▪ Headache Medicine 2022, 13(3):179-185 ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

▪ DOI: 10.48208/HeadacheMed.2022.18

Review

Impacts of the preempt protocol on chronic migraine: an integrative review

Melissa Helena Rodrigues Silva[1], Joaquim Fechine de Alencar Neto[2], Otávio da Cunha Ferreira Neto[1], Luiz Bandeira Alves Neto[3], Nilson Batista Lemos[2], Arthur Oliveira Lira[2], Maria Luísa Rocha[4], Luís Felipe Ferreira Marques[5], Victor Egypto Pereira[6], Victoria Rodrigues Durand[2], Ana Cristina Veiga Silva[7,8], Luiz Severo Bem Junior[2,8], Hildo Rocha Cirne de Azevedo Filho[8]

[1]Catholic University of Pernambuco, Recife, Pernambuco, Brazil.
[2]College of Medical Sciences, Unifacisa University Center, Campina Grande, Paraiba, Brazil.
[3]University of Pernambuco, Recife, Pernambuco, Brazil.
[4]Brasília University Center, Brasília, Distrito Federal, Brazil.
[5]Federal University of Mato Grosso, Cárceres, Mato Grosso, Brazil.
[6]University of São Paulo Ribeirão Preto, Sao Paulo, Brazil.
[7]Federal University of Pernambuco, Recife, Pernambuco, Brazil
[8]Hospital da Restauração. Recife, Pernambuco, Brazil.

Melissa Helena Rodrigues Silva
melissahelenars@gmail.com

Edited by:
Marcelo Moraes Valença

Keywords:
PREEMPT Protocol
OnabotulinumtoxinA
Chronic Migraine
Botulinum Toxin A

Abstract

Chronic migraine is an important cause of functional disability and quality of life deficits, affecting 12% of the world population. Therefore, more treatment alternatives that promote better pain control are needed. So, botulinum toxin type A presents itself as a therapeutic option for this purpose. This integrative review aimed to analyze the functionality of the PREEMPT protocol applied for the treatment of chronic migraine, analyzing the time of pain control, the frequency of repetition of the treatment and the possible subtypes of pain that benefit most from botulinum toxin. Data were collected from the National Library of Medicine and Lilacs databases, and the research concluded in July 2022. 31 articles were found, of which only 22 publications were considered eligible to compose this study, and those that contemplated the research objectives were selected. above. Botulinum toxin type A presents an effective, safe and well-tolerated preventive profile for patients with chronic migraine, increasing the patient's quality of life and works in pain control.

Received: September 12, 2022
Accepted: September 21, 2022

Introduction

Chronic migraines are recurrent episodes of headache on 15 or more days per month in patients with a history of moderate to severe migraine, which may be followed by concomitant neurological symptoms such as nausea and vomits and sensory changes, as known as aura.[1] According to the Global Burden of Disease Study, migraine acts as the second leading cause of years lived with disability around the world[2] and affects individual well-being, causing cognitive and socioeconomic impairments and represents a significant cause of absenteeism and productivity deficits nowadays.[3,4] In addition, the most diverse pharmacological therapies that are widely available often can not promote a good solution to the problem.[5] This scenario makes it imperative to search for effective alternatives for the treatment and prevention of migraines[6], since the etiology of migraines is multifactorial and involves extra and intracerebral factors.[7] The release of peptides in neuronal terminals works in the genesis of the painful condition of migraines, with the glutamate, the peptide related to the calcitonin gene and substance P working as the main mediators that implies for this context.[8,9]

In this scenario, the advent of botulinum toxin (onabotulinumtoxinA) appears as a promising therapy, given its regulatory mechanisms on the pathophysiological processes of migraine. This one, applied through a standardized model known as the PREEMPT Protocol, which establishes the application of a fixed dose subcutaneously of 5 units (U) of BoNTA in 31 to 39 defined regions of the scalp and neck at 12-week intervals, in a total of 155-195U applied, works by promoting pain modulation through peripheral and central pathways[10], which potentially results in a decrease of the pain intensity and in the recurrence of crises and an increase in the patient's quality of life.[11]

In this study, we aimed to verify the benefit of botulinum toxin, used through the PREEMPT protocol, the only one approved by the FDA, in patients with chronic migraine.

Methodology

This article consists in an integrative review about the effectiveness of the PREEMPT Protocol as a standard application of botulinum toxin applied for the treatment of chronic migraine. Data collection strategy was completed in July 2022, being made in the U.S. National Library of Medicine (Medline) and the Latin American Health Sciences Literature System (LILACS) databases. The search terms researched were "preempt protocol", "chronic migraine" and "onabotulinumtoxinA", chosen based on a previous literature review. Furthermore, the Boolean operator "AND" was used and it was chosen to alternate the last two terms with the first.

In all, 31 articles were found in the PubMed database and 01 in LILACS. Ten of these articles were excluded because they did not match the inclusion criteria. Twenty-two publications were selected, which the results are related to the specific objectives of this integrative review: 1- verify the frequency of treatment repetition: quarterly or half-yearly; 2- analyze the pain control time; 3- identify possible types of pain that have a better prognosis with botulinum toxin. The inclusion and exclusion criteria for this integrative review were guided based on the research objectives. Articles available in English and Spanish were selected. There were no restrictions regarding the study design, however, repeated works in databases that did not permeate the main theme of the present study were excluded.

Results

Twenty-two publications were selected, the results of which will be shown in this section and summarized in Table 1.

Table 1. Sample characteristics

Data Base	Article Title	Authors	Findings
Medline	OnabotulinumtoxinA in the treatment of patients with chronic migraine: clinical evidence and experience	Chia-Chun Chiang, Amaal J Starling[12]	OnabotulinumtoxinA is an effective and well-tolerated preventive medication for chronic migraine. However, more long-term reports on effectiveness and cost-benefit analyzes are needed.
Medline	OnabotulinumtoxinA treatment for chronic migraine: experience in 52 patients treated with the PREEMPT paradigm	María Isabel Pedraza et al.[13]	In conclusion, when used according to the PREEMPT paradigm, OnabotA is a safe and effective treatment in a real clinical setting, even when there are criteria of refractoriness to oral preventives.
Medline	Onabotulinumtoxin A for chronic migraine with medication overuse: clinical results of a long-term treatment	L Grazzi[14]	BoNTA seems to be effective for patients with chronic migraine, particularly for patients who are not adherent to oral preventive medications. The early stages of the disease result in better treatment outcome. Future studies are needed to determine the management strategy of patients after 1 year of treatment.
Medline	Onabotulinum toxin A (Botox) for chronic migraine treatment: an Italian experience	Licia Grazzi, S Usai[15]	The results reinforce the clinical benefit obtained with the first year of treatment, due the intense efforts to evaluate the analgesic properties of Onabotulinumtoxin A and its clinical applicability for a period longer than 1 year.
Medline	Influence of headache pain intensity and frequency on migraine-related disability in chronic migraine patients treated with OnabotulinumtoxinA	Marta Torres-Ferrus, et al.[16]	When evaluating the improvement of headache disability in patients with chronic migraine, the variables "pain intensity" and "pain frequency" are equally important and act as a significant primary outcome measure in patients after treatment with OnabotulinumtoxinA.
Medline	Botulinum toxin A in chronic refractory migraine: premarketing experience	Álvaro-González LC et al.[17]	The OnabotulinumtoxinA has shown a good efficacy in the preventive treatment of chronic migraine, clinically expressed through the decreasing of the headache intensity and analgesic abuse.
Medline	Effects of onabotulinumtoxinA treatment on efficacy, depression, anxiety, and disability in Turkish patients with chronic migraine	Demiryurek BE, Ertem DH, Tekin A, Ceylan M, Aras YG, Gungen BD.[18]	Treatment with OnabotulinumtoxinA is efficient and reliable for patients with chronic migraine. There was a clinical decline (worsening of headache frequency and anxiety severity) in the third month compared to the first.
Medline	Prospective analysis of the use of OnabotulinumtoxinA (BOTOX) in the treatment of chronic migraine; real-life data in 254 patients from Hull, UK	Khalil M, Zafar HW, Quarshie V, Ahmed F.[19]	A prospective analysis of 254 patients concluded that onabotulinumtoxinA reduced the number of migraine days and increased the number of headache-free days, as well as improving the patient's quality of life. It also advocated that this treatment should be offered to patients who do not benefit from oral prophylactic agents or invasive options.
Medline	Guideline on the use of onabotulinumtoxinA in chronic migraine: a consensus statement from the European Headache Federation	Bendtsen L, Sacco S, Ashina M, Mitsikostas D, Ahmed F, Pozo-Rosich P, Martelletti P.[20]	Treatment with OnabotulinumtoxinA should be stopped if there is no response within the first two to three cycles. Assessment of response to treatment should be made by comparing the 4 weeks prior to the 4 weeks after each cycle. Patients should be reassessed 4 to 5 months after stopping botulinum toxin and treatment should be stopped in those who have reduced headache pain to less than 10 days/month for 3 months.
Medline	The efficacy of botulinum toxin type-A for intractable chronic migraine patients with no pain-free time	Atraszkiewicz D, Ito R, Bahra A.[21]	We conclude that botulinum toxin is effective in one in five patients with chronic migraine without pain-free time previously unresponsive to drugs, including patients with persistent-onset headache.
Medline	Quarterly repeat cycles of onabotulinumtoxinA in chronic migraine patients: the benefits of the prolonged treatment on the continuous responders and quality-of-life conversion rate in a real-life setting	Santoro A, Fontana A, Miscio AM, Zarrelli MM, Copetti M, Leone MA.[22]	Real-life results exhibited efficacy and safety of repeated cycles of onabotulinum toxin and showed that an 18-month (six-quarter cycle) of treatment is able to sustain and significantly improve efficacy outcomes and the quality of life achieved at 6 and 12 months.
Medline	Onabotulinumtoxin-A in Chronic Migraine: Should Timing and Definition of Non-Responder Status Be Revised? Suggestions From a Real-Life Italian Multicenter Experience	Vernieri F, Paolucci M, Altamura C, Pasqualetti P, Mastrangelo V, Pierangeli G, Cevoli S, D'Amico D, Grazzi L.[23]	The results of the present real-life study indicate that the definition of responders/non-responders to botulinum toxin patients should probably be delayed at least after 1 year of treatment, ie 4 cycles.
Medline	OnabotulinumtoxinA: An Effective Tool in the Therapeutic Arsenal for Chronic Migraine With Medication Overuse	Edoardo Caronna, Victor José Gallardo, Natalia Hernández-Beltrán, Marta Torres-Ferrus, Patricia Pozo-Rosich.[24]	OnabotulinumtoxinA is effective and beneficial, acting as an important tool in acute medication discontinuation in patients with chronic migraine and medication overuse.
Medline	Real-life data in 115 chronic migraine patients treated with Onabotulinumtoxin A during more than one year	I Aicua-Rapun, E Martínez-Velasco, A Rojo, A Hernando, M Ruiz, A Carreres, E Porqueres, S Herrero, F Iglesias, A L Guerrero.[25]	The effectiveness of OnabotA in patients with chronic migraine lasts beyond the first year of treatment. Prolonged discontinuation of treatment is unlikely, but decreasing overuse of acute medications and decreasing the frequency of procedures are realistic long-term goals.
Medline	Onabotulinumtoxin A for prophylaxis in chronic migraine: preliminary data from Headache Regional Centre of Aosta Valley	C Lia, P Tosi, G Giardini, L Caligiana, E Bottacchi.[26]	The safety and tolerability of onabotulinumtoxinA stand out. It's long time duration of action, 3 months, makes it an attractive option for drug overuse patients.
Medline	Increased efficacy of regularly repeated cycles with OnabotulinumtoxinA in MOH patients beyond the first year of treatment	Guerzoni S, Pellesi L, Baraldi C, Pini LA.[27]	There was a significant reduction in analgesic intake on days of fainting in the first and second months after BoNTA injection, with an increase in the third month.
Medline	Botulinum toxin A: a new option for treatment of chronic migraine with medication overuse	Licia Grazzi, Susanna Usai.[28]	Botulinum toxin is effective for patients with chronic migraine. Its long duration of action and low adverse reactions stand out, making it an effective alternative. Future studies are needed to better identify possible predictors of response to this treatment.
Medline	Factors associated with favorable outcome in botulinum toxin A treatment for chronic migraine: A clinic-based prospective study	Mi Ji Lee, Chungbin Lee, Hanna Choi, Chin-Sang Chung.[29]	Good results for treatment with botulinum toxin (BTA) are associated with shorter disease duration. Further studies are needed to assess the pathophysiological mechanisms and outcomes of BoNTA treatment.
Medline	Clinical experience of treatment with onabotulinumtoxin A in patients with refractory migraine	José A Palma, Pablo Irimia, Roberto Fernandez-Torron, Sara Ortega-Cubero, Mario Riverol, María R Luquin, Eduardo Martinez-Vila.[30]	It was concluded that treatment with OnabotulinumtoxinA is safe and useful for patients with refractory episodic and chronic migraine, including patients with medication-overuse headache.
Medline	Long-term experience with onabotulinumtoxinA in the treatment of chronic migraine: What happens after one year?	Eva Cernuda-Morollón, César Ramón, Davinia Larrosa, Rocío Alvarez, Nuria Riesco, Julio Pascual.[31]	The results confirm a long-term response to Botulinum Toxin in three-quarters of patients with chronic migraine. The lack of response occurs in about one in 10 patients after one year. Uninterrupted injections, however, can be delayed up to four months in approximately 40% of patients
LILACS	Botulinum toxin type A wear-off phenomenon in chronic migraine patients: how long does the maximum efficiency last	Pak, Aygul Tantik; Üstün, Ismet; Sengul, Yildizhan.[8]	Botulinum toxin was effective in reducing analgesic intake and headache days in the first and second months after injection, with an increase registered in the third month..
Medline	OnabotulinumtoxinA: A Review in the Prevention of Chronic Migraine	James E. Frampton, Stephen Silberstein.[32]	The totality of clinical trials and studies indicate that botulinum toxin is effective and well tolerated for the prevention of chronic migraine, being particularly useful for patients who have previously failed to respond or are intolerant to oral medications.

A study performed in Turkey with 60 patients maintained the treatment cycle every 3 months and obtained results considered effective and reliable for patients with chronic migraine, reflected in the decrease in headache frequency and severity with a 50% reduction in the number of days with the headache. In addition to this finding, it was found that in the third month, compared to the first, the frequency of headache worsened, a fact justified by the researchers as the end of the "placebo effect".[18]

Bendtsen et. al[20] conducted a study on the use of botulinum toxin, in which it was chosen to follow the treatment cycling regimen at an interval of three months, as recommended by the PREEMPT Protocol. This study highlights the difficulty of evaluating the continuous therapeutic response, since the effect may initially only last 2-3 months, a fact that reinforces the need for reapplication within the described time interval, followed by clinical follow-up.

Accordingly, an interesting prospective observational cohort published in 2021 followed 80 patients with chronic migraine monthly and concluded that treatment with BoNTA did, in fact, reduce the use of analgesic medications and the days/month of headache (the baseline mean was 18 .95±2.69 days/month; in the first month it decreased to 10.55±3.15 days/month ($p<0.001$); in the second month it decreased to 9.31±2.43 days/month ($p<0.001$) and in the third month there was an increase to 11.97±3.27 days/month ($p<0.001$). Simultaneously, from the third month onwards, there was an increase in headache and a return to the use of analgesic drugs from the second to the third month ($p<0.001$).[8]

Still keeping up the same protocol strategy, but extending its duration to a longer final period, Santoro et. al22 concluded through a retrospective evaluation in which they analyzed 47 patients diagnosed with chronic migraine, that the prolonged treatment with onabotulinumtoxinA for 18 months (T18) - six quarterly cycles - would act to substantially increase the results of efficacy and quality of life compared to those achieved in the 12-month period (T12). This finding was reflected in the statistically significant reduction in the mean monthly headache hours, which decreased over time T12, 90.4 ± 93.9; T18, 53.2 ± 79.2) ($p < 0.001$).

To this end, some works already published are being guided in this direction. A small subgroup of 16 patients previously treated at the total PREEMPT time underwent a second treatment for another additional year and had promising results: there was a decrease in medication intake by each month (23.8 ± 6.8 baseline; 13, 8 ± 7.68 in the first year and 15.8 ± 8.48 in the second year) and in the headache: (25.3 ± 6.1 at baseline; 15.1 ± 7.8 at 1 year and 15, 5 ± 8.7 in 2 years).[14]

Cernuda-Morollon et. al31 evaluated some long-term prognostic aspects of treatment in migraine patients. It was found that 90% of patients need to continue with OnabotulinumtoxinA injections after the first year of treatment so that the frequency of migraine remains under control. However, it is worth noting that the results of this study also reiterate the long-term response to OnabotulinumtoxinA injections, which can be maintained for periods longer than two years.

Dodick et. al[33], in a post hoc analysis, evaluated populations using onabotulinumtoxinA after the first treatment. In addition to good tolerability, treatment with onabotulinumtoxinA was found to promote progressive headache improvement, confirmed in subsequent years of treatment with a sustained reduction in the headache days. Regarding the subtype of pain mentioned in the publications, a prospective observational study developed in South Korea only explained that among the 42 patients "responsive" to the therapy, 37 (88.1%) had migraine without aura and five (11, 9%) with aura. Likewise, among the 28 patients "unresponsive" to BoNTA therapy, 23 (82.1%) had migraine without aura and five (17.9%) had aura. In this study, it was also observed that the shorter the duration of the disease, the better the response to treatment with botulinum toxin ($p = 0.019$).[29] The application of BoNT-A is also indicated in the initial phase of the disease, thus resulting in a better treatment result.

Discussion

According to the results of this review in which we analyzed the efficiency of the PREEMPT Protocol in the injection of Botulinum Toxin (BoNTA) in patients with migraine, there was a significant decrease in the number of days with headache, migraine severity, disabilities and other complaints, in other words, that's a consistent aspect across all analyzed studies.

Chronic migraine primarily affects the most productive years of an individual's life, given its higher incidence in middle age. In addition, the high costs of chronic migraine attacks are not only due to factors such as absenteeism, but also to medical costs arising from the large need for medication, visits to the emergency room, hospitalizations, and others.[4] Despite this significant burden of disease and behavior that is refractory to most of the therapeutic

arsenal, prophylactic treatment with botulinum toxin A compared to placebo provided significant improvements in several spectrum of symptoms of this type of headache.[6]

Botulinum toxin works to inhibit pain through peripheral and central pathways, plays the role of blocking the neurotransmitter's discharge such as substance P and especially CGRP from the meninges and portions outside the calvaria that would lead to the release of cytokines.[10] At the cellular level, modulation of ion channels occurs and the botulinum toxin chains bind to nerve receptors in the terminal portion of type C conducting fibers, so that endocytosis occurs and its concomitant passage into the nervous system, resulting in modulation of the nociceptive process, modifying the threshold of its perception.[34,35]. Such changes start in two to five days and last up to two weeks to reach the maximum effect at the synaptic level.[36,37]

The effects of botulinum toxin tend to appear around five to six weeks after inoculation and its recovery after 12 weeks, this reason justifies the frequency of quarterly administration[38], reinforcing the need for reapplication within the described time interval, followed by clinical follow-up.[22] This time of action makes botulinum toxin a really viable therapeutic option for refractory patients or patients with low adherence to oral medications[14], since within the therapeutic window, the need for the concomitant use of other medications is drastically reduced.

In general, it is necessary to investigate the continuity of treatment with OnabotulinumtoxinA beyond the limits set out in the PREEMPT Protocol[22] and also its clinical applicability in a period longer than 01 year to confirm the improvement observed in the first year of treatment[15], in view of the fact that some studies have shown that the duration of efficiency tends not to be as long as believed.[8]

In this scenario, few data and studies have been published evaluating the long-term experience with botulinum toxin in a "real-life environment".[26] There is a lack of information about the end of treatment with BoNTA after the PREEMPT period in patients who had a good response, given that the interruption promotes an important deficit in quality of life. Another open question is the possibility of terminating therapy with OnabotulinumtoxinA after the first year in patients who had a good response, since it has been shown that when treatment is stopped, quality of life parameters decline.[34] However, it is worth noting that the results of this study also reiterate the long-term response to OnabotulinumtoxinA injections, which can be maintained for periods longer than two years.[31]

Conclusion

In all analyzed works, clinical trials and studies, OnabotulinumtoxinA appears as an effective, safe and well-tolerated preventive drug for patients with chronic migraine, acting directly in the decrease of headache days per month, increase in pain-free days and in the reduction of headache. need for analgesic medications, which reflects in a substantial increase in the patient's quality of life in the reduction of the huge costs used for pain control. It was concluded that some patients benefit from prolonged treatment longer than the initial 12 months, confirming the trend towards improvement achieved in the first year.

Conflict of interest: The authors report no conflict of interest

Funding: No

Author's contribution: All authors had the same contribution

Melissa Helena Rodrigues Silva
https://orcid.org/0000-0001-9846-3801
Joaquim Fechine de Alencar Neto
https://orcid.org/0000-0003-2042-4874
Otávio da Cunha Ferreira Neto
https://orcid.org/0000-0003-0517-0212
Luiz Bandeira Alves Neto
https://orcid.org/0000-0003-3245-1036
Nilson Batista Lemos
https://orcid.org/0000-0002-2331-6871
Arthur Oliveira Lira
https://orcid.org/0000-0002-5746-5728
Maria Luísa Rocha
https://orcid.org/0000-0001-8717-2363
Luís Felipe Ferreira Marques
https://orcid.org/0000-0001-7461-8637
Victor Egypto Pereira
https://orcid.org/0000-0002-4764-6402
Victoria Rodrigues Durand
https://orcid.org/0000-0002-3623-5317
Ana Cristina Veiga Silva
https://orcid.org/0000-0002-1149-4427
Luiz Severo Bem Junior
https://orcid.org/0000-0002-0835-5995
Hildo Rocha Cirne de Azevedo Filho
https://orcid.org/0000-0002-1555-3578

References

1. Wiggers A, Ashina H, Hadjikhani N, Sagare A,

Zlokovic BV, Lauritzen M and Ashina M. **Brain barriers and their potential role in migraine pathophysiology.** *The Journal of Headache and Pain* 2022;23(1):Doi:10.1186/s10194-021-01365-w

2. Steiner T and Saylor D. **The Global Burden of Headache.** *Seminars in Neurology* 2018;38(02):182-190 Doi:10.1055/s-0038-1646946
3. Goadsby PJ, Lantéri-Minet M, Michel MC, Peres M, Shibata M, Straube A, . . . Hitier S. **21st century headache: mapping new territory.** *The Journal of Headache and Pain* 2021;22(1):Doi:10.1186/s10194-021-01233-7
4. Burch RC, Buse DC and Lipton RB. **Migraine.** *Neurologic Clinics* 2019;37(4):631-649 Doi:10.1016/j.ncl.2019.06.001
5. Mungoven TJ, Henderson LA and Meylakh N. **Chronic Migraine Pathophysiology and Treatment: A Review of Current Perspectives.** *Frontiers in Pain Research* 2021;2(Doi:10.3389/fpain.2021.705276
6. Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB, . . . Brin MF. **OnabotulinumtoxinA for Treatment of Chronic Migraine: Pooled Results From the Double-Blind, Randomized, Placebo-Controlled Phases of the PREEMPT Clinical Program.** *Headache: The Journal of Head and Face Pain* 2010;50(6):921-936 Doi:10.1111/j.1526-4610.2010.01678.x
7. Ashina M and Ropper AH. **Migraine.** *New England Journal of Medicine* 2020;383(19):1866-1876 Doi:10.1056/NEJMra1915327
8. Pak AT, ÜStÜN İ and Sengul Y. **Botulinum toxin type A wear-off phenomenon in chronic migraine patients: how long does the maximum efficiency last?** *Arquivos de Neuro-Psiquiatria* 2021;79(10):886-890 Doi:10.1590/0004-282x-anp-2020-0542
9. Aoki KR. **Evidence for Antinociceptive Activity of Botulinum Toxin Type A in Pain Management.** *Headache: The Journal of Head and Face Pain* 2003;43(s1):9-15 Doi:10.1046/j.1526-4610.43.7s.3.x
10. Sposito MMdM. **Toxina Botulínica do Tipo A: mecanismo de ação.** *Acta Fisiátrica* 2009;16(1):25-37 Doi:10.11606/issn.2317-0190.v16i1a103037
11. Aurora SK, Winner P, Freeman MC, Spierings EL, Heiring JO, DeGryse RE, . . . Turkel CC. **OnabotulinumtoxinA for Treatment of Chronic Migraine: Pooled Analyses of the 56-Week PREEMPT Clinical Program.** *Headache: The Journal of Head and Face Pain* 2011;51(9):1358-1373 Doi:10.1111/j.1526-4610.2011.01990.x
12. Chiang C-C and Starling AJ. **OnabotulinumtoxinA in the treatment of patients with chronic migraine: clinical evidence and experience.** *Therapeutic Advances in Neurological Disorders* 2017;10(12):397-406 Doi:10.1177/1756285617731521
13. 13. Pedraza MI, de la Cruz C, Ruiz M, López-Mesonero L, Martínez E, de Lera M and Guerrero ÁL. **OnabotulinumtoxinA treatment for chronic migraine: experience in 52 patients treated with the PREEMPT paradigm.** *SpringerPlus* 2015;4(1):Doi:10.1186/s40064-015-0957-z
14. 14. Grazzi L. **Onabotulinumtoxin A for chronic migraine with medication overuse: clinical results of a long-term treatment.** *Neurological Sciences* 2017;38(S1):141-143 Doi:10.1007/s10072-017-2864-2
15. 15. Grazzi L and Usai S. **Onabotulinum toxin A (Botox) for chronic migraine treatment: an Italian experience**. *Neurological Sciences* 2015;36(S1):33-35 Doi:10.1007/s10072-015-2140-2
16. 16. Torres-Ferrus M, Gallardo VJ, Alpuente A and Pozo-Rosich P. **Influence of headache pain intensity and frequency on migraine-related disability in chronic migraine patients treated with OnabotulinumtoxinA**. *The Journal of Headache and Pain* 2020;21(1):Doi:10.1186/s10194-020-01157-8
17. 17. Álvaro González LC, Fernández García JM, Aranzábal Alustiza I, Castillo Calvo B, Iriondo Etxenagusia I and Rodríguez Antigüedad A. **Toxina botulínica tipo A en la migraña crónica refractaria: experiencia en uso compasivo preautorización.** *Revista de Neurología* 2012;55(07):Doi:10.33588/rn.5507.2012210
18. 18. Demiryurek BE, Ertem DH, Tekin A, Ceylan M, Aras YG and Gungen BD. **Effects of onabotulinumtoxinA treatment on efficacy, depression, anxiety, and disability in Turkish patients with chronic migraine**. *Neurological Sciences* 2016;37(11):1779-1784 Doi:10.1007/s10072-016-2665-z
19. 19. Khalil M, Zafar HW, Quarshie V and Ahmed F. **Prospective analysis of the use of OnabotulinumtoxinA (BOTOX) in the treatment of chronic migraine; real-life data in 254 patients from Hull, UK**. *The Journal of Headache and Pain* 2014;15(1):Doi:10.1186/1129-2377-15-54
20. 20. Bendtsen L, Sacco S, Ashina M, Mitsikostas D, Ahmed F, Pozo-Rosich P and Martelletti P. **Guideline on the use of onabotulinumtoxinA in chronic migraine: a consensus statement from the European Headache Federation.** *The Journal of Headache and Pain* 2018;19(1):Doi:10.1186/s10194-018-0921-8
21. 21. Atraszkiewicz D, Ito R and Bahra A. **The efficacy of botulinum toxin type-A for intractable**

chronic migraine patients with no pain-free time. *British Journal of Pain* 2021;16(1):41-49 Doi:10.1177/20494637211014544

22. 22. Santoro A, Fontana A, Miscio AM, Zarrelli MM, Copetti M and Leone MA. **Quarterly repeat cycles of onabotulinumtoxinA in chronic migraine patients: the benefits of the prolonged treatment on the continuous responders and quality-of-life conversion rate in a real-life setting**. *Neurological Sciences* 2017;38(10):1779-1789 Doi:10.1007/s10072-017-3054-y
23. 23. Vernieri F, Paolucci M, Altamura C, Pasqualetti P, Mastrangelo V, Pierangeli G, . . . Grazzi L. **Onabotulinumtoxin-A in Chronic Migraine: Should Timing and Definition of Non-Responder Status Be Revised? Suggestions From a Real-Life Italian Multicenter Experience**. *Headache: The Journal of Head and Face Pain* 2019;59(8):1300-1309 Doi:10.1111/head.13617
24. 24. Caronna E, Gallardo VJ, Hernández-Beltrán N, Torres-Ferrus M and Pozo-Rosich P. **OnabotulinumtoxinA: An Effective Tool in the Therapeutic Arsenal for Chronic Migraine With Medication Overuse.** *Frontiers in Neurology* 2018;9(Doi:10.3389/fneur.2018.00808
25. Aicua-Rapun I, Martínez-Velasco E, Rojo A, Hernando A, Ruiz M, Carreres A, . . . Guerrero AL. **Real-life data in 115 chronic migraine patients treated with Onabotulinumtoxin A during more than one year**. *The Journal of Headache and Pain* 2016;17(1):Doi:10.1186/s10194-016-0702-1
26. Lia C, Tosi P, Giardini G, Caligiana L and Bottacchi E. **Onabotulinumtoxin A for prophylaxis in chronic migraine: preliminary data from headache regional centre of aosta valley**. *Neurological Sciences* 2014;35(S1):175-176 Doi:10.1007/s10072-014-1764-y
27. Guerzoni S, Pellesi L, Baraldi C and Pini LA. **Increased efficacy of regularly repeated cycles with OnabotulinumtoxinA in MOH patients beyond the first year of treatment.** *The Journal of Headache and Pain* 2016;17(1):Doi:10.1186/s10194-016-0634-9
28. Grazzi L and Usai S. **Botulinum toxin A: a new option for treatment of chronic migraine with medication overuse**. *Neurological Sciences* 2014;35(S1):37-39 Doi:10.1007/s10072-014-1739-z
29. Lee MJ, Lee C, Choi H and Chung C-S. **Factors associated with favorable outcome in botulinum toxin A treatment for chronic migraine: A clinic-based prospective study**. *Journal of the Neurological Sciences* 2016;363(51-54 Doi:10.1016/j.jns.2016.01.054
30. Palma Carazo JA, Irimia Sieira P, Fernández Torrón R, Ortega Cubero S, Riverol Fernández M, Luquin Piudo MR and Martínez Vila E. **Experiencia clínica del tratamiento con onabotulinumtoxin A en pacientes con migraña refractaria**. *Revista de Neurología* 2012;54(12):Doi:10.33588/rn.5412.2012141
31. Cernuda-Morollón E, Ramón C, Larrosa D, Alvarez R, Riesco N and Pascual J. **Long-term experience with onabotulinumtoxinA in the treatment of chronic migraine: What happens after one year?** *Cephalalgia* 2014;35(10):864-868 Doi:10.1177/0333102414561873
32. Frampton JE and Silberstein S. **OnabotulinumtoxinA: A Review in the Prevention of Chronic Migraine.** *Drugs* 2018;78(5):589-600 Doi:10.1007/s40265-018-0894-6
33. Dodick DW, Silberstein SD, Lipton RB, DeGryse RE, Adams AM and Diener H-C. **Early onset of effect of onabotulinumtoxinA for chronic migraine treatment: Analysis of PREEMPT data.** *Cephalalgia* 2019;39(8):945-956 Doi:10.1177/0333102418825382
34. Burstein R, Zhang X, Levy D, Aoki KR and Brin MF. **Selective inhibition of meningeal nociceptors by botulinum neurotoxin type A: Therapeutic implications for migraine and other pains.** *Cephalalgia* 2014;34(11):853-869 Doi:10.1177/0333102414527648
35. Pellesi L, Do TP, Ashina H, Ashina M and Burstein R. **Dual Therapy With Anti-CGRP Monoclonal Antibodies and Botulinum Toxin for Migraine Prevention: Is There a Rationale?** *Headache: The Journal of Head and Face Pain* 2020;60(6):1056-1065 Doi:10.1111/head.13843
36. Gazerani P, Staahl C, Drewes AM and Arendt-Nielsen L. **The effects of Botulinum Toxin type A on capsaicin-evoked pain, flare, and secondary hyperalgesia in an experimental human model of trigeminal sensitization**. *Pain* 2006;122(3):315-325 Doi:10.1016/j.pain.2006.04.014
37. Wheeler A and Smith HS. **Botulinum toxins: Mechanisms of action, antinociception and clinical applications.** *Toxicology* 2013;306(124-146 Doi:10.1016/j.tox.2013.02.006
38. Farinelli I, Coloprisco G, De Filippis S and Martelletti P. **Long-term benefits of botulinum toxin type A (BOTOX) in chronic daily headache: a five-year long experience**. *The Journal of Headache and Pain* 2006;7(6):407-412 Doi:10.1007/s10194-006-0344-9