other prophylactics, such as calcitonin gene-related peptide receptor antagonists, concerning the withdrawal of medication overuse. In chronic migraine cases, some studies have indicated that there may be a wear-off effect of Onabot-A during the treatment cycle. A study conducted in Spain focused on 193 patients during their first treatment cycle and found that 70% experienced a 50% reduction in five to eight weeks.[25] Among these patients, two-thirds maintained this level of response until week 12; however, one-third did not achieve a ≥50% reduction in headache days when considering weeks 7 to 10 or 9 to 12 (these individuals were referred to as wear-off responders).

The second research study involved 143 patients from the USA. The physician's notes were used to identify both the response to Onabot-A and wear-off.[26] However, the headache diaries were not taken into account during the analysis. It was found that two-thirds of patients experienced wear-off between weeks 6 and 12, particularly during the first cycle. When it comes to preventing chronic migraine, it is believed that Onabot-A acts on primary afferent C-fibers. However, there has been no investigation into how long Onabot-A remains active on these C-fibers. In mice, after injection with botulinum neurotoxin A, there is

a loss of exocytotic function in motor neurons. However, partially functional dendritic sprouts appear after 28 days, and normal function is restored in the original nerve terminal after 91 days.[27,28] The typical length of time that the human frontalis muscle remains affected by Onabot-A is between 77 and 87 days, which is equivalent to approximately 12 weeks.[29] When treating motor disorders, it is assumed that the effects of Onabot-A last for about three months. However, in the case of axillary hyperhidrosis and motor disorder treatment with Onabot-A, the effects can persist for more than six months.[30] In patients with neurogenic detrusor overactivity, retreatment with Onabot-A was typically requested after a median period of 42 weeks or around 10 months.[31] Based on this information, it can be concluded that the duration of action varies significantly depending on the specific indication being treated and cannot be directly estimated based on chronic migraine treatment. Reducing injection intervals to less than 12 weeks could be considered as a potential strategy to address potential wear-off in certain patients who experience repeated wear-off episodes. However, this approach must also consider the risk of developing neutralizing antibodies with long-term treatment.[32,33] Nonetheless, in an editorial published in response to Albrecht's analysis in 2019 and a subsequent meta-analysis in 2023, these neutralizing antibodies did not manifest in many patients.[34,35] In our study, we observed instances where wear-off occurred at around 12 weeks or even longer after starting treatment. Some researchers have proposed that increasing the dosage might prolong the effectiveness of Onabot-A.[25,26] The present study did not find any correlation between the dosage range of 155 U of Onabot-A and the wear-off effect. Some patients, particularly after the first year of treatment, reported successful delay of injections without worsening their headaches. This study utilized quantitative data from headache diaries to accurately determine the number of headache days monthly, which helped identify when the effectiveness of Onabot-A began to diminish in the study group. We should address a clinically important question regarding when chronic migraine patients who initially responded well to Onabot-A treatment experienced a wear-off effect. Our research focused on detecting wear-off effects during Onabot-A treatment starting from the fifth cycle, thus making our findings applicable to subsequent cycles as well. Although we did not know exactly how long the effects of Onabot-A lasted in chronic migraine cases, we aimed to observe if there was a reduction in effectiveness within the recommended dosing interval of 12 weeks or thereafter.

The limitations of the study include the low number of patients and the lack of data on the number of antibodies, which is a valuable data to investigate the reasons behind wear-off in Onabot-A treatment.

In conclusion, the effectiveness of treatment for migraine patients is determined by how much it reduces the number or severity of headache days compared to their baseline. Onabot-A treatment offers an effective option for those who have not responded well to traditional medication and experience long periods without headaches. In this study, patients with chronic migraine who had previously tried preventive treatments without success were given injections of Onabot-A, and a wear-off effect was experienced by some patients during the treatment cycle. Repeated treatments using Onabot-A appear to be safe and well tolerated, but the effectiveness of the drug is affected by phases of wear-off that may occur during long-term treatment with Onabot-A. For this reason, it may be a more effective approach to try newer pharmacological agents instead of Onabot-A after using 5 cycles as recommended in the PREEMPT study. More studies are needed for an effective migraine treatment.

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Ethics Committee Approval: The study protocol was approved by the Altınbaş University Clinical Research Ethics Committee (date: 08.12.2022, no: 162). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: Onabot-A injection, informed consent was obtained from every patient involved.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Did the literature research: G.H.; Wrote the manuscript: E.R., G.H.; Analysed the statistical calculations, all the authors contributed to writing, editing and reviewing the manuscript: Y.T.

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