International Journal of General Medicine

Dovepress

open access to scientific and medical research

Open Access Full Text Article

COMMENTARY

DAXI (DaxibotulinumtoxinA) – An Innovative Approach for Frown Lines

Abdullah Mussarat, Muhammad Saqlain Mustafa, Syed Talal Azam, Muhammad Musab Nafees uddin, Rana Muhammad Umer Nasrullah, Mohammad Arham Siddiq

Department of Medicine, Jinnah Sindh Medical University, Karachi, Pakistan

Correspondence: Mohammad Arham Siddiq, Department of Medicine, Jinnah Sindh Medical University, Iqbal Shaheed Road, Karachi, Pakistan, Tel +923412127759, Email arhammusani99@gmail.com

Abstract: Glabellar frown lines, also known as worry lines, are a common sign of aging. The current treatment option for glabellar lines is subjective and ranges from economical anti-wrinkle creams and skin resurfacing techniques such as microdermabrasion and fillers to highly expensive facelifts. Botox® has been the mainstream treatment for decades, but the suggested time between treatments for most toxins is 12–16 weeks, and evidence shows that patients being treated for glabellar lines want longer-lasting results. Recently, on September 16th, the US Food and Drug Administration (FDA) approved the development of daxibotulinumtoxinA (DAXI) for injection based on clinical trials (SAKURA 1, 2, and 3). These encouraging findings followed by FDA approval mean that the need for repeated treatments to sustain the desired outcome has decreased. DAXI could be a reliable and secure choice for reducing the appearance of wrinkles on the face caused by muscle activity, and its long duration has the potential to enhance the treatment of both therapeutic and cosmetic disorders.

Keywords: glabellar lines, Botox, daxibotulinumtoxinA, SAKURA, wrinkles

Glabellar frown lines, also known as worry lines, are commonly perceived as a prominent sign of aging can manifest as early as in 2nd decade of life.[1] This is due to the contraction of various muscles including the corrugator, depressor supercilii, and/or procerus muscles of the face, which leads to the formation of "brow furrows", or gaps between eyebrows. This may ultimately create a false impression of emotions such as anger or sorrow.[2–6] Over decades repeated contractions, smoking, and UV-radiation leads to thinning of the muscle and loss of muscle elasticity which may even be visible as normal facial repose.[7,8] As the majority of the population is affected by their physical appearance, these wrinkles could potentially be a reason for low self-confidence, avoidance of social gatherings, and ultimately hampering their well-being and quality of life.[9] It was also found that people suffered from dysphoria not only mentally but physically due to discrepancies between physical image and mental perception.[10]

When injected, botulinum toxin causes partial paralysis and atrophy by preventing pre-synaptic release of the neurotransmitter (acetylcholine) at the neuromuscular junction and chemically denervating the muscle fiber reversibly.[11] One of the seven botulinum toxin serotypes (A-G), known as BoNT-A, is created by the gram-positive anaerobic bacterium *Clostridium botulinum*. The authorized serotype A is not only limited to its cosmetology use in order to treat glabellar lines but has an extended use in medical treatment for mild conditions like overactive bladder, chronic migraine headaches, or serious conditions like upper limb spasticity, blepharospasm, and cervical dystonia. Despite the fact that BoNTAs are frequently used for medicinal and cosmetic purposes, the duration of action is a drawback of all currently available BoNTA products.[12,13]

The current treatment regime for treating glabellar lines is very subjective starting from economically friendly anti-wrinkle creams, and skin resurfacing techniques like microdermabrasion, and fillers, to highly expensive facelift surgeries.[7] However, Botox®, a very familiar name among people, patients, and cosmetologists, has been the "main-stream" treatment for decades. Due to the results as quick as a few days while achieving maximum outcomes in 2–4

Received: 10 February 2023
Accepted: 2 April 2023
Published: 10 April 2023

weeks.[14] The glabellar complex muscles can be injected to smooth out the muscles that cause frown lines. Currently, AbobotulinumtoxinA (Dysport®), onabotulinumtoxinA (Botox®), and incobotulinumtoxinA (Xeomin®) are the three BoNT-A products that are marketed and sold globally.[15] The suggested time between treatments for the majority of BoNTAs that are currently licensed in the USA is 12–16 weeks (3–4 months) and there is evidence that patients being treated for glabellar lines want longer-lasting results.[13]

On September 16th, 2022, the US Food and Drug Administration (FDA) based on the promising findings of clinical trials (SAKURA 1, 2, and 3) approved the development of daxibotulinumtoxinA (DAXI) for injection.[16] The results were calculated by a 2-point improvement in glabellar line severity according to both investigator and subject ratings at maximum frown at week 4. Following three rounds of treatment with DAXI, the response rates were significantly improved, with over 96% of patients experiencing no or mild severity of frown wrinkles, as evaluated by the Investigator Global Assessment–Frown Wrinkle Severity (IGA-FWS) scale. The most substantial response was observed between Weeks 2 and 4, indicating that the effects of the treatment were both rapid and long-lasting. The SAKURA 1 and 2 studies, which included a combined total of 609 individuals, provided consistent results that supported the high level of efficacy reported with DAXI.[17] In order to further evaluate the safety profile of DAXI in a significantly wider patient group and with a greater number of injectors, SAKURA 3—an expansion of the key Phase 3 studies—was conducted.[18]

An innovative, proprietary stabilizing peptide excipient (RTP004) that is substantially positively charged and attaches to the negatively charged core neurotoxin is used in the formulation of DAXI. This particular peptide assures stability at room temperature prior to reconstitution and enables the formulation of DAXI without the need for human serum albumin (which is utilized in the existing BoNTA products).[19] One of the distinguishing features that render this superior to its peers is the lack of animal products used in its production. The other feature is its prolonged duration of improvement for reducing glabellar line confirmed and expanded upon by the phase 3 data. In contrast to existing licensed botulinum toxin products, DAXI for Injection offers prolonged efficacy between treatments and might enable less frequent injections.[20] Moreover, the DAXI procedure may lessen or eliminate mechanical stress in the glabellar region as well as repetitive skin folding (and thus chronic stress applied to the dermis). It may also weaken the glabellar complex muscles, which leads to an unopposed elevation and lifting effect from the (untreated) brow elevators. DAXI therapy may have various effects including local muscle relaxation (which explains the early improvements in glabellar lines) and tissue remodeling due to decreased muscle activity.[21]

Botulinum toxin is a very safe medicine with few side effects in therapeutic doses. A few adverse events were documented in the SAKURA clinical trials of additional BoNTA products for the treatment of glabellar lines. Regardless of the cause, headache, nasopharyngitis, injection site discomfort, and injection site erythema were the most frequent adverse events (reported in less than 1% of patients). A total of 480 individuals overall (17.8%) out of 2691 had adverse events associated with DAXI treatment. There were 31 significant adverse events, but none of them was thought to be related to the treatment. BoNTA treatments need to be used again in order to maintain glabellar smoothness, therefore the length of response should be considered while assessing the risk of adverse effects.[22]

The encouraging findings of SAKURA 1, 2 and 3 trials followed by FDA approval the need for repeated treatment to sustain the desired outcome has decreased. In these clinical trials, patients reported a significant improvement in wrinkle appearance and satisfaction with the treatment. DAXI could be a reliable and secure choice for lowering the appearance of wrinkles on the face caused by muscle activity and its long duration has the capacity to enhance the treatment of both therapeutic and cosmetic disorders, but it should be used only with proper consultation with a health care professional. DAXI has limitations in pregnant and breastfeeding women. DAXI can be a relatively expensive treatment when compared to other non-invasive wrinkle treatments. Further research is required to reduce the limitations and make it cost-effective as compared to other available regimes.

Disclosure

The authors declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

References

1. Wong QYA, Chew FT. Defining skin aging and its risk factors: a systematic review and meta-analysis. *Sci Rep*. 2021;11(1):22075. doi:10.1038/s41598-021-01573-z
2. Charles finn J, Cox SE, Earl ML. Social implications of hyperfunctional facial lines. *Dermatol Surg*. 2003;29(5):450–455. doi:10.1046/j.1524-4725.2003.29112.x
3. Coleman S, Grover R. The anatomy of the aging face: volume loss and changes in 3-dimensional topography. *Aesthet Surg J*. 2006;26(1):S4–S9. doi:10.1016/j.asj.2005.09.012
4. Dayan S, Yoelin SG, De Boulle K, Garcia JK. The psychological impacts of upper facial lines: a qualitative, patient-centered study. *Aesthet Surg J Open Forum*. 2019;1:2. doi:10.1093/asjof/ojz015
5. Yi K-H, Lee J-H, Hu H-W, Kim H-J. Novel anatomical guidelines on botulinum neurotoxin injection for wrinkles in the nose region. *Toxins*. 2022;14:342. doi:10.3390/toxins14050342
6. Yi KH, Lee JH, Hu HW, Kim HJ. Anatomical proposal for botulinum neurotoxin injection for glabellar frown lines. *Toxins*. 2022;14(4):268. PMID: 35448877; PMCID: PMC9032255. doi:10.3390/toxins14040268
7. Wrinkles; 2022. Available from: https://my.clevelandclinic.org/health/articles/10984-wrinkles. Accessed January 26, 2023.
8. Swift A, Liew S, Weinkle S, Garcia JK, Silberberg MB. The facial aging process from the "inside out". *Aesthet Surg J*. 2021;41(10):1107–1119. PMID: 33325497; PMCID: PMC8438644. doi:10.1093/asj/sjaa339
9. Cohen JL, Kaufman J, Peredo MI, Down R, Mashburn J. Assessment of psychological well-being after abobotulinumtoxina treatment: a comparison of 2 reconstitution volumes. *Dermatol Surg*. 2020;46(2):289–292. doi:10.1097/dss.0000000000001940
10. Cosio T, Campione E. A new hypothesis in botulin therapy for depression: insula cortex modification. *Dermatol Ther*. 2019;32. doi:10.1111/dth.13008
11. Lagueny A, Burbaud P. Mécanisme d'action, indication et résultats des traitements par la toxine botulinique [Mechanism of action, clinical indication and results of treatment of botulinum toxin]. *Neurophysiol Clin*. 1996. 26(4):216–226. French. PMID: 8975111. doi:10.1016/s0987-7053(96)85003-9
12. Pirazzini M, Rossetto O, Eleopra R, Montecucco C. Botulinum neurotoxins: biology, pharmacology, and toxicology. *Pharmacol Rev*. 2017;69(2):200–235. doi:10.1124/pr.116.012658
13. Solish N, Carruthers J, Kaufman J, et al. Overview of daxibotulinumtoxinA for injection: a novel formulation of botulinum toxin type A. *Drugs*. 2021;81:2091–2101. doi:10.1007/s40265-021-01631-w
14. Kaufman-Janette J, Cox SE, Dayan S, Joseph J. Botulinum toxin type A for glabellar frown lines: what impact of higher doses on outcomes? *Toxins*. 2021;13(7):494. doi:10.3390/toxins13070494
15. Field M, Splevins A, Picaut P, et al. AbobotulinumtoxinA (Dysport®), OnabotulinumtoxinA (Botox®), and incobotulinumtoxinA (Xeomin®) neurotoxin content and potential implications for duration of response in patients. *Toxins*. 2018;10(12):535. PMID: 30551641; PMCID: PMC6316182. doi:10.3390/toxins10120535
16. Revance announces FDA approval of DAXXIFY™ (daxibotulinumtoxinA-lanm) for injection, the first and only peptide-formulated neuromodulator with long-lasting results; 2023. Available from: https://www.businesswire.com/news/home/20220908005320/en. Accessed: January 26, 2023.
17. Carruthers JD, Fagien S, Joseph JH, et al. DaxibotulinumtoxinA in the treatment of glabellar lines: results from each of two multicenter, randomized, double-blind, placebo-controlled phase 3 studies (SAKURA 1 and SAKURA 2). *Plast Reconstr Surg*. 2020;145:45–58.
18. Fabi SG, Cohen JL, Green LJ. DaxibotulinumtoxinA for injection for the treatment of glabellar lines: efficacy results from SAKURA 3, a large, open-label, phase 3 safety study. *Dermatol Surg*. 2021;47(1):48–54. doi:10.1097/DSS.0000000000002531
19. Malmirchegini R, Too P, Oliyai C, Joshi A. Revance's novel peptide excipient, RTP004, and its role in stabilizing daxibotulinumtoxinA (DAXI) against aggregation. *Toxicon*. 2018;156:S72–3. doi:10.1016/j.toxicon.2018.11.174
20. Bertucci V, Solish N, Kaufman-Janette J, et al. DaxibotulinumtoxinA for injection has a prolonged duration of response in the treatment of glabellar lines: pooled data from two multicenter, randomized, double-blind, placebo-controlled, phase 3 studies (SAKURA 1 and SAKURA 2). *J Am Acad Dermatol*. 2020;82(4):838–845. PMID: 31791824. doi:10.1016/j.jaad.2019.06.1313
21. Glogau R, Kontis TC, Liu Y, Gallagher CJ. Progressive improvement in static glabellar lines after repeated treatment with daxibotulinumtoxinA for injection. *Dermatol Surg*. 2021;47(12):1579–1584. PMID: 34417396; PMCID: PMC8612903. doi:10.1097/DSS.0000000000003211
22. Green JB, Mariwalla K, Coleman K, et al. A large, open-label, phase 3 safety study of daxibotulinumtoxinA for injection in glabellar lines: a focus on safety from the SAKURA 3 study. *Dermatol Surg*. 2021;47:42–46. doi:10.1097/DSS.0000000000002463