Abstract

Aims: To assess effects of repeat treatment with onabotulinumtoxin A (onaBoNT-A) in women with refractory idiopathic detrusor overactivity (DO)

Methods: Analysis of an open-label extension study of a large randomised placebo controlled trial of onaBoNT-A. Participants had been randomised to receive 200 IU onaBoNTA or placebo and were offered up to two further onaBoNTA injections over a 5-year period. For this analysis, the primary outcome was duration of treatment effect by patient-reported symptom return. Weibull proportional hazards regression models were fitted in a Bayesian framework to estimate missing times. Multivariable hazard regression analysis (hazard ratio, 95% credible intervals (HR, 95% CrI) compared repeated injections adjusting for differences in baseline symptom severity. Secondary outcomes included inter-injection interval, incontinence, urgency and voiding episodes six weeks after injection.

Results: 442 active injections were administered: 228 patients had one, 155 had two, and 59 had three injections. Time to symptom return for injection number 1 and 2 was 84 (95% CI: 63, 112) and 180 (95% CI: 135, 223) days respectively. Median inter-injection intervals for receiving second and third injection were 266 days (range: 130, 1400) and 372 days (range: 134, 1283). No statistically significant differences in symptom outcomes or time to symptom return (HR 0.88, 95% CrI 0.37, 2.07 for injection 2, HR 0.33, 95% CrI 0.09, 1.03 for injection 3) were observed.

Conclusions: Repeated onaBoNT-A injections have consistent efficacy, and duration of action. There appears to be long-term placebo effects in both groups of randomised patients, with implications for open-label extension studies.

250 words

Key words:

Botulinum toxin, efficacy, detrusor overactivity, treatment; overactive bladder

Introduction

Botulinum toxin (BoNTA) is an established treatment for overactive bladder (OAB) and detrusor overactivity (DO) when conservative and medical treatments fail[1 2]. Several randomised studies[3-8] and numerous uncontrolled reports demonstrate high efficacy with long duration of action, although it is recognised that around 10% patients have problems with voiding dysfunction or urinary tract infections. Only onabotulinum toxin is current licensed at a dose of 100 units for non-neurogenic OAB. Outcomes of repeated injections from uncontrolled series of both 100 and 200 units have been reported, suggesting repeat injections are equally effective, although the number of patients included in these reports has been low[9-14]. For all these reports, repeated injections were compared using diary data, and quality of life measures. All demonstrated comparable effects on improvements in the objective outcomes and quality of life measures for each treatment, with no evidence of a decline in efficacy over time, and stable incidences of complications. The inter-injection interval remained stable at around 300 days between injections.

We present an analysis of an open label extension of a large randomised trial of 200 units of onabotulinum toxin A (onaBoNTA)[5] evaluating the efficacy of repeated injections on objective outcome measures and also compare the duration of treatment effect defined by time to repeat injection and time to patient-reported return of symptoms . We have used Bayesian methods to account for missing data, adjusting for baseline symptoms and any potential selection effect due to the response to first treatment. Relative treatment efficacy of repeat injections is also presented.

Patients and Methods

The RELAX trial recruited 240 women with proven DO on urodynamics within two years of recruitment and refractory to standard treatment, with at least eight voids and at least two “moderate” or “severe” urgency episodes per 24 hours [5]. The trial and extension study received ethical approval from the Scottish Multicentre Research Ethics Committee (ref: 04/MRE10/67) and was registered on Current Controlled Trials (ISRCTN26091555) on 26th May 2005. Women were randomised on a 1:1 basis to receive 200 units of onaBoNT-A or placebo, injected in 20 sites, sparing the trigone. Blinded outcome data were collected at baseline, six weeks, three months, and six months. Following completion of the blinded trial, participants entered a 5 year open label extension study after further informed, written consent and were offered a maximum of two further onaBoNT-A injections, administered as per local practice at each research site. When the protocol was designed, there were few published data on the use of botulinum toxin for idiopathic DO, so the dose of 200 units of onaBoNT-A (BOTOX®, Allergan USA) was used because this was the dose currently being offered by most investigators. The dose ranging study supported by Allergan was not published until 2010[3], when all women were already enrolled in the extension study follow up, and the randomised trial data on 100 units was not published until 2013/14[6-8]. The provision of two injections was determined by the level of drug provision support provided by Allergan. The final treatment for the final patient occurred at the end of May 2013.

Outcome data (bladder diary, urgency episode frequency (Indevus Urgency Severity Scale (IUSS)[15], International Consultation on Incontinence Questionnaire short form (ICIQ-SF)[16], Incontinence Quality of Life (IQOL) questionnaire[17], and Patient Global Impression of Improvement (PGI-I)[18 19]) were collected by post every six months

from the date of the first (randomised) injection throughout the extension. Data on complications (self-reported voiding difficulty or urinary tract infection) were collected on the follow up data form at each review. The patients were in regular contact with the local continence nurse specialists and thus we adopted this simplified reporting for the extension study.

With each follow up, injection requests could be initiated by patient request in response to the question “Do you wish to have a repeat injection at this time?”. Patients could also request treatment at any time between follow-up contact. Treatment duration was based solely on self-reported return of symptoms in response to the question “have your symptoms returned?”, without reference to original baseline symptom frequency or severity. Patients were sent a follow-up pack 6 weeks after every subsequent injection in addition to the scheduled 6 monthly review.

Statistical analysis

For the comparison of repeated treatments, we grouped patients according to the sequence of *active* injection (termed injection 1, 2, and 3). We analysed time to patient-reported recurrence of symptoms, in response to the questions “have your symptoms returned?” and “When did they return?” Data on time to patient reported return of symptoms were displayed using Kaplan-Meier curves and analysed using Weibull proportional hazards regression models. We accounted for differences in baseline symptom severity at time of injection using PGI-S[19], treatment at randomisation, potential interactions between these factors and we further accounted for the similarity of repeated events within the same individuals.

Analysis of variance (ANOVA) adjusting for differences in baseline symptoms was used to assess the variability of mean diary data at 6 weeks post-injection for each of the active injections. Logistic regression was used to assess differences in the number of individuals with urinary tract infections (UTIs) and voiding difficulty. A result was considered significant if $p<0.05$. Statistical analyses were performed using STATA, version 13.1 (StataCorp, College Station, TX, USA).

Results

A total of 240 women were enrolled and treated; 122 women were initially randomised to onaBoNT-A and 118 to placebo[5]. A total of 442 active injections were administered during the randomised study and 5 year extension period: 228 participants received first active, 155 received second active, and 59 received third active injections (Figure 1).

A total of 189 (83%), 112 (72%) and 31 (53%) patients experienced symptom return after active injection 1, 2 and 3, respectively. Median time to symptom return (i.e. duration of treatment effect) for injection number 1 and 2 were 84 (95% CI: 63, 112) and 180 (95% CI: 135, 223) days from the time of injection, respectively. We were unable to calculate median time to symptom return for injection 3 as there were insufficient data on the number of events. For injection number 1 and 2, 47 (25%) and 25 (22%) patients failed to report the time of symptom return. Figure 2 displays the survival curve of patient-reported return of symptoms for each number of injections. Table 1 records the hazard ratios (HR) and credible intervals (CrI) for symptom return after each number of injections after accounting for differences in baseline severity. There was a reduced hazard of reporting symptom return for injection number 2 (HR: 0.88, 95% CrI: 0.37, 2.07) and 3 (HR: 0.33, 95% CrI: 0.09,

1.03) compared to injection 1; however, the 95% credible intervals span the point of no difference suggesting that in reality repeated injections are similar in duration of effect to the first.

We found that patients randomised to onaBoNT-A in the double-blinded trial had a considerably more rapid rate of symptom return for injection 1 compared to patients initially randomised to placebo (HR: 2.69, 95% CrI: 1.66, 4.68) (Figure 3a). However, for onaBoNT-A patients receiving their second active injection, the time to symptom return was significantly longer compared to first active injection (HR: 0.39, 95% CrI: 0.21, 0.71) which is further illustrated through the comparison of onaBoNT-A curves in Figures 3a and 3b.

The median inter-injection intervals for receiving second and third injection were 266 days (range: 130, 1400) and 372 days (range: 134, 1283) respectively. Tables 2 & 3 record the average symptom outcomes (Table 2) and adverse events (Table 3) at 6 weeks for all patients receiving each number of repeated onaBoNT-A injections. We observed a slight improvement in mean symptom severity with the second and third injection rounds but comparison of injections 1 and 2, and 1, 2, and 3 showed no statistically significant difference for any outcome variable (Table 2). Notably, women who opted for further injection had less severe symptoms at the preceding 6 week follow-up compared to the entire cohort, although these differences cannot be examined using statistical t-tests because these patients contribute to both statistics (i.e. the entire cohort of patients and the subgroup continuing treatment). The difference in symptom severity between those who did, and did not opt for further injection is particularly apparent for incontinence episodes. Patients (n=50) receiving a third active injection experienced on average 1.71 incontinence episodes daily at 6 weeks following the first onaBoNT-A injection compared to 2.53 incontinence

episodes daily for the entire cohort, suggesting that there was a clear selection effect for women continuing treatment.

There was no statistically significant difference between the number of individuals experiencing UTIs or voiding difficulty for each of the active injections (Table 3). Notably, individuals who opted for all 3 active injections did not experience UTIs or voiding difficulty with injection 1. 75% of patients experienced UTIs, and 40% experienced voiding difficulty with injection 2 but continued to receive a third active injection, suggesting that in this case, occurrence of complications did not influence the decision for re-treatment. However, it should be noted that the overall number of patients who report UTI and voiding difficultly status, whether positive or negative, are particularly low with only 48 (21%) reporting UTI status, and 47 (21%) reporting voiding difficulty status out of a possible 228 individuals for injection 1. Reporting increased slightly for injection 2 and 3 with 30-40% of individuals reporting UTI and voiding difficulty status. Due to the number of missing data, these estimates should be interpreted with a degree of caution; a crude estimate of overall risk indicates about 20% of women report UTI after two or three injections, but with an estimate of overall voiding dysfunction of around 10%.

Discussion

Repeated injections of onaBoNT-A appear equally effective in patients with refractory detrusor overactivity (DO). Median time to return of symptoms was 84 days after the first injection and 180 days after the second. Alongside this, we observed that the proportion of patients reporting symptom return was lower with second and third injections, and we observed a reduced hazard ratio of reporting return of symptoms with each injection, although there was uncertainty in these

estimates so this apparent difference should be interpreted carefully. These data suggest either that repeat injections have a slowly cumulative effect, or that there is a selection process whereby only those patients who observe benefit return for further treatment. Indeed, we found that participants who opt for re-injection appear to have better symptom profiles at the preceding 6 week follow up compared to the entire cohort. This would suggest that patients with less severe symptoms, or those who obtain a greater treatment benefit, choose further treatment. This finding has not, to our knowledge, been reported before and represents a potential selection effect for each subsequent injection.

Although the time between treatments in our cohort mirrors that of other papers (see below), we feel the time to reported symptom return is a more “real” measure of treatment effect. In any healthcare system, there will inevitably be a delay between the patient reporting to her carer the return of symptoms and the time of treatment. This will vary between countries and healthcare delivery systems. In our centres, there was a typical delay due to waiting time to have patients admitted or attending for treatment (during the study most procedures took place within the operating theatre). Simply comparing time between treatments would overestimate the efficacy of treatment. Hence our presentation of patient-reported return of symptoms. The use of Bayesian methodology to analyse the time to patient-reported return of symptoms, accommodating potential confounding factors, provided robust data that repeat injections demonstrate consistent and similar efficacy in the duration of effect.

This result adds to findings in the current literature that suggests no difference in clinical efficacy of repeated injections based on symptom profiles. The average inter-injection interval from our data was approximately 9 months between first and second treatment, and over a year between second and third treatments, intervals

which are comparable with the work of several other authors. Sahai et al[12] reported a mean inter-injection period of 377, 378, and 256 days between injection numbers 1 and 2, 2 and 3, and 3 and 4, respectively among 20 patients having repeat treatment of 200 units onaBoNTA for idiopathic DO. They found urinary frequency, urgency, incontinence, and quality of life assessments showed equivalent improvements after each injection, with pre-injection symptoms being similar to those at baseline. Dowson et al[13] extended that cohort, and reported a mean inter-injection period of 322 days in 53 patients receiving a second injection of 200 units of onaBoNT-A for refractory overactive bladder with outcomes after each injection (up to the fifth analysed) showed no difference from each other. Granese et al[10] and Gousse et al[11] demonstrated equivalent efficacy of 100 or 150 units in repeat injection received by 20 or 31 patients respectively. Our data are from a larger cohort of patients (all women) where 155 women had a second injection and 59 received a third and thus provide more robust confirmation of these earlier published papers. After accounting for differences in baseline severity, we have also found that there was little evidence to suggest repeat injections differ in terms of patients' urinary diary data.

Using "time to return of symptoms" is not without limitations; this was an absolute response and did not allow assessment of the complexities regarding how patients process the return of a symptom, which does not yet become bothersome enough to seek repeat treatment. This threshold is likely to vary between individuals, and also between each symptom, where perhaps return of urgency is more immediately bothersome than a return of greater frequency. Thus, we have shown a shorter apparent duration of efficacy from onaBoNT-A than other workers, but a similar inter-injection interval. There is clearly more work to be done to explore this complex relationship, and to examine how different definitions of cure, efficacy, and

thresholds for re-injection will impact the long-term cost-effectiveness of this treatment. There are still no long-term, robust cost-effectiveness data available in comparison to alternative treatments.

A limitation of this study was sporadic patient follow-up following the end of the blinded trial. Complete data was obtained for 6 week follow-up after every subsequent injection but thereafter, and over the 5 year extension study, it became increasingly difficult to monitor patients' symptom return. It was unclear whether some patients were lost to follow-up or simply, their symptoms hadn't returned. For patients with symptom return, but missing data on time of symptom return, typically the average reported time from known events is assumed. However, this may exaggerate repeated treatment effects when patients continuing follow-up are different (e.g. by having better baseline symptom profiles and/ or longer duration of treatment effect) compared to patients discontinuing follow-up. To help ameliorate a potential reporting bias in this situation, we used a Bayesian approach. This has several advantages, including the ability to obtain predictive estimates for missing data and associated uncertainty[20]. Given that we know the interval in which symptoms returned for each individual with missing data (i.e. it is assumed to fall between last complete follow-up and date of repeat injection) we predicted estimates within this time interval for each missing observation. Models were fitted using WinBUGs 1.4.3[20 21].

We noted an interesting finding that patient-reported duration of effect appeared to be influenced by initial treatment randomisation. Patients randomised to placebo had a considerably decreased rate of symptom return for their first onaBoNT-A injection (received in the open label extension) compared to patients initially randomised to onaBoNT-A (who received their first active drug in a blinded fashion). This may

represent an extended placebo effect, which has not been noted before in trials of interventions for DO or overactive bladder. It is known from migraine research that the placebo effect in randomised studies of onaBoNT-A treatment can remain at a steady rate for up to six months[22 23] and that the placebo effect is greater for more invasive treatments[24] but we are unaware of any literature demonstrating that patients who receive placebo initially, subsequently report greater efficacy of active treatment when they receive it. We also noted that patients who received active drug initially, subsequently reported a greater duration of effect with the second injection during the extension phase. Thus, it would seem that both groups (those randomised to both active and placebo) reported greater efficacy for the second injection, received during the extension study. This over-reporting by both groups effectively means that open label extension studies following randomisation may be biased towards more positive outcomes compared to the true (randomised and blinded) effects. This observation has wide implications if this effect can be confirmed, because nearly all drug studies for medication for OAB and DO have a pooled open label extension included to generate additional data in support of the licensing and use of the product.

Conclusions

The data we present here represent the largest cohort of patients receiving two and three injections of onaBoNT-A, and have been analysed using novel and robust statistical methods to account for real and potential biases of selection among patients choosing to continue with repeated treatment. As far as we are aware, we are the only authors to analyse the duration of treatment effect accounting for these variables when comparing efficacy of repeat treatments. Based on our data, there appears to be no loss of effect after second and third injections of onaBoNT-A, either

in terms of the expected duration of action, or the magnitude of relevant urinary diary outcomes.

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