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Original Article

Patient-reported outcomes following a break in ophthalmic botulinum toxin therapy during the COVID-19 pandemic

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Objective: To evaluate the effect of a break in botulinum toxin treatment, necessitated by the COVID-19 pandemic, on patients' quality of life.

Methods: Prospective cohort study of all patients undergoing incobotulinumtoxinA treatment in our department—for benign essential blepharospasm (BEB), hemifacial spasm (HFS), aberrant facial regeneration (AFR), or crocodile tears—who were affected by the break in service (March 18, 2020–June 17, 2020). All patients who received treatment both before and after the break in service were included. Data gathered included subjective patient-reported measure of "time until treatment failure" and disease rating scale scores: Blepharospasm–Dystonia Functional Disability Assessment Scale (BDFDAS; for BEB, HFS, and AFR); Jankovic Rating Scale (JRS; for BEB and HFS); and TEARS Epiphora Grading Scale (for crocodile tears).

Results: Across 72 patients, there was a mean treatment delay of 3.9 months (range, 0–9.8 months). After a period of effect, treatment failed in all patients, with a mean time until treatment failure of 3.9 months (range, 0.5–12.0 months). All patient-reported outcome measurements increased, with greatest effect seen in AFR (178% increase in BDFDAS) and BEB (41% increase in JRS). At least 2 patients sought and underwent retreatment elsewhere in the private sector because of their symptom severity.

Conclusions: Patients with AFR and BEB are likely to tolerate a break in service least, whereas patients with crocodile tears appear to be less affected. This real-world snapshot allows quantification of the harm caused by a break in botulinum toxin service or a treatment delay. This study provides valuable information should further breaks in service or treatment delay be considered in the future due to a further wave of COVID-19 or other reasons.

The effect that the COVID-19 pandemic has had on every conceivable part of the health care services, not just the acute-care setting, is now well recognized. One example, which has affected countless patients across the United Kingdom and abroad, has been the impaired provision of elective and outpatient procedures, which for the most part have been postponed in order to decrease numbers of patients attending hospitals, reduce transmission rates, and redirect workforces, workspaces, and personal protective equipment to more acute, essential services.

Botulinum toxin was first approved for medical use as an injection into the extraocular muscles for the treatment of strabismus but has since proven useful in the management of a variety of medical conditions.[1,2] The Corneoplastic Unit at the Queen Victoria Hospital (QVH) offers botulinum toxin treatment for benign essential blepharospasm (BEB), hemifacial spasm (HFS), and aberrant facial regeneration (AFR, or synkinesis)—often collectively referred to as *facial movement disorders*—and also in the management of crocodile tears.[3–6] During the first wave of the COVID-19 pandemic, all botulinum toxin treatments were considered nonessential and were postponed. At QVH, botulinum toxin treatments were halted from March onward and were reintroduced only gradually for facial movement disorders in June 2020 and later in 2020 for crocodile tears and epiphora. Anecdotally, this negatively affected many long-term patients. Having been spotlighted by a recent U.K. press article, this experience has clearly been shared by many others.[7]

This sudden, unexpected, and undesirable cessation of botulinum toxin treatment across an entire service has provided an opportunity to answer questions that cannot, ethically, be studied under normal circumstances. We undertook this prospective audit to evaluate the effect that this recent break in treatment had on patients' quality of life, as assessed using various patient-recorded outcome measures and disease rating scales.

Methods

The QVH botulinum toxin service offers incobotulinumtoxinA (Xeomin; Merz Pharmaceuticals, Dessau, Germany) injections to patients with BEB, HFS, AFR, or crocodile tears, injected at flexible treatment intervals, based on the patient's reported response to previous treatments. Quantitative measures of patient-reported response to treatment were chosen based on the condition being treated: the

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Blepharospasm–Dystonia Functional Disability Assessment Scale (BDFDAS; for BEB, HFS, and AFR), the Jankovic Rating Scale (JRS; for BEB and HFS), or the TEARS Epiphora Grading Scale (for crocodile tears).[8–11] The TEARS Epiphora Grading Scale is a new tool for the monitoring and grading of epiphora that was designed by one of our authors (R.M.) and has been accepted for publication in the *European Journal of Ophthalmology* (Schulz CB, Malhotra R. The "TEARS" score: a tool for monitoring and grading the clinical severity of epiphora). The TEARS scale combines the preexisting Munk scale (which constitutes the "T") with measurements of the effect of epiphora on the patient's quality of life ("EA"), indicators of a reflex tearing component ("R"), and response to treatment ("S").[12]

All patient-reported disease rating scales were completed with a single clinician (M.F.). All treatments, except for treatments to the lacrimal gland, were performed by the same clinician (M.F.).

The authors undertook a review of a prospective audit of all patients undergoing incobotulinumtoxinA treatment at the Corneoplastic Unit at QVH who were affected by the break in service (March 18, 2020–June 17, 2020) during the COVID-19 pandemic. All patients who received treatment in the 6 months prior to the break in service (i.e., from September 2019) were identified, and of these patients, all those who have reattended the clinic since the recommencement of service were included in the study. Data gathered included basic demographic data, dates and dosages of incobotulinumtoxinA treatments, disease rating scale scores (i.e., BDFDAS, JRS, and TEARS), and a subjective patient-reported measure of how long the effects of botulinum toxin treatment took to completely wear off. This information was recorded in the clinical records at every visit, as per normal clinical practice.

Disease rating scale scores recorded at both time points were compared using parametric paired *t* tests. The delay in follow-up was calculated by taking the difference between the clinician's requested follow-up, made prior to the first wave of the pandemic, and the actual follow-up achieved. Time until treatment failure also was recorded, based on patients' self-reporting of symptoms. Comparative statistical analyses have not been performed for such results because they are likely insufficiently powered to be considered valid and add to the presented summary statistics.

This audit was approved by the Queen Victoria Hospital NHS Foundation Trust Research and Development Department, which deemed that ethical approval was not required. This audit adhered to the tenets of the Declaration of Helsinki.

Results

One-hundred and eight patients underwent botulinum toxin treatment in the 6 months prior to the break in service, and of these, 72 received treatments both before and after the break. The mean age of this cohort was 67.9 years (Table 1), and 38.9% (n = 28) received treatment for BEB, 19.4% (n = 14) for epiphora, 18.1% (n = 13) for HFS, 9.7% (n = 7) for AFR, 12.5% (n = 9) for more than 1 indication, and 1.4% (n = 1) for the treatment of entropion.

During the study period, the mean follow-up delay was 3.9 months (range, 0–9.8 months). Treatment had, after a period of effect, failed for all of our patients, with a mean time until treatment failure of 3.9 months (range, 0.5–12.0 months). The follow-up that was arranged following each patient's postbreak visit was a mean 0.4 month (range, −6.0 to +6.0 months) greater than had been requested at their last visit prior to the break.

The mean total treatment dose at prebreak visits was 15.1 units (range, 2.5–60 units). The mean total dose at the first postbreak visit was 15.6 units (range, 2.5–60 units; breakdown by condition available in Table 1). This represents an increased dose in just 4 patients (6%, with a mean dose increase in this group of 44%), while the dose remained unchanged in the remaining 68 patients (94%).

There was increase in all patient-reported outcome measurements from the prebreak appointment to the postbreak appointment, indicating a greater level of symptoms and effect on quality of life. This effect was seen across conditions, as detailed in Table 2. When considering the

Table 1—Changes in treatment dose and planned follow-up duration by condition category.

Factor	All	BEB	HFS	AFR	Epiphora
N	72	28 (38.9%)	13 (18.1%)	7 (9.7%)	14 (19.4%)
Age, y, mean (range)	67.9 (36.8–90.4)	70.9 (43.7–90.4)	66.5 (36.8–89.9)	71.2 (51.7–83.6)	56.5 (37.6–81.3)
Time until treatment failed, months, mean (range)	3.9 (0.5–12.0)	3.7 (0.5–9.0)	3.9 (1.5–9.0)	4.0 (2.5–6.0)	4.9 (3.0–6.0)
Treatment dose, IU, mean (range)					
– Before break in service	15.1 (2.5–60.0)	25.0 (2.5–60.0)	13.4 (5.0–37.5)	6.8 (2.5–12.0)	3.0 (2.5–5.0)
– After break in service	15.6 (2.5–60.0)	26.0 (2.5–60.0)	13.6 (5.0–37.5)	6.8 (2.5–12.0)	3.0 (2.5–5.0)
– Change in dose between visits	+0.5 (0.0–25.0)	+1.0 (0.0–25.0)	+0.2 (0.0–2.5)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Appointment timings, months, mean (range)					
– Follow-up planned at prebreak visit	4.0 (2.5–12.0)	3.8 (2.5–12.0)	3.7 (3.0–5.0)	3.9 (3.0–6.0)	4.8 (3.0–6.0)
– Follow-up delay (actual – planned)	3.9 (0.0–9.8)	4.0 (0.0–9.8)	3.1 (0.6–7.2)	3.0 (0.3–5.4)	5.2 (2.0–8.1)
– Follow-up planned at postbreak visit	4.4 (3.0–9.0)	4.3 (3.0–9.0)	3.9 (3.0–5.0)	4.3 (3.0–6.0)	5.3 (3.0–6.0)
– Change in planned follow-up	+0.4 (−6.0 to +6.0)	+0.5 (−6.0 to +6.0)	+0.2 (−1.0 to +1.0)	+0.4 (−0.5 to +2.0)	+0.5 (−2.0 to +2.5)

BEB, benign essential blepharospasm; HFS, hemifacial spasm; AFR, aberrant facial regeneration

Table 2—Changes in patient-reported disease rating scales by condition category.

Scale*	BEB	HFS	AFR	Epiphora
BDFDAS score, mean (range)				
– Prebreak visit [100]	35.5 (0–80)	9.3 (0–25)	9.2 (0–44)	—
– Postbreak visit [100]	38.4 (0–88)	10.6 (0–38)	25.6 (0–67)	—
– Change in score (i.e., percentage point change)	+2.9 (−42 to +37)	+1.3 (−10 to +29)	+16.4 (0–50)	—
– Percentage change	8.2% ↑	14.0%↑	178.3%↑	—
– *p* Value	*0.1533*	*0.3231*	*0.0235*	—
Jankovic Rating Scale, mean (range)				
– Prebreak visit[8]	2.7 (0–5)	1.8 (0–4)	—	—
– Postbreak visit[8]	4.6 (2–8)	2.3 (0–6)	—	—
– Change in score	+1.9 (−2 to +7)	+0.5 (−4 to +4)	—	—
– Percentage change	41.3%↑	27.8%↑	—	—
– *p* Value	*0.00002*	*0.1784*	—	—
TEARS score (sum of T/E/A/R scores), mean (range)				
– Prebreak visit[22]	—	—	—	8.4 (4–14)
– Postbreak visit[22]	—	—	—	8.6 (4–15)
– Change in score	—	—	—	+0.2 (−3 to +2)
– Percentage change	—	—	—	2.4%↑
– *p* Value	—	—	—	*0.3099*
Patient-reported symptom improvement, mean (range)				
– Prebreak visit (%)	81.8 (0–100)	89.9 (70–100)	86.4 (80–100)	74.8 (50–100)
– Postbreak visit (%)	84.2 (70–100)	89.5 (75–100)	86.3 (80–95)	76.8 (45–100)
– Change in score (i.e., percentage point change)	+2.4 (−10 to +70)	−0.4 (−10 to +10)	−0.1 (−5 to +5)	+2.0 (−25 to +20)
– Percentage change	2.9% ↑	0.4%↓	0.1%↓	2.7%↑
– *p* Value	*0.2330*	*0.4096*	*0.4612*	*0.2873*

BEB, benign essential blepharospasm; HFS, hemifacial spasm; AFR, aberrant facial regeneration; BDFDAS, Blepharospasm–Dystonia Functional Disability Assessment Scale

*Numbers in brackets indicate the maximum score for each scale.

BDFDAS scores in isolation, the greatest effect of a break in service was seen in AFR patients. An increase in score from 9.2% to 25.6% (a 178% relative increase) effectively represents a global worsening of function across most, or all, of the defined activities (e.g., reading, watching TV, driving, cleaning, etc.).

Considering the Jankovic ratings, in patients with BEB there was a significant increase in severity and frequency of blepharospasm due to the delay in treatment (mean increase in score of 1.9 points, or a 41.3% increase). This increase was greater than that noted in the HFS group (27.8%).

Finally, of the 108 patients who underwent treatment in the 6 months prior to the break in service, 2 are known to have sought and obtained repeat treatments elsewhere, within the private health sector, due to the severity of their symptoms. The first, a patient with HFS, underwent treatment in February 2020 (when BDFDAS was 1, Jankovic 0). In the midst of the break in service, patients were telephoned on the day of their previously planned retreatment appointments. During this patient's telephone consultation in June, their BDFDAS was 4 (Jankovic unknown), and the patient proceeded to receive repeat treatment at a private clinic elsewhere in August. The second patient, with BEB, received treatment in February 2020 (BDFDAS 8, Jankovic 2). At the telephone consultation in May, the patient had a BDFDAS of 3, and in June 2020, the patient also sought and underwent retreatment in a private clinic elsewhere.

Discussion

The COVID-19 pandemic has had an unprecedented effect on the provision of elective health care that, in our practice, included the need for a break in botulinum toxin treatment service for patients with involuntary facial movement disorders and epiphora. While this break unfortunately has had detrimental effects on patients, it has provided a unique opportunity to study the effects of stopping treatment across an entire service. This study demonstrates the effects of a sudden cessation of treatment within a botulinum toxin service and a delay in treatment. Of note, it has allowed quantification of the effect that this has on the patients and their quality of life. All patient-reported outcome measures showed a worsening of symptoms and effect on quality of life after the break in service, although patients with AFR appear to have been the worst affected. Patients with HFS started with similar BDFDAS scores to those with AFR, but their scores rose much less following the break in service, suggesting that those with AFR are a more sensitive group and more susceptible to disability because of their synkinesis when treatment is not performed on time.

Patient-reported symptom improvement was recorded at both the pre- and postbreak visits and in both cases relate to the improvement gained from the *previous* visit. Increased symptom improvement was noted between the 2 visits in both the BEB and epiphora groups (2.9% and 2.7%

increases, respectively). This may have occurred as a result of the break in treatment giving patients a truer sense of their baseline, untreated symptom severity and therefore the full effectiveness of their treatment.

Over the course of this break in service, treatments were delayed a mean 3.9 months (range, 0–9.8 months), although it should be noted that not all delays will have been due to the pandemic. Because all patients were left long enough between appointments for their incobotulinumtoxinA treatment effect to wear off, time until treatment failure could be reliably measured across the entire cohort: BEB, 3.7 months; HFS, 3.9 months; AFR, 4.0 months; and epiphora, 4.9 months. In each of these groups, duration of treatment effect was greater than those reported in the literature (as follows).

Duration of treatment effect has been presented in numerous previous reports, most commonly for BEB: onabotulinumtoxinA (Botox; Allergan, Dublin, Ireland), 1.7–3.9 months[13–20]; incobotulinumtoxinA (Xeomin; Merz), 2.6–3.0 months[19,21]; and abobotulinumtoxinA (Dysport; Ipsen Pharmaceuticals, Cambridge, Mass.), 1.7–2.0 months.[17,18] Nussgens and Roggenkamper [14] separated their patients into 2 easily identifiable groups: "good responders," whose effect lasted 3.7 months, and "poor responders," whose effect lasted a mean 1.7 months. Duration of effect in HFS has been reported to be as follows: Botox, 2.3–3.2 months[15,18-20,22]; Xeomin, 3.0 months [19]; and Dysport, 1.5–2.0 months.[18–22] In AFR, the duration of effect for Botox was 3.3–4.0 months[19,23] and that for Xeomin was 3.3 months.[19]

The follow-up arranged after each patient's postbreak visit was 0.4 month greater than that requested at their prebreak appointment. The authors believe that this slight elongation in follow-up interval was due, at least in part, to the patient and clinician now knowing the patient's time until treatment failure, specific to their own condition and to them as an individual. Prior to this break in service, many of these decisions on treatment intervals would be based on when the effect decreased noticeably rather than when effect wore off completely.

The findings of this study suggest that if a further break in service were ever required, patients with AFR should be prioritized to receive treatment where possible because of the potential effect on their quality of life caused by stopping treatment. At the other end of the spectrum, patients undergoing treatment for crocodile tears (epiphora) are likely to tolerate a break in treatment better given that the treatment effect lasted the longest (4.9 months) in this group, and the change in TEARS score caused by a delay in treatment was comparatively low.

All the patient-reported disease rating scales presented are collected prospectively for all patients, which means that this retrospectively designed study benefits from many of the characteristics normally associated with a prospective study—in particular, consistency of data recording. A further strength of this study is that all disease rating scales and all treatments, except treatment to the lacrimal gland, were administered by the same clinician. Limitations of this study include low sample size in a couple of the subgroups, particularly AFR (n = 7). Furthermore, given sufficient staff or time resources, it would have been useful to complete the disease rating scales via telephone consultation in the week of each patient's planned follow-up or retreatment, although this was not possible at our centre during the first wave of the pandemic.

These findings suggest that patients with AFR are likely to tolerate a break in service least, whereas patients with crocodile tears may not be so greatly affected. Separate from this, patients with BEB and HFS for whom the ability to drive is essential (e.g., for work or for caring responsibilities) also should be prioritized, and this information should be recorded preemptively. This real-world snapshot, made possible by a global pandemic, has allowed quantification of the harm caused by a break in botulinum toxin service. It provides valuable information should further breaks in service or any delay in treatment be required in the future, whether due to COVID-19 or otherwise.

References

1. Ross AH, Elston JS, Marion MH, Malhotra R. Review and update of involuntary facial movement disorders presenting in the ophthalmological setting. Surv Ophthalmol 2011;56:54–67.
2. Miller NR. Reply to: Review and update of involuntary facial movement disorders presenting in the ophthalmological setting, "eyelid myokymia. Surv Ophthalmol 2011;56:277–8.
3. Keegan DJ, Geerling G, Lee JP, Blake G, Collin JR, Plant GT. Botulinum toxin treatment for hyperlacrimation secondary to aberrant regenerated seventh nerve palsy or salivary gland transplantation. Br J Ophthalmol 2002;86:43–6.
4. Montoya FJ, Riddell CE, Caeser R, Hague S. Treatment of gustatory hyperlacrimation (crocodile tears) with injection of botulinum toxin into the lacrimal gland. Eye (Lond) 2002;16:705–9.
5. Whittaker KW, Matthews BN, Fitt AW, Sandramouli S. The use of botulinum toxin A in the treatment of functional epiphora. Orbit 2003;22:193–8.
6. Ziahosseini K, Al-Abbadi Z, Malhotra R. Botulinum toxin injection for the treatment of epiphora in lacrimal outflow obstruction. Eye (Lond) 2015;29:656–61.
7. Calman B. Lockdown Botox ban that's been torture for facial palsy patients after treatment for condition is deemed cosmetic and non-essential. Daily Mail. 2021 Available at https://www.dailymail.co.uk/health/article-9358471/Lockdown-Botox-ban-thats-torture-facial-palsy-patients.html accessed 12 Jun.
8. Jankovic J, Orman J. Botulinum A toxin for cranial-cervical dystonia: a double-blind, placebo-controlled study. Neurology 1987;37:616–23.
9. Brin MF, Jankovic J, Comella C, Blitzer A, Tsui J, Pullman SL, Kurlan R. Treatment of dystonia using botulinum toxin. Treatment of movement disorders. New York: Lippincott; 1995. p. 183–230.
10. Thussu A, Barman CR, Prabhakar S. Botulinum toxin treatment of hemifacial spasm and blepharospasm: objective response evaluation. Neurol India 1999;47:206–9.

11. Grivet D, Robert P-Y, Thuret G, et al. Assessment of blepharospasm surgery using an improved disability scale: study of 138 patients. Ophthalmic Plast Reconstr Surg 2005;21:230–4.
12. Munk PL, Lin DT, Morris DC. Epiphora: treatment by means of dacryocystoplasty with balloon dilation of the nasolacrimal drainage apparatus. Radiology 1990;177:687–90.
13. Mauriello Jr JA, Dhillon S, Leone T, Pakeman B, Mostafavi R, Yepez MC. Treatment selections of 239 patients with blepharospasm and Meige syndrome over 11 years. Br J Ophthalmol 1996;80:1073–6.
14. Nussgens Z, Roggenkamper P. Long-term treatment of blepharospasm with botulinum toxin type A. Ger J Ophthalmol 1995;4:363–7.
15. Quagliato EM, Carelli EF, Viana MA. Prospective, randomized, double-blind study, comparing botulinum toxins type A Botox and Prosigne for blepharospasm and hemifacial spasm treatment. Clin Neuropharmacol 2010;33:27–31.
16. Roggenkamper P, Jost WH, Bihari K, Comes G, Grafe S. NT 201 Blepharospasm Study Team. Efficacy and safety of a new botulinum toxin type A free of complexing proteins in the treatment of blepharospasm. J Neural Transm (Vienna). 2006;113:303–12.
17. Nussgens Z, Roggenkamper P. Comparison of two botulinumtoxin preparations in the treatment of essential blepharospasm. Graefes Arch Clin Exp Ophthalmol 1997;235:197–9.
18. Bihari K. Safety, effectiveness, and duration of effect of BOTOX after switching from Dysport for blepharospasm, cervical dystonia, and hemifacial spasm dystonia, and hemifacial spasm. Curr Med Res Opin 2005;21:433–8.
19. Bladen JC, Favor M, Litwin A, Malhotra R. Switchover study of onabotulinumtoxinA to incobotulinumtoxinA for facial dystonia. Clin Exp Ophthalmol 2020;48:1145–51.
20. Ababneh OH, Cetinkaya A, Kulwin DR. Long-term efficacy and safety of botulinum toxin A injections to treat blepharospasm and hemifacial spasm. Clin Exp Ophthalmol 2014;42:254–61.
21. Jankovic J, Comella C, Hanschmann A, Grafe S. Efficacy and safety of incobotulinumtoxinA (NT 201, Xeomin) in the treatment of blepharospasm—a randomized trial. Mov Disord 2011;26:1521–8.
22. Sampaio C, Ferreira JJ, Simoes F, et al. DYSBOT: a single-blind, randomized parallel study to determine whether any differences can be detected in the efficacy and tolerability of two formulations of botulinum toxin type A—Dysport and Botox—assuming a ratio of 4:1. Mov Disord 1997;12:1013–8.
23. Toffola ED, Furini F, Redaelli C, Prestifilippo E, Bejor M. Evaluation and treatment of synkinesis with botulinum toxin following facial nerve palsy. Disabil Rehabil 2010;32:1414–8.

Footnotes and Disclosure

The authors declare that there are no conflicts of interest.

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