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Biotherapeutic medicines: use of botulinum toxins in the era of biosimilars

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Abstract

Introduction: Botulinum toxins are biotherapeutic drugs with great applications in the field of neurology such as headache and abnormal movements. Due to the medical importance and the increase in therapeutic indications of botulinum toxin, this article aims to clarify the basic terminology regarding the nature of this drug, the structural differences with conventional drugs and important aspects in relation to its biological potency and immunogenicity in order to understand the potential differences between the available toxins and conceptualize regarding the non-interchangeability or substitution of one toxin for another.

Materials and methods: Non-systematic review as recommended in the Scale for the Verification of Narrative Review Articles (SANRA).

Conclusions: Biological drugs are not interchangeable with each other, even if they demonstrate bioequivalence. They cannot be evaluated as interchangeable generic drugs because they are biologics. There are no head-to-head comparative studies. They are different due to the individual manufacturing process.

Keywords: Biosimilar pharmaceuticals, Inumogenicity, Interchange of drugs, Botulinum toxins, type A.

Medicamentos bioterapéuticos: uso de toxinas botulínicas en la era de biosimilares

Resumen

Introducción: las toxinas botulínicas son medicamentos bioterapéuticos con grandes aplicaciones en el campo de la neurología, como la cefalea y los movimientos anormales. Debido a la importancia médica y al incremento de las indicaciones terapéuticas de la toxina botulínica, este artículo pretende hacer claridad acerca de la terminología básica con respecto a la naturaleza de este medicamento, a las diferencias estructurales con medicamentos convencionales y aspectos importantes en relación con su potencia biológica e inmunogenicidad, para así comprender las potenciales diferencias entre las toxinas disponibles y conceptuar en torno a la no intercambiabilidad o sustitución de una toxina por otra.

Materiales y métodos: revisión no sistemática, según lo recomendado en la Escala para la Verificación de los Artículos Revisiones Narrativas (Sanra).

Conclusiones: los medicamentos biológicos no son intercambiables entre sí, aunque demuestren bioequivalencia. No se pueden evaluar como medicamentos genéricos intercambiables porque son biológicos; no existen estudios comparativos cabeza a cabeza; son diferentes, debido al proceso individual de manufactura.

Palabras clave: biosimilares farmacéuticos, inmunogenicidad, intercambiabilidad de medicamentos, toxinas botulínicas tipo A.

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Objective

To review the information regarding the use of botulinum toxins in Neurology, their safe practice, the impact of non-differentiation, interchangeability and non-medical switching.

Methodology

This non-systematic review followed the recommendations of the Scale for the Assessment of Narrative Review Articles (SANRA), recently created and validated by expert editors of scientific journals (1). This scale assesses the following methodological items:

1. Explanation of the article's importance for the reader.

Although the botulinum toxin is frequently prescribed by different medical specialties such as Neurology and Physical Medicine, its security not only depends on the administration technique, but the deep knowledge of the product characteristics. Given that for biological products it is recognized that the process determines the product, it is feasible that botulinum toxins are commercialized for medical use that in principle are not identical, so their potency and dosage would be specific to each preparation. Acknowledging the differences can promote safer and more responsible use of the drug.

2. Statement of concrete aims or f ormulation of questions.

Based on the available literature, what are differences between the botulinum toxins from different manufacturers that may limit interchangeability or automatic substitution of one toxin for another?

3. Description of the literature search.

The literature search was conducted in Medline/PubMed and Google Scholar, using as descriptors the combination of the following terms in Spanish and English: botulinum toxins, biosimilars, guidelines, interchangeability, immunogenicity. For the analysis of the documents related to the topic, those available in full text were chosen, without distinction by type of article. Of the 101 results obtained, those focused specifically on botulinum toxin as a biological product and not only on the topic of biologics and biosimilars were preferably selected.

4. Referencing

Each key statement was supported by the references found.

5. Scientific reasoning

In order to strengthen the arguments, the articles reviewed were shared among authors, who then gathered to discuss the information available, for which they used a presentation made by one of the authors as a discussion guide for each topic described in this manuscript. Thus, the review summarizes the key conclusions derived from the expert's dissertation on the topic. When a key statement was supported by a clinical study, the type of study (i.e., randomized clinical trial) and its quality were mentioned. Although there were more than five experts on the subject, the authors did not find scientific information or positions on the subject in the Spanish literature. Therefore, they chose to start with this narrative review to create some basic concepts applicable to our practice hoping that this work will encourage Latin American scientific associations to subsequently develop expert panels under the Delphi methodology, which can increase the evidence on the subject.

6. Appropriate presentation of data

The relevant data from the articles obtained from the search were presented summarizing the conclusion or main outcome, and if possible, the effect size was accompanied by a confidence interval. In other cases, the summary of the data obtained was presented as absolute results.

Introduction

Drugs are the mainstay of medical therapy; they can be small molecules of low molecular weight (< 5 kDa) manufactures by chemical synthesis, or large molecules obtained or extracted from biological resources by biotechnological processes, which is why they are preferably referred to as "biotherapeutics".

Due to the medical importance and increasing therapeutic indications of botulinum toxin, this article aims to clarify the basic terminology regarding the nature of this drug, the structural differences with conventional drugs and important aspects related to its biological potency and immunogenicity, to understand the potential differences between the botulinum toxins available and to understand the non-interchangeability or substitution of one toxin for another.

General aspects

Biological products are used to diagnose, prevent, treat and cure diseases and medical conditions. They are a diverse category of products and are generally big and complex molecules. They can be obtained by biotechnology in a living system like a microorganism, a plant or animal cell, and are often more difficult to characterize than small molecule drugs. There are many types of biologicals approved for clinical use, included therapeutic proteins (like filgrastim) monoclonal antibodies (like adalimumab) and vaccines (like influenza and tetanus) (2).

The nature of biological products, including the inherent variations that can result from the manufacturing process, can present challenges in the characterization and manufacture of these products that often do not exist in small-molecule drug development. Slight differences between manufactured batches of the same biological product (i.e., acceptable variations within the product) are normal and expected within the manufacturing process. As part of their review, regulatory agencies such as the FDA in the United Stated, evaluate the manufacturing process and the manufacturer's strategy to control variations within the product. These control strategies are implemented to help guarantee that the manufacturers produce biologics with a consistent clinical performance (2).

Once the patent protection period of a reference drug expires, the opportunity to develop competitors arises. Worldwide, drug competition is promoted as a way to obtain cheaper products and the approval of these competitors tend to follow defined standards that allow obtaining small-molecule generics and biosimilars of biological products.

A generic drug is a biochemically identical drug with the same active ingredients and offers the same clinical benefits than a small-molecule or chemical synthesis reference drug. It is created to have identical dosage form, safety, potency, route of administration, quality, performance characteristics and intended use. However, biosimilars are not a generic version of the biologics, as it is not feasible to demonstrate identity with absolute certainty between large molecules of living origin. Therefore, the term highly similar is preferred, mainly due to the inherent complexity of proteins and therapeutic carbohydrates, including their three-dimensional nature, as well as their as their specific manufacturing processes (3).

Occasionally, the manufacturer of a generic drug also seeks to demonstrate that its product is bioequivalent to the reference drug. However, biosimilar manufacturers must comparatively demonstrate that the product is very similar to the reference product, in analytical, functional, preclinical and clinical terms, accepting minor differences in the clinically inactive components (2).

Unlike biosimilars, generics do not require extensive clinical trials. So far, with this comparative exercise, at least 29 biosimilars have been approved for various indication in the United Stated and 64 biosimilars in Europe. The European Medical Agency (EMA) was the first to approve a biosimilar (in 2006) and in offering guidance for the development and approval of biosimilars (4-7).

Table 1 shows a summary comparison of the structural, pharmacokinetic, pharmacodynamic, economic and safety profile characteristics between chemically synthesized products and biologics (8).

Botulinum toxins mechanism of action

The original proposed mechanism of BoNT was a simple blockage of acetylcholine release at the neuromuscular junction, which occurred by cleavage and inhibition of proteins involved in presynaptic vesicle fusion at the synapse, which weakens muscle contraction. Additional mechanisms of action and modifying factors are implicated by the dissociation between weakness, pain relief and efficacy in dystonia. BoNT is primarily taken up by more highly active axons and inhibits gamma motor neuron afferent of intrafusal stretch muscle fibers and spindle afferents leading to the tonic stretch reflex. Finally, BoNT is retrogradely transported in its active state, which can produce a central action at both the spinal cord and brain levels (9-15).

In chronic migraine, the BoNT mechanism of action is not yet fully elucidated, but it is recognized that it may involve axonal transport to the trigeminal and dorsal root ganglia, modulation of calcitonin gene-

Table 1. Characterization of chemically synthesized versus biological and biotechnological products

Characteristic	Chemicals	Biologics and biotechnological
Chemical and structural		
Nature	Basic inorganic or organic substances	Peptides and proteins (mixed with sugars in some cases)
Molecular weight (kDa)	< 5	5-900
Results	Standard chemical reactions	Genetic engineering (DNA recombination, hybridoma)
Administration route	Oral or injectable	Parenteral injections (subcutaneous, intramuscular)
Storage	Long average life	Very short (requires refrigeration)
Stability	High	Unstable
Pharmacokinetics and pharmacodynamics		
Comparison criteria	Area under the curve (AUC) and maximum concentration of the test product (generic) over the reference (innovator).	Preclinical (including animal models) and clinical (phase I, II and III) comparative studies plus active pharmacovigilance.
Does therapeutic drug monitoring (serum level) apply?	Yes	Rarely (very difficult to determine serum levels)
Does bioequivalence apply?	Yes	No
Designation for non-innovative versions	Generic	Biosimilar, similar biological medicine or follow-on protein product)
Safety		
Immunogenicity risk	Low	Very high
Effect-blocking antibodies	No	Generally

Source: Own elaboration based on Kresse (8)

related peptide, substance P and other neurotransmitters, as well as modulation of surface expression of nociceptive receptors and cytokines (9,16-18).

Botulinum toxins mechanism of action

The BoNT complex is packaged in standard vials and either vacuum dried (in the case of onabotulinumtoxinA) or lyophilized (in the case of abobotulinumtoxinA and incobotulinumtoxinA), which requires reconstitution with normal saline without preservatives, or in ready-to-use solution (in the case of rimabotulinumtoxinB). The package for each vial provides specific instructions, but a few points are worth highlighting. When reconstituting, it should be noted that lack of vacuum may indicate a loss of sterility. The "dried botulinum" is difficult to visualize, and the saline solution should be injected and shaken gently to the bottom of the vial. After mixing, avoid inverting the vial when aspirating into an administration syringe, as small volumes of the reconstituted botulinum may clog along the walls or cap of the vial (9,19).

Types of botulinum toxins

There are 7 serotypes of the gram-positive anaerobic bacterium Clostridium botulinum (A, B, C, D, E, F and G), each of which produces a unique neurotoxin, also designated A through G, which is distinguished by animal antisera. Serotypes A and B are commonly used in medical practice. The most recent sequence analysis has identified many genes encoding new BoNTs with variable amino acid sequences; these "subtypes" are organized under traditional serotypes followed by numbers (i.e., BoNT/ A1, BoNT/ A2).

Each serotype targets different components of the presynaptic vesicle binding protein complex. These mechanic differences lead to a nonlinear dose conversion from one serotype to the next (9,19).

However, there are proximate, empirical attempts in the literature to guide ranges of "conversion" ratios (i.e., in comparison to onabotulinumtoxinA [OnaA], estimated ratios are 1:1 for incobotulinumtoxinA [IncoA], 1:2.5 to 4 for abobotulinumtoxinA [AboA], and 1:50 to 100 for rimabotulinumtoxinB [RimaB]) (9,20,21).

Biological potency (the process is the product, the potency-dose ratio is product-specific)

Based on the current evidence, there are several arguments justifying that the potency units are NOT equivalent between the different toxins, among which the following are highlighted:

- Differences in manufacturing, formulation and how botulinum toxins type A are evaluated by specific assays can affect clinical characteristics such as dose, duration, efficacy and immunogenicity.
- Each manufacturer uses its own proprietary assay methods and reference standards, which results in differences in non-interchangeable unit doses.

It is important to emphasize that the chemical formulations of the toxins, their clinical potency, dosage and safety profile are different. Individual BoNT/A brands should not be treated as interchangeable due to different purification methods and differences in the final product, different ways of assessing activity, as well as different units in which their activity is expressed (22-24).

In other words, the potency of different BoNTs is measured in Units (U), in some cases derived from a mouse protection assay (MPA): 1U is the amount of toxin injected intraperitoneally capable of killing 50% (LD50) of a group of mice. The product dose for patient treatment is determined by each manufacturer's LD50 potency assay result. These assays use different diluents and standards, so the unit of measurement for commercially available BoNT/A preparations are unique to each manufacturer. No formula reliably predicts what dose of one brand will produce identical effects in a patient already treated with another brand (23, 25-30).

Concept of biosimilarity and interchangeability

A biosimilar is a biological product that is very similar to and has no clinically significant differences from an existing reference product (known as the original biologic or reference product). Biosimilars are made from the same types of natural sources as the original drug to which they were compared, are administered in the same way, have the same concentration and dose and have the same potential side effects. A biosimilar provides the same treatment benefits as the original biologic.

An interchangeable product is a biosimilar that needs additional information to demonstrate that it produces the same clinical outcome as the reference product in any given patient. In addition, for products administered to a patient more than once, the risk in terms of reduced safety and efficacy of switching between an interchangeable and a reference product will have been assessed (2).

An interchangeable product can be safely replaced by the reference product, without the involvement of the prescriber. But this must be supported by evidence provided by the aforementioned additional studies (2).

Non-interchangeability implications

Due to differences in clinical performance (duration, dose, efficacy, immunogenicity, etc.) and the lack of interchangeability studies, currently BoNT/A products cannot be considered interchangeable. These clinical differences are the result of underlying differences in basic manufacturing processes, formulation and potency testing methods that result in different unit potencies and dose response curved for each product (22, 34-36).

Non-interchangeability has direct implications for clinical efficacy and patient safety. These two intertwined dimensions are not independent, as each product established a specific risk-benefit profile. These factors are also influenced by the quality of the product (22, 34-36).

The risk-benefit approach of one product cannot be applied to another product. For example, if a product with lower biological activity were administered in unit doses based on a more potent product, patients would not experiment adequate symptom relief. Therefore, the products used in suboptimal doses may not meet patient expectations, which could lead to unsatisfaction. Moreover, patients may require more frequent office visits for reinjection, which can be inconvenient and increase costs. Frequency of treatment is a contributing dimension to antibody formation for proteins in general with more frequent injections increasing the potential to neutralize antibody formation. Equally important, if a product with more biological activity is administered in unit doses based on a less potent product, patients could experience an unacceptable safety profile (22).

Interchangeability of toxins in chronic migraine

OnabolutinumtoxinA (OnaBoNTA) is the preparation that has been used in pivotal studies of chronic migraine and is the only BoN-TA preparation that has been approved for the treatment of this condition by regulatory agencies (37,38).

There are studies with other toxins that have not demonstrated efficacy in the control of chronic migraine. There is a 12-week double-blind randomized study of AboBoNTA (120 or 240 units) in six centers in Thailand, to assess efficacy, security and optimal dose for migraine prophylaxis. A total of 127 patients were included. The results were inconclusive and AboBoNTA patients reported an improvement in headache intensity, but no change in overall migraine frequency compared to placebo (39).

Currently, OnabolutinumtoxinA is the only botulinum toxin recommended for chronic migraine patients by the American Academy of Neurology, and it is the only one that has studies supporting its use after several years of approval by regulatory agencies (40-43).

Immunogenicity with the use of botulinum toxin

It is important to know some concepts and based on these, as well as on clinical practice, to have a guide for the adequate use of botulinum toxin. The first concept is primary non-response (PNR), which refers to the patient who does not present any type of clinical response from the first application or after the subsequent applications. Primary non-responders are clinically rare cases and therefore it is important to review other explanations mentioned below.

Some studies have considered as PNR those patients with a response of less than 25% from the first application.

Secondary non-response (SNR) is when the patient benefits from at least one injection but loses that benefit in subsequent cycles. The loss of response can be partial or complete. There are many reasons for this to occur, one of which is the development of neutralizing antibodies (NAbs) (44).

In general, botulinum toxin injections introduce a foreign protein, capable of acting as an antigen, which is why antibody formation has been a constant concern since the introduction of this therapy in the 1980s. Repeated injections of botulinum toxin type A entail the risk of Nabs induction. The incidence of Nabs during continuous treatment of dystonia or spasticity with BoNT ranges between 0.5% and 1.5% per year. This indicates that up to 15% of patients may develop Nabs after 10 years of treatment, but their presence does not guarantee that this is the cause of therapeutic failure. The evaluation of other causes is important before classifying a patient as a non-responder, either primary or secondary.

In addition to the presence of antibodies, changes in the disease pattern, insufficient drug dosage, inappropriate application schedule, poor application technique or even poor preservation of the toxin must be considered (45-48).

In some patients, the natural progression of their disease may explain the loss of benefit from the BoNT therapy, which has been confirmed in multiple series of patients with SNR, showing that only a fraction of these patients has NAbs. In patients with SNR due to Nab, 81% start with a partial loss of the effect before progressing to a complete loss, in an average of 2.5 injections (49).

All BoNT serotypes can induce both neutralizing and non-neutralizing antibodies which may increase treatment efficacy. Antibodies are not routinely measured in clinical practice, but blood samples can be tested if there is a concern for acquired immunity.

Treatment- and patient-related factors for the existence of NAbs are:

- Frequency of injections
- Cumulative dose
- Administration in short intervals (less than 12 weeks)

- High doses per application
- Genetic background (patients likely to induce production of antibodies)
- Previous exposure
- Hyperthyroidism or hypothyroidism and some autoimmune conditions
- Injection sites and muscles.

However, the precise relationship between neutralizing antibodies and neurotoxin resistance is unclear since a positive titer does not directly indicate lack of response or treatment failure. Further research is needed to determine the association of antibody formation with clinical response (9,51).

If the patient is suspected to be a SNR due to NAbs, in-vivo and in-vitro tests are available to perform NAbs measurement; the most used for safety and ethics are in vitro tests such as ELISA technique. In an article by Srinoulprasert and Wanitphakdeedecha (52), published in 2019, a management algorithm is proposed with the aim of avoiding re-exposure to BoNT/A in patients and decreasing adverse effects.

The authors (52) use two techniques, an ELISA inhibition to detect antibodies against all BoNT/A active sites. If the inhibition test is positive, it means there are significant levels of BoNT/A inactive sites in the patient's serum, so it is suggested that the patient undergo an Elisa inhibition test within the next 6 months. If the result is negative, any formulation of BoNT/A (such as BoNT/A complexed with accessory proteins) could be applied and its clinical response evaluated.

If there is no clinical response, it is recommended to perform an ELISA, which detects antibodies against accessory or complexing proteins. If the result is positive, it means there is a significant presence of antibodies against the complete BoNT/A; in this case choosing its formulation is a challenge. If the result is negative, it means that most of the antibodies in the patient's serum are antibodies against accessory or complexing proteins, so it is recommended to administer the oure BoNT/A formulation (BoNT/A without accessory proteins) and evaluate the response.

Some studies have shown that reaching a negative or undetectable Nab status in the previously diagnosed patient could take up to 5 to 6 years (52).

In Colombia, unfortunately, we do not have this type of tests. It is necessary to consider that even when the probability of NAbs formation is low, it can occur and should be suspected.

Conclusions

The manufacture of biological products is complex and hard to replicate. They require strict quality control during the manufacturing process which will affect the final product, as well as the efficacy and safety clinical results.

For a biologic to be considered a biosimilar, it must pass standards previously defined by the regulatory entities of each country. Comparative quality studies, pharmacodynamic, pharmacokinetic, immunogenicity, efficacy and safety studies are required. Currently there are no biosimilar products for toxins available.

Botulinum toxins are not interchangeable with each other, even if they demonstrate bioequivalence. This is explained for several reasons: they do not meet the FDA definition of biosimilar; they cannot be evaluated as interchangeable generic drugs because they are biologics; there are no head-to-head comparative studies. They are different due to the individual manufacturing process.

The potency units are not equivalent among the different toxins. Potency depends on the type of test, the procedure performed, and the standard used.

Medical evidence shows that the only molecule that should be used for the treatment of chronic migraine is Onabotulinumtoxin A. There is no evidence about the medical and non-medical switch in this condition. The most important clinical outcomes of the non-medical switch are changes in effectiveness, inadequate dose equivalence, increased possibility of generating antibodies and dosing and administration errors.

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References

1. Baethge C, Goldbeck-Wood S, Mertens S. SANRA - a scale for the quality assessment of narrative review articles. Res Integr Peer Rev. 2019;4:5. https://doi.org/10.1186/s41073-019-0064-8
2. U.S. Food & Drug Administration (FDA). Biosimilar and interchangeable products [consultado el 19 de junio del 2022]. https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products#generic
3. Verrill M, Declerck P, Loibl S, Lee J, Cortes J. The rise of oncology biosimilars: from process to promise. Future Oncol. 2019;15(28):3255-65. https://doi.org/10.2217/fon-2019-0145
4. Biosimilars info sheet. Generics and biosimilars. https://www.fda.gov/media/154912/download
5. U.S. Food & Drug Administration (FDA). Biosimilar product information [consultado el 19 de abril del 2021]. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information
6. European Medicines Agency. Medicines type-biosimilars [consultado el 26 de abril del 2021]. https://www.ema.europa.eu/en/medicines/search_api_aggregation_ema_medicine_types/field_ema_med_biosimilar
7. Gherghescu I, Delgado-Charro MB. The biosimilar landscape: an overview of regulatory approvals by the EMA and FDA. Pharmaceutics. 2021;13(1):48. https://doi.org/10.3390/pharmaceutics13010048
8. Kresse GB. Biosimilars - science, status, and strategic perspective. Eur J Pharm Biopharm. 2009;72(3):479-86. https://doi.org/10.1016/j.ejpb.2009.02.014
9. Chiu SY, Burns MR, Malaty IA. An update on botulinum toxin in neurology. Neurol Clin. 2021;39(1):209-29. https://doi.org/10.1016/j.ncl.2020.09.014
10. Burstein R, Blumenfeld AM, Silberstein SD, Manack Adams, A, Brin MF. Mechanism of action of onabotulinumtoxinA in chronic migraine: a narrative review. Headache. 2020;60:1259-72. https://doi.org/10.1111/head.13849
11. Davletov B, Bajohrs M, Binz T. Beyond Botox: Advantages and limitations of individual botulinum neurotoxins. Trends Neurosci. 2005;28(8):446-52. https://doi.org/10.1016/j.tins.2005.06.001
12. Chen R, Karp BI, Goldstein SR, Bara-Jimenez W, Yaseen Z, Hallett M. Effect of muscle activity immediately after botulinum toxin injection for writer's cramp. Mov Disord. 1999;14(2):307-12. https://doi.org/10.1002/1531-8257(199903)14:2<307::AID-MDS1016>3.0.CO;2-3
13. Eleopra R, Tugnoli V, De Grandis D. The variability in the clinical effect induced by botulinum toxin type A: The role of muscle activity in humans. Mov Disord. 1997;12(1):89-94. https://doi.org/10.1002/mds.870120115
14. Rosales RL, Arimura K, Takenaga S, Osame M. Extrafusal and intrafusal muscle effects in experimental botulinum toxin-A injection. Muscle Nerve. 1996;19(4):488-96. https://doi.org/10.1002/(SICI)1097-4598(199604)19:4%3C488::AID-MUS9%3E3.0.CO;2-8
15. Trompetto C, Currà A, Buccolieri A, Suppa A, Abbruzzese G, Berardelli A. Botulinum toxin changes intrafusal feedback in dystonia: a study with the tonic vibration reflex. Mov Disord. 2006;21(6):777-82. https://doi.org/10.1002/mds.20801
16. Ramachandran R, Lam C, Yaksh TL. Botulinum toxin in migraine: Role of transport in trigemino-somatic and trigemino-vascular afferents. Neurobiol Dis. 2015;79:111-22. https://doi.org/10.1016/j.nbd.2015.04.011
17. Pellett S, Yaksh TL, Ramachandran R. Current status and future directions of botulinum neurotoxins for targeting pain processing. Toxins. 2015;7(11):4519-63. https://doi.org/10.3390/toxins7114519
18. Zhang X, Strassman AM, Novack V, Brin MF, Burstein R. Extracranial injections of botulinum neurotoxin type A inhibit intracranial meningeal nociceptors' responses to stimulation of TRPV1 and TRPA1 channels: Are we getting closer to solving this puzzle? Cephalalgia. 2016;36(9):875-86. https://doi.org/10.1177/0333102416636843

19. Smith TJ, Hill KK, Raphael BH. Historical and current perspectives on Clostridium botulinum diversity. Res Microbiol. 2015;166(4):290–302. https://doi.org/10.1016/j. resmic.2014.09.007

20. Dashtipour K, Chen JJ, Espay AJ, Mari Z, Ondo W. Onabotulinumtoxin A and abobotulinumtoxin A dose conversion: a systematic literature review. Mov Disord Clin Pract. 2016;3(2):109–15. https://doi.org/10.1002/mdc3.1223

21. Scaglione F. Conversion ratio between Botox®, Dysport®, and Xeomin® in clinical practice. Toxins (Basel). 2016;8(3):65. https://doi.org/10.3390/toxins8030065

22. Brin MF, James C, Maltman J. Botulinum toxin type A products are not interchangeable: a review of the evidence. Biologics. 2014;8:227–41. https://doi.org/10.2147/BTT.S65603

23. Car H, Bogucki A, Bonikowski M, Dec-Ćwiek M, Drużdż A, Koziorowski D, et al. Botulinum toxin type-A preparations are not the same medications – basic science (part 1). Neurol Neurochir Pol. 2021;55:133–40. https://doi.org/10.5603/PJNNS.a2021.0027

24. Becker WJ. Botulinum toxin in the treatment of headache. Toxins (Basel). 2020;12(12):803. https://doi.org/10.3390/toxins12120803

25. Bentivoglio AR, Del Grande A, Petracca M, Ialongo T, Ricciardi L. Clinical differences between botulinum neurotoxin type A and B. Toxicon. 2015;107(Pt A):77–84. https://doi.org/10.1016/j.toxicon.2015.08.001

26. Fonfria E, Maignel J, Lezmi S, Martin V, Splevins A, Shubber S, et al. the expanding therapeutic utility of botulinum neurotoxins. Toxins. 2018;10(5):208. https://doi.org/10.3390/toxins10050208

27. Allergan I. Package insert, Botox (botulinum toxin type A purified neurotoxin complex). Madison, NJ: Irvine Allergan; 2019.

28. Merz Pharmaceuticals. Package insert, Xeomin (incobotulinumtoxintype A). Frankfurt: Merz Pharmaceuticals GmbH; 2018.

29. Solstice Neurosciences. Package Insert, Myobloc (botulinum toxin type B injectable solution). Louisville (KY): Solstice Neurosciences, LLC; 2019.

30. Ipsen. Package insert, Dysport (abobotulinumtoxin A). Basking Ridge (NJ): Ipsen Biopharmaceuticals; 2019.

31. Field M, Splevins A, Picaut P, van der Schans M, Langenberg J, Noort D, et al. AbobotulinumtoxinA (Dysport®), OnabotulinumtoxinA (Botox®), and IncobotulinumtoxinA (Xeomin®) Neurotoxin content and potential implications for duration of response in patients. Toxins (Basel). 2018;10(12):535. https://doi.org/10.3390/toxins10120535

32. Wenzel R, Jones D, Borrego JA. Comparing two botulinum toxin type A formulations using manufacturers' product summaries. J Clin Pharm Ther. 2007;32(4):387–402. https://doi.org/10.1111/j.1365-2710.2007.00835.x

33. Rupp D, Nicholson G, Canty D, Wang J, Rhéaume C, Le L, et al. OnabotulinumtoxinA displays greater biological activity compared to IncobotulinumtoxinA, demonstrating non-interchangeability in both in vitro and in vivo assays. Toxins (Basel). 2020;12(6):393. https://doi.org/10.3390/toxins12060393

34. Hunt T, Clarke K. Potency evaluation of a formulated drug product containing 150-kd botulinum neurotoxin type A. Clin Neuropharmacol. 2009;32(1):28–31. https://doi.org/10.1097/WNF.0b013e3181692735

35. Brown M, Nicholson G, Ardila MC, Satorius A, Broide RS, Clarke K, et al. Comparative evaluation of the potency and antigenicity of two distinct BoNT/A-derived formulations. J Neural Transm. 2013;120(2):291–8. https://doi.org/10.1007/s00702-012-0854-3

36. Hunt T, Clarke K, Rupp D, Shimizu G, Weidler J. 50-U incobotulinumtoxinA drug product demonstrates lower potency when compared to 50-U onabotulinumtoxinA drug product with concurrent lower light-chain activity and atypical substrate cleavage; Poster presented at 6th European Master's in Aesthetic and Anti-Aging Medicine; October 15–17, 2010; París, Francia.

37. Aurora SK, Dodick DW, Turkel CC, DeGryse RE, Silberstein SD, Lipton RB, et al; PREEMPT 1 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the Preempt 1 trial. Cephalalgia. 2010;30(7):793–803. https://doi.org/10.1177/0333102410364676

38. Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGryse RE, Lipton RB, et al; PREEMPT 2 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the Preempt 2 trial. Cephalalgia. 2010;30(7):804–14. https://doi.org/10.1177/0333102410364677

39. Chankrachang S, Arayawichanont A, Poungvarin N, Nidhinandana S, Boonkongchuen P, Towanabut S, et al. Prophylactic botulinum type A toxin complex (Dysport®) for migraine without aura. Headache. 2011;51(1):52–63. https://doi.org/10.1111/j.1526-4610.2010.01807.x

40. Simpson DM, Hallett M, Ashman EJ, Comella CL, Green MW, Gronseth GS, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016;86(19):1818–26. https://doi.org/10.1212/WNL.0000000000002560

41. Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. JAMA. 2012;307(16):1736-45. https://doi.org/10.1001/jama.2012.505

42. Shamliyan TA, Kane RL, Taylor FR. Migraine in adults: preventive pharmacologic treatments. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.

43. Tassorelli C, Sances G, Avenali M, De Icco R, Martinelli D, Bitetto V, et al. Botulinum toxin for chronic migraine: Clinical trials and technical aspects. Toxicon. 2018;147:111-5. https://doi.org/10.1016/j.toxicon.2017.08.026

44. Bellows S, Jankovic J. Immunogenicity associated with botulinum toxin treatment. Toxins (Basel). 2019;11(9):491. https://doi.org/10.3390/toxins11090491

45. Albrecht P, Jansen A, Lee JI, Moll M, Ringelstein M, Rosenthal D, et al. High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy. Neurology. 2019;92(1):e48-54. https://doi.org/10.1212/WNL.0000000000006688

46. Lange O, Bigalke H, Dengler R, Wegner F, deGroot M, Wohlfarth K. Neutralizing antibodies and secondary therapy failure after treatment with botulinum toxin type A: much ado about nothing?. Clin Neuropharmacol. 2009;32(4):213-8. https://doi.org/10.1097/WNF.0b013e3181914d0a

47. Naumann M, Carruthers A, Carruthers J, Aurora SK, Zafonte R, Abu-Shakra S, et al. Meta-analysis of neutralizing antibody conversion with onabotulinumtoxinA (Botox(R)) across multiple indications. Mov Disord. 2010;25(13):2211-8. https://doi.org/10.1002/mds.23254

48. Gelb DJ, Yoshimura DM, Olney RK, Lowenstein DH, Aminoff MJ. Change in pattern of muscle activity following botulinum toxin injections for torticollis. Ann Neurol. 1991;29(4):370-6. https://doi.org/10.1002/ana.410290407

49. Dressler D. Clinical presentation and management of antibody-induced failure of botulinum toxin therapy. Mov Disord. 2004;19 Suppl 8:S92-S100. https://doi.org/10.1002/mds.20022

50. Fabbri M, Leodori G, Fernandes RM, Bhidayasiri R, Marti MJ, Colosimo C, et al. Neutralizing antibody and botulinum toxin therapy: a systematic review and meta-analysis. Neurotox Res. 2016;29(1):105-17. https://doi.org/10.1007/s12640-015-9565-5

51. Brashear A, Bergan K, Wojcieszek J, Siemers ER, Ambrosius W. Patients' perception of stopping or continuing treatment of cervical dystonia with botulinum toxin type A. Mov Disord. 2000;15(1):150-3. https://doi.org/10.1002/1531-8257(200001)15:1%3C150::AID-MDS1024%3E3.0.CO;2-X

52. Srinoulprasert Y, Wanitphakdeedecha R. Antibody-induced botulinum toxin treatment failure: A review and novel management approach. J Cosmet Dermatol. 2020;19(10):2491-6. https://doi.org/10.1111/jocd.13637