



Migraine treatment with biological therapies. The state of the art

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Abstract

Migraine is a highly prevalent and debilitating neurological disorder. Most patients do not receive a correct diagnosis and effective treatments. Apart of the few specialists and tertiary centers worldwide, the treatment of migraine is usually symptomatic and prevention, as well as treatments of the underlying mechanisms, are not aimed. It results in frustration and substantial burden. The last few years witnessed the releasing of specific biological therapies, mostly addressing one of the peptides involved in migraine pathophysiology, the calcitonin gene-related peptide (CGRP). Either the small molecules as well as the monoclonal antibodies against CGRP or its canonical receptor have been launched in markets across the globe, and represent interesting options for the treatment of migraine. Onabotulinumtoxin A has also been proposed for chronic migraine as well, but not for episodic migraine, based on its unique ability to inhibit the SNARE complex formation and the release of numerous potential mediators of migraine. However, despite the favorable figures on efficacy and tolerability of these compounds, the regulations and particulars of different countries, regarding the structures and reimbursement of medical care, demonstrated different adhesion profiles of chosen populations to receive these emerging weapons against migraine-imposed suffering. This review addresses the use and characteristics of biological therapies used in migraine treatment.

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Introduction

Migraine is an incapacitating neurological disease with a substantial impact on individual's lives.^{1,2} The preventive treatment or the treatment of migraine as a chronic condition, and not only the intermittent headache attacks, should result in reducing the frequency, intensity, and duration of the head pain, as well as improving the response to acute treatments and amelioration of functional ability or quality of life.³⁻⁵

However, even sufferers receiving effective approaches in prevention, discontinue their medications after months, or repeatedly cycle through treatment options. This behavior is frequently due to suboptimal efficacy, bothersome adverse events or even concerns regarding the safety and tolerability of currently (2022) available oral preventive medications.⁵⁻⁷ In Brazil, additionally, the cost of care is also a limiting factor to adhere, regarding the use of daily medications and regularity of medical visits, especially with specialized professionals.⁸

The patients also ranked peculiar characteristics of efficacy, speed of onset, and oral formulations for treatment options among the imperative attributes, when choosing a preventive medication.^{9,10}

In the last decade, biological therapies have been approved for migraine treatment. Initially, onabotulinumtoxin A, for chronic migraine. More recently, monoclonal antibodies aiming at one of the peptides involved in migraine mechanisms. All these options are switching the paradigm and adhesion profile of migraine treatment.⁹⁻¹¹

Taking it all, when analyzing individual preferences of patients and the various treatment strategies carried out by health professionals in the existing instances of care of Brazil, interesting differences are revealed.^{8,11} Migraineurs seeking care in public nonpaying centers, may receive non comprehensive approaches, monotherapy for either acute or preventive treatments, and mostly do not receive prevention. When preventive treatments are prescribed to these patients, it is usually either tricyclic antidepressants or β -blockers due to their availability as free medications, rendered by treating professionals. Usually, biological therapies are not available, but onabotulinumtoxin A has been used in few centers.^{8,11}

Differently, in private centers, which are usually directed to paying people, or users of private insurance plans, as well as in the few meritorious public centers of excellence, the approach is clearly different. Multidisciplinary treatments and combination of drugs are common. Most patients from these centers receive the prescription of preventive treatments, which are generally rational combinations of tricyclic antidepressants and/or neuromodulators and/or

β -blockers.^{8,11} Onabotulinumtoxin A has been extensively used in private tertiary centers of Brazil, frequently at an extorsive cost and even in the absence of formal indications, such as for episodic migraineurs.¹²

The monoclonal antibodies have been prescribed for numerous patients seeking care in private tertiary clinics of Brazil as well.^{13,14} The body of evidence with Brazilian headache care providers is growing and preliminary results have been published.^{13,14}

The aim of this review is to present advances and pragmatism regarding the use of biological therapies in the treatment of migraine.

Aiming on calcitonin gene-related peptide (CGRP) or its receptor

CGRP is a potent vasodilator and inflammatory mediator known to play a paramount role in migraine pathophysiology.¹⁵⁻¹⁷ It localizes almost everywhere migraine mechanisms are present, including the cortex, thalamus, limbic system, brainstem, dura mater, trigeminal and dorsal root ganglia, trigeminocervical complex, and spinal lamina 1.^{15,16} CGRP levels increase during attacks, and its concentrations can be elevated even between attacks, especially in sufferers with high attack frequency or chronic migraine.¹⁵⁻¹⁸ Furthermore, an infusion of CGRP has been shown to trigger migraine-like attacks in patients who have migraine with or without aura.¹⁵⁻¹⁸ Blocking CGRP, either the neuropeptide or its receptor, is effective for the preventive treatment of migraine.¹⁵⁻¹⁹

The idea of using monoclonal antibodies (mAbs) targeting the CGRP or its receptor was initially taught due to the observed liver toxicity of the early CGRP antagonists, known as gepants, and to the fact that mAbs are eliminated through the reticuloendothelial system with no interaction with liver or kidneys. They are large molecules that for the most part do not penetrate the blood-brain barrier, therefore making peripheral mechanisms of action most likely. However, some central nervous system penetrations do exist, and because it is not known the amount necessary for clinical effects, it remains possible that mAbs also present central effects as well.^{15,17}

Four of these biological agents have been exhaustively tested clinically in humans, either for episodic and chronic migraine prevention, with and without aura, with and without medication overuse, and with and without various psychiatric and medical comorbidities. Three target the CGRP ligand itself, galcanezumab, fremanezumab and eptinezumab, while erenumab targets the canonical CGRP receptor.¹⁵⁻¹⁹



The mAbs for episodic migraine prevention

Erenumab

Erenumab is a fully human monoclonal antibody of IgG2 type, which targets the canonical CGRP receptor. Erenumab was extensively studied in two randomized clinical trials lasting, respectively, 3 and 6 months for the prevention of episodic migraine (EM) and a third study for EM patients who had had a lack of success with ≥ 2 –4 previous migraine preventive medications, which lasted 3 months.^{20–22} Eight monthly migraine days was the average baseline frequency for the initial two studies, and the primary endpoint of decreasing monthly migraine days, was around -3 days in comparison to baseline for both studies. One study (ARISE, the 3-month study) evaluated placebo and 70 mg erenumab, while the other (STRIVE, the 6-month study) evaluated placebo, 70 mg, and 140 mg doses.^{20,21} Regarding secondary end points, the 70 mg dose provided 40% and 140 mg-dose 50% of sufferers presenting $\geq 50\%$ reduction in mean monthly migraine days.

The third trial, which evaluated erenumab 140 mg for non-responding patients (LIBERTY), had a primary endpoint of patient's percentage with at least $\geq 50\%$ reduction in mean monthly migraine days at 3 months, when compared with placebo. Respectively, 30% (erenumab 140 mg) and 14% (placebo) of the studied patients achieved the endpoint, suggesting that erenumab may work even in subjects with previous preventive medication failures.²²

The most common adverse events were injection site reactions or respiratory symptoms, but in clinical practice the constipation is what we most see. Erenumab was withdrawn from the Brazilian market so far in 2022.

Galcanezumab

Galcanezumab is a humanized ($\approx 10\%$ murine) monoclonal antibody of IgG4 type, which targets the CGRP ligand itself. It was also studied for EM prevention in two randomized controlled trials lasting 6 months (EVOLVE 1 and 2).^{23,24} Both studies evaluated the doses 120 mg and 240 mg in comparison with placebo. Interestingly, the 240 mg dose was not more effective than the 120 mg dose. The baseline mean monthly migraine days was 9 days with subsequent reduction in frequency of -4.5 days. The percentages of patients with $\geq 50\%$ and $\geq 75\%$ reduction in migraine days were also studied and presented by nearly 60% and 33% of the patients at six months.^{23,24}

Subsequently, 100% responder rates, defined as having a 100% reduction in mean monthly migraine days for a month in a row, was evaluated and presented by 13.5% of the patients using galcanezumab 120 mg and 5.9% of those with placebo. The authors also emphasized that few galcanezumab patients had ≥ 4 months of 100% response, but more than a third of the sufferers with

episodic migraine treated with galcanezumab 120 mg, achieved 100% response for at least 1 month.²⁵

The most common adverse events were injection site reactions, but neither constipation nor respiratory symptoms exceeded placebo.^{23,24}

The 1-year open-label data for both episodic and chronic migraineurs was assessed as well.²⁶ The treatment-attributed adverse events had a frequency of $\geq 10\%$ of patients and were mostly injection site pain and reactions, upper respiratory tract infection, including sinusitis and nasopharyngitis, as well as back pain. Other parameters such as laboratory values or vital signs did not show any clinically meaningful differences between both galcanezumab doses and placebo.²⁶ Overall mean reduction in monthly migraine headache days over 12 months for the galcanezumab dose groups was -5.6 .²⁶ It must be remembered that galcanezumab requires, in the first month, a 240 mg loading dose followed by 120 mg subcutaneous monthly thereafter, according to the product prescribing information.

Fremanezumab

Fremanezumab is an IgG2 fully humanized ($\approx 5\%$ murine) monoclonal antibody also targeting the CGRP ligand. It was studied in one 3-month trial for the preventive treatment of episodic migraine (HALO). HALO study compared two dose regimens, a monthly 225 mg dose and a quarterly 675 mg dosing, and placebo. Both doses revealed better performance than placebo and the reduction of monthly migraine days was about -3.5 days, in comparison to a baseline of 9 migraine days per month. In addition, respectively 45% and 33% of the patients presented with $\geq 50\%$ and $\geq 75\%$ reductions in migraine days at 12 weeks.²⁷

A randomized controlled trial of fremanezumab was also carried out in patients with a lack of success having used ≥ 2 –4 previous migraine preventive medication classes. Among 838 participants, 329 (39%) had episodic migraine and 509 (61%) chronic migraine. The patients were randomly assigned to placebo ($n = 279$), monthly 225 mg of fremanezumab ($n = 283$) and quarterly 675 mg of fremanezumab ($n = 276$). Both doses were superior to placebo in reductions from baseline in monthly average migraine days over 12 weeks. Quarterly dose of fremanezumab provided a reduction of -3.7 vs -2.8 (placebo) and monthly fremanezumab revealed a change of -4.1 days vs -2.8 (placebo), $p < 0.0001$ for both comparisons. Tolerability was similar for placebo and fremanezumab. Again, injection site reactions and respiratory symptoms were the adverse events most frequently reported for fremanezumab.²⁸

In a post hoc analysis, a sub-group of patients with chronic migraine from the FOCUS study, who had prior inadequate response to either topiramate, valproic acid or



onabotulinumtoxin A, was evaluated for fremanezumab efficacy. Results were quite similar to the general FOCUS study, with demonstrated superiority of fremanezumab in reducing monthly migraine days for patients who have failed specifically to onabotulinumtoxin A or the neuromodulators topiramate or valproic acid.²⁹

Eptinezumab

Eptinezumab is a humanized monoclonal antibody of type IgG1 (≈10% murine), which also targets the CGRP itself. It is the only mAb to be administered intravenously. It was studied in a randomized controlled trial including 888 patients that lasted for one year and administered quarterly infusions (PROMISE-1). In Brazil, if launched, the dose is likely to be 300 mg, but so far, the industry producer didn't show any interest in hearing the reliable headache specialists. In the trial, baseline monthly migraine days were around 8.6 and the reduction from baseline, over weeks 1–12, was –4.3 for the 300 mg dose. Adverse events were observed in 57.6% of the patients versus 59.5% of the placebo, mostly related to upper respiratory tract infection and fatigue. Efficacy of eptinezumab was high, reaching 55% of patients with ≥ 75% reduction in mean monthly migraine days.³⁰

The mAbs for chronic migraine prevention

Erenumab

In the erenumab pivotal trial for chronic migraine, patients with around 18 monthly migraine days at baseline, had a decreasing of –6.6 days for both the 70 mg and the 140-mg dose by 12 weeks.³¹ When analyzing the extension of the trial, which was carried out in an open-label design, at one year, the reduction achieved –8.5 days for the 70 mg and –10.5 days for the 140 mg dose.³² Other secondary end points such as the percentage of patients who had ≥ 50% reduction in monthly migraine days, was 40% for the 70 mg dose and 50% for the 140 mg dose, at 12 weeks. For those patients who continued to use erenumab, the open-label extension demonstrated, at one year, a further improvement of responder rates with both doses, showing, respectively, 67% of patients with ≥ 50% responder rates and 41% of patients having a ≥75% responder rate for the 140mg dose.^{32,33} The days in which symptomatic medication (SM) was used also dropped for the active group compared to placebo. Moreover, the pattern conversion of chronic to episodic migraine, as well as from overuse to non-overuse of SM, were observed in over half of patients treated with erenumab, by 12 weeks.³³

Galcanezumab

As with the other commercially available mAbs, galcanezumab was studied for chronic migraine (CM) prevention in a 3-month randomized controlled trial (REGAIN) comparing placebo, and the doses 120 mg and 240 mg. The mean monthly migraine days at baseline was around 19 days and the obtained reduction, at 12 weeks, was –4.8 days for the 120 mg galcanezumab dose.

Regarding secondary endpoints, the observed percentage of patient who had ≥ 50% reduction in mean monthly migraine days was 27.6% at 12 weeks, for the 120 mg dose. As with all the monoclonal antibodies for migraine, mean acute migraine medication days decreased and patient-reported outcomes improved substantially.³⁴

In another trial, consecutive chronic migraineurs completing one year of observation were enrolled. The sufferers were treated with galcanezumab and data on monthly migraine days, in pain intensity and in monthly acute medication intake, from baseline to the 12 month visit, were collected as well. Of the 155 patients who were enrolled, 75% (116/155) reverted to the episodic form of migraine at every visit and 52.3% (81/155) for the entire 1-year treatment period. At 12 months (V12), 83 participants (53.5%) presented with 0-7 monthly migraine days, considered by the authors, as a substantial reduction presentation to a median or low frequency migraine. The medication overuse discontinuation rate at V12 was 82.8% and occurred during the 11 months of observation. From baseline to V12, the days with acute medications use decreased by 17 ($p < 0.001$), while the pain intensity score reduced by almost 2 points ($p < 0.001$). A consistent transition to episodic migraine for the entire treatment year was observed in 81 (52.3%) patients.³⁵

Fremanezumab

Fremanezumab was studied for chronic migraine in a phase 3 randomized controlled trial, lasting three months, and denominated HALO. The study included 1130 patients, when 376 were randomly assigned to fremanezumab quarterly, 379 to fremanezumab monthly, and 375 to placebo. The mean number of baseline headache days per month was 13.2, 12.8, and 13.3, respectively.³⁶ The primary endpoint was the mean change from baseline in the average number of headache days. These were defined as days in which headache pain lasted ≥4 consecutive hours and had a peak severity of at least a moderate level, or days with the use of triptans or ergots to treat a headache of any severity or duration per month, during the 12 weeks after the first dose. The reduction in the average number of headache days per month was 4.3 ± 0.3 with quarterly fremanezumab, 4.6 ± 0.3 with the monthly use of fremanezumab, and 2.5 ± 0.3 with placebo ($P < 0.001$ for both comparisons with placebo). The percentage of patients with a reduction of at least 50% in the average number of headache days per month was 38% in the fremanezumab-quarterly group, 41% in the fremanezumab-monthly group, and 18% in the placebo group ($P < 0.001$ for both comparisons with placebo).³⁶

In a 12-week multicenter, prospective, cohort, real-life study, with consecutive patients from nine Italian headache centers who were suffering with high frequency (HFEM) or chronic migraine (CM), eligible subjects were given subcutaneous fremanezumab 225 mg monthly or 675



mg quarterly, according to their preference.³⁷ The primary study endpoints were the change in monthly migraine days (MMDs) in HFEM and monthly headache days (MHDs) in CM patients, at weeks 9-12, compared to baseline.

Secondary endpoints evaluated the reduction in monthly analgesic intake (MAI), Numerical Rating Scale (NRS), HIT-6 and MIDAS scores, and $\geq 50\%$, $\geq 75\%$ and 100% responder rates at the same time intervals. Sixty-seven migraine patients had received \geq one subcutaneous fremanezumab dose and were considered for safety analysis, while 53 patients completed 12 weeks of treatment and were included also in the effectiveness analysis. Fremanezumab was effective in both HFEM and CM, leading, at week 12, to a significant reduction in MMDs (-4.6, $p < 0.05$), MHDs (-9.4, $p < 0.001$), MAI (-5.7, $p < 0.05$; -11.1, $p < 0.001$), NRS (-3.1, $p < 0.001$; -2.5, $p < 0.001$), and MIDAS scores (-58.3, $p < 0.05$; -43.7; $p < 0.001$). HIT-6 was significantly reduced only in HFEM patients (-18.1, $p < 0.001$). Remission from CM to episodic migraine and from medication overuse to a non-medication overuse pattern, occurred in 75% and 67.7% of the patients. The $\geq 50\%$, $\geq 75\%$ and 100% responder rates, at week 12, were respectively, 76.5%, 29.4% and 9.9% in HFEM and 58.3%, 25% and 0% in CM. Younger age emerged as a positive response predictor (OR = 0.91; 95% CI 0.85-0.98, $p = 0.013$). Treatment-emergent adverse events were uncommon (5.7%) and mild. No patient discontinued fremanezumab for any reason.³⁷

The art and real-world use of the mAbs

The favorable outcomes in the studies performed by researchers with heavy funding are not always replicated in real-world patients. Additionally, the sufferers from tertiary centers may not frequently behave as the subjects studied in industry supported trials. Therefore, real-world studies and experience reports, from various clinics, are needed to guide clinicians involved in migraine treatment.³⁸⁻⁴⁰ Although most will observe and report favorable outcomes and follow, unconditionally, the data available in medical literature, the satisfaction with the use of mAbs, among treating professionals and patients, may stand below the expected by both.

Erenumab, for instance, was withdrawn from the Brazilian market nearly two years after being commercially launched. Despite its demonstrated effectiveness, even in trials with real patients presenting previous treatment failures, with reductions in headache days and disability varying from 40% to 69%, was not successful regarding revenues. The high prices for Brazilian standards, bothering constipation and fears of adverse events related to immunogenicity, resulted in low adherence and prescriptions. In addition, as with other specific migraine treatments such as triptans, non-neurologists rarely prescribe erenumab or any other monoclonal antibody. Moreover, relying in political indications for the conduction of medical education and

marketing strategies, as constantly observed in Brazil, resulted in underachievement of expectations either for industry or patients.

However, the use of monoclonal antibodies in migraine is undoubtedly interesting for responders. Those with substantial headache frequency reductions, as demonstrated by a percentage of patients in the pivotal studies, and who revealed favorable tolerability profiles, are consistently adherent and satisfied with this treatment option. It is indeed referred by part of the patients, especially if the monoclonal antibody has not been purchased with the patient's own resources. Nevertheless, despite economic limitations, mAbs have clear lower costs than in other countries, a prescription unrestricted to any treating physician, of any medical specialty, and have been used by any migraine sufferer, not only chronic migraineurs or patients with a failure history to numerous pharmacological agents, including onabotulinumtoxin A.⁴¹

It is far from the reality observed in the excessively governed socialized medicine of European countries, in which mAbs are prescribed to selected patients and paid by the public health systems, or what is observed in the money-driven medicine exercised in United States, where approaches, studies and prescriptions are mostly related to financial compensations.

We believe that in Brazil, the mAbs will be prescribed by familiarized physicians to improve outcomes or to complement current treatments, if the parameters of headache and disability reduction are not achieved according to the treaters or the patient's expectations. The single use of a mAb for migraine will be rarely seen, except in specific subpopulations of patients such as those who do not tolerate or do not want to use traditional pharmacological agents, rather than in sufferers who didn't improve with medications. In fact, initial published reports of anti-CGRP monoclonal antibodies treatment by Brazilians, demonstrated headache decreasing frequency of $\geq 50\%$ in 57.7% of the patients. A mean of 15.3 ± 8.5 monthly headache days was reduced to 7.9 ± 7.7 and 6.8 ± 7.0 respectively, at three and six months either with erenumab, galcanezumab or fremanezumab.¹¹ The subjects also used other medications for migraine prevention, had episodic (60%) or chronic migraine (40%) and were not necessarily previously failures in treatment. The tolerability was like the pivotal studies on mAbs, with mild adverse events presented by around 18% of the patients.

Regarding chronic migraine, the Brazilian reality is different. We rarely see subjects without concurrent medication overuse headache as reported in numerous studies from abroad. Most chronic migraineurs, especially seen in tertiary centers, are indeed over users of symptomatic medications and may not respond well to the use of a



mAb with or without other pharmacological agents. Such a lack of frequent treatment success, especially in those who didn't withdraw, is indeed reported regardless of favorable figures presented by studies involving mAbs from other countries and different realities. We expect that these biological therapies, if remaining available in the Brazilian market, will always have its role and place in the arsenal of anti-migraine weapons.

Onabotulinumtoxin A (Botox) for chronic migraine

Onabotulinumtoxin A inhibits N-ethylmaleimide-sensitive fusion attachment protein receptor (SNARE)-mediated vesicle trafficking by cleaving one of its essential proteins, the SNAP-25. It is present in both motor and sensory nerves, and this inhibition down regulates exocytosis of motor and sensory neurochemicals and proteins, as well as membrane insertion of peripheral receptors that convey pain from the periphery to the brain. It also decreases exocytosis of pro-inflammatory and excitatory neurotransmitters such as CGRP, substance P, and glutamate from primary afferent fibers and the insertion of pain-sensitive ion channels such as transient receptor potential cation channel subfamily V member 1 (TRPV1) into the membranes of nociceptive neurons. For chronic migraine prevention, onabotulinumtoxin A is injected into 31-39 sites in 7 muscles of the head and neck. Through inhibition of sensory nerve endings, it reduces pain signals that reach the brain and sensitization of central neurons.⁴²

Since the PREEMPT studies published in 2010 and the benevolent offers from the industry to sensitive physicians, Botox became a star in migraine treatment, especially in tertiary centers or centers devoted to financial compensations (Preempt 1 e 2).^{43,44} It happened despite conflicting results in previous trials for episodic as well as chronic migraine.⁴⁵⁻⁴⁷ The studies responsible for the approval of botox in chronic migraine were carried out in various centers in 1384 (688 onabotulinumtoxin A and 696 placebo) patients, with 18-65 years and a history of migraine excepting continuous headache, who were not exposed to any prophylactic treatments within 4 weeks prior to start the baseline period. The mean headache and migraine episodes among the two groups were less for botox. The percentage of patients with medication overuse was also low, around 65% for both groups, in comparison to the reality of chronic migraineurs in Brazil. After the double-blind phase, an open label extension was carried out up to 56 weeks.

A total of 607 (88.2%) onabotulinumtoxin A and 629 (90.4%) placebo patients continued into the open-label phase. Despite the statistically "significant" superiority of onabotulinumtoxin A, the reduction of headache-day frequency vs placebo in patients with chronic migraine at week 56, was -11.7 for onabotulinumtoxin A vs. -10.8 for placebo. There were other statistically significant reductions at this timepoint (week 56). The frequencies of

migraine days (-11.2 onabotulinumtoxin A versus -10.3 placebo; $P=.018$) and moderate/severe headache days (-10.7 onabotulinumtoxin A, -9.9 placebo; $P=.027$) favored the active biological therapy. After the open-label phase, statistically significant within-group changes from baseline were observed for all efficacy variables. Most patients (72.6%) completed this extension study phase and few discontinued because of adverse events. The authors concluded that repeated treatment with ≤ 5 cycles of onabotulinumtoxin A was effective, safe, and well tolerated in adults with chronic migraine.⁴⁸ However, the impartial analysis of the results, despite statistical significance, is clearly overestimated. In addition, the allegations that a meaningful proportion of patients with CM treated with onabotulinumtoxin A who did not respond to the first treatment cycle, did indeed respond in the second and third cycles of treatment may not be observed in clinical practice. Even with the data presented in a pooled PREEMPT data of two previous studies, a third cycle, at 32-week, during the open-label phase, evaluated onabotulinumtoxin A (155-195 U) for chronic migraineurs.⁴⁹ End points included the proportion of patients who first achieved a $\geq 50\%$ reduction in headache days, moderate/severe headache days, total cumulative hours of head pain on headache days, or a ≥ 5 -point improvement in Headache Impact Test (HIT)-6. Three cycles were better than 1 or 2, but again, in a study funded by the manufacturer of onabotulinumtoxin A.⁴⁹

The art and real-world use of Botox

It is difficult to fight the money. The avalanche of funded studies pushing this treatment for migraineurs is unstoppable. Lay media periodicals claim that onabotulinumtoxin A is also good for hundreds of diseases, as a magical therapy.¹² Outdoors located in high traffic roads disseminate botox as a miracle treatment and "botoclinics" are propagated even in shopping centers from all over the world.¹² Those struggling against the power of perks succumbed. The appeal is clear, as it is the repulsive behavior of contumacious onabotulinumtoxinA prescribers. Studies demonstrating reductions in headache days as well as improvement in all sources of secondary endpoints flourish with, indeed, a better performance for patients suffering with higher frequencies and daily headaches.⁵⁰ In addition, new treatment paradigms, using lower dosages and fewer injection points were recently published suggesting that a less expensive approach may show efficacy as well.⁵¹ However, a trend for botox recommendation in larger populations of patients has also been released. Not only sufferers with headache in ≥ 15 days are targets. Migraineurs with 8-14 monthly day shave a comparable burden, therefore requiring such a valuable therapy.⁵² In fact, procedure volume and total allowed charge regarding reimbursement trends and providers for chronic migraine (CM) chemodenervation treatment skyrocketed. It rose from 37,863 in 2013 to 135,023 in 2018 in a near-linear pattern and total allowed



charges rose from ~\$5,217,712 to \$19,166,160. Most of high-volume providers were neurologists (78.4%; 1060 of 1352), but a substantial proportion were advanced practice providers (APPs) (10.2%; 138 of 1352). Among physicians, neurologists performed a higher mean number of procedures per physician compared to non-neurologists (59.6 [95% CI: 56.6-62.6] vs. 45.4 [95% CI: 41.0-50.0], $p < 0.001$).⁵³ It is so far clear that Brazil is not different. The Botox wave will continue, despite constant complaints of lack of improvement and the feeling of being “ripped off”, by patients. Few, as the present writers, were not successful in finding efficacy studies that were not funded, but will remain in this quest, for the sake of patients.

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