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Long term safety outcomes and continuation rates of repeated Intravesical Botulinum Toxin A injections for Detrusor Overactivity: 16 year's experience of a Tertiary Centre in the UK

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ABSTRACT

Introduction: Overactive bladder (OAB) affects 27% of women in the UK with an adverse impact on quality of life. Medical treatment with anticholinergics has a high discontinuation rate due to side effects. OnabotulinumtoxinA (BOTOX®) is an established treatment for refractory OAB, although there are little published data regarding safety with long term use.

Objective: To report the long-term safety and continuation rates of intravesical Botox for OAB.

Methods: This was a retrospective cohort study of patients treated with botulinum toxin A for OAB in a tertiary centre from 2007–2023. Data were collected retrospectively from medical records.

Results: 132 patients were identified, with a total of 574 episodes of intravesical Botox. Mean age at first treatment was 55 years. After 1st Botox treatment, 21% of patients developed urinary tract infections. Clean intermittent self-catheterisation (CISC) was performed in 33% of patients, 5% of whom were performing CISC prior to treatment. The range of number of Botox treatments per patient was 1–18; 74% had more than one treatment. 52% of patients were lost to follow-up and 30% are ongoing patients. Recurrent UTIs developed in 23%.

Conclusion: Repeated Botox injections appear to be a safe form of treatment for refractory OAB. Long term complications include recurrent UTIs, which affects 1 in 4 women, and voiding dysfunction, which affects 1 in 5. Only 1 in 3 women continue long term Botox treatment.

1. Introduction

Overactive bladder (OAB) is defined as 'urinary urgency, with or without urge incontinence, and usually with frequency and nocturia' [1]. Studies have shown OAB to have a prevalence of 27% and 33% in the United Kingdom and the United States respectively [2,3] and it is known to have a significant impact on quality of life [4]. Detrusor overactivity is a urodynamic observation which describes the involuntary contraction of the detrusor muscle and is found to be demonstrated in an estimated 64% of women with OAB symptoms [5].

Lifestyle changes are first line conservative measures for the management of OAB. These include weight loss, bladder retraining and fluid intake advice [6]. Anticholinergic medications are recommended as the first line medical treatment for OAB [6] and their efficacy, when compared to placebo, has been demonstrated repeatedly [7]. However, at effective doses, they are often poorly tolerated by patients due to side effects including blurred vision, dry mouth and constipation, with some studies reporting almost an 80% discontinuation rate at 12 months [8,9]. There is also evidence that their use may lead to a reduction in cognitive function, an increased risk of dementia [10] and an increase in mortality [11].

Mirabegron, a beta 3 adrenergic receptor agonist, has been available as an alternative to anticholinergics in the UK since 2013 [12]. Mirabegron has been demonstrated to be as efficacious as anticholinergics in managing OAB symptoms with lower discontinuation rates [13,14]. It should however be avoided in those that have severe uncontrolled hypertension, tachycardia or long QT syndrome [13].

Intravesical OnabotulinumtoxinA (BoNt-A) injections offer an alternative treatment to those who do not respond to, or cannot tolerate, pharmacological treatment. Its use has been licensed in the UK since 2013 and it is recommended as the first line treatment option for refractory OAB in women willing and able to perform clean intermittent self-catheterisation (CISC) [6].

Known complications of BoNt-A include voiding dysfunction and urinary tract infections (UTIs) [15]. However, current data report wide discrepancies in the rates of these complications, for example, rates of

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UTI have been documented between 0.4% and 44% [16]. There is also a lack of long term real world safety data on repeated injections.

This study therefore reports on the long-term safety and discontinuation rates of repeated intravesical BONT-A injections in women with OAB.

2. Methods

We undertook a retrospective analysis of all female patients treated with intravesical botulinum toxin A injections for OAB from 2007 to 2023, in a tertiary Urogynaecology centre in the United Kingdom (King's College Hospital, London).

Patients were identified via the coding department and data were collected from medical records.

All patients had diagnostic urodynamics (UDS), which involved uroflowmetry, filling cystometry and pressure flow studies. Other baseline data collected were patient demographics such as, age, ethnicity, BMI and parity, bladder diaries and baseline King's Health Questionnaire (KHQ) scores. The medical records allowed us to obtain information on the initial medical management options and reasons for discontinuation.

The primary outcome was the incidence of adverse events, including hospitalisation, development of a UTI, the need to perform clean intermittent self-catheterisation (CISC) and any long-term side effects including recurrent UTI. Secondary outcomes included the frequency of BoNt-A injections, intervals between treatments and reasons for discontinuation were also recorded.

Standard practice between the years of 2007 and 2013 involved administration of 200u of BoNt-A under general anaesthetic with antibiotic prophylaxis. From the year 2011, we began to offer BoNt-A under flexible cystoscopy, with 1 g ciprofloxacin orally as prophylaxis. In line with prescribing guidelines, we began to give 100u to patients with idiopathic DO from 2013 and to give 200u to those with neurogenic DO or to those that did not respond to 100u treatment. The unit protocol is that all patients learn to perform CISC prior to the first procedure and perform it at 2 weeks following injection, to exclude a significant post-void residual (PVR). CISC is recommended in those who are symptomatic with a PVR greater than 100 mls or those with a PVR greater than 150 mls regardless of symptoms. All patients were followed up at two to three weeks following their treatment to inform us of their PVR. At this consultation, patients were asked whether they had an UTI symptoms or positive urine cultures. We recommend patients continue their oral medication for OAB until two to three weeks following their treatment, in order to allow the BoNt-A to take full effect. They can recommence medication at the stage at which their symptoms recur, prior to repeat BoNt-A injections which are permissible at a minimum of six months between treatments.

This project was registered with the local audit department. Ethical approval was not required due to the retrospective anonymised collection of data. Data analysis was performed using SPSS.

3. Results

We identified 132 patients, with a total of 574 episodes of intravesical botulinum toxin injections.

The mean age at initial BoNt-A treatment was 54 (range 20–87). 73% (n = 96) presented with pure OAB symptoms and 27% (n = 36) presented with mixed incontinence symptoms. The median length of follow up was 58 months.

3.1. Urodynamic findings

All women had UDS to investigate their incontinence symptoms. 80% (n = 106) had DO on UDS, 9% (n = 12) had normal laboratory UDS but confirmed DO on ambulatory UDS, 6% (n = 8) had normal laboratory and ambulatory UDS and 5% (n = 6) had no UDS notes available for analysis.

Of the women diagnosed with DO, 22% (n = 26) had high pressure contractions, defined as the highest detrusor contraction measuring greater than or equal to 40 cmH20. 13% (n = 17) had neurogenic DO.

In 10% (n = 13), the DO was associated with low compliance and in 19% (n = 24) there was reduced bladder capacity. 2% of women (n = 3) had incomplete bladder emptying, defined as a PVR > 100 ml.

The median bladder capacity was 400 mls (range 50 to 500 mls) and the median highest detrusor contraction measured 35 cmH20 (range 12 to 135 cmH20).

Table 1
Risk factors associated with CISC.

	Performing CISC	Not performing CISC	P value
Age[a] (mean)	70.4	65.4	0.52
Low capacity[b] n(%)	5 (17)	20 (20)	0.47
Low compliance[b] n(%)	4 (13)	11 (11)	0.46
Voiding dysfunction[b] n(%)	3 (10)	27 (7)	0.33
High pressure DO[b] n(%)	5 (17)	30 (29)	0.12
Neurogenic DO[b] n(%)	4 (13)	13 (13)	0.57
Higher dose of BoNt-A[b] n(%)	21 (31)	21 (37)	0.75

[a] Mann-Whitney U.
[b] Chi-squared.

3.2. Medical management

All patients in our cohort had trialled medical therapy, with all patients having tried at least two different anticholinergics. The median number of different anticholinergics used was four (range two to nine). Fig. 1 illustrates the proportions of different anticholinergics trialled. 30% of patients (n = 39) had used combination therapy with Mirabegron.

Reasons for discontinuation of medical treatment were reported as inefficacy in 76% (n = 100), side effects in 14% (n = 19) and a combination of both reasons in 10% (n = 11).

In our cohort, 8% (n = 11) of women had previously undergone posterior tibial nerve stimulation (PTNS) before BoNt-A.

3.3. CISC

The ability to perform CISC is a pre-requisite for BoNt-A treatment for OAB. 92% (n = 122) were successfully taught CISC prior to treatment. 4% (n = 5) were already performing CISC and 4% (n = 5) had a suprapubic catheter (SPC) inserted due to an inability to perform CISC, two of which were eventually removed.

3.4. BoNt-A treatments

73% (n = 97) women had more than one administration of BoNt-A treatment, with the maximum number of treatments being 18. The median number of treatments was three. There was a mean of 14 months in between treatments. Fig. 2 highlights the frequency of total BoNt-A treatments.

3.5. Immediate complications

There were no hospital admissions following BoNt-A treatment. 21% (n = 28) developed a UTI following their first BoNt-A injection. The median number of UTIs following first BoNt-A injection was 2 (range 1–5). Fig. 3 illustrates the frequency of UTIs following first BoNt-A injection.

Overall, 22% of patients (n = 29) needed to perform CISC for incomplete bladder emptying. There was no association between the need to perform CISC and age, pre-intervention UDS findings or the dose of BoNt-A administered. The p values are demonstrated in Table 1.

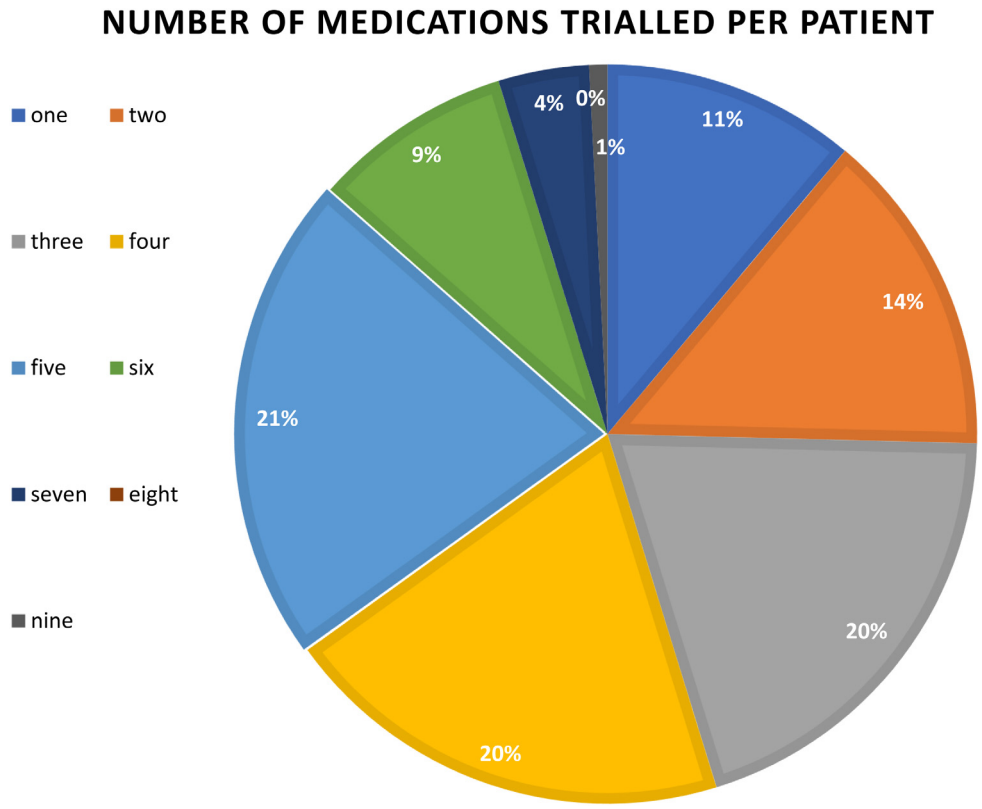

Fig. 1. Number of medications trialled per patient.

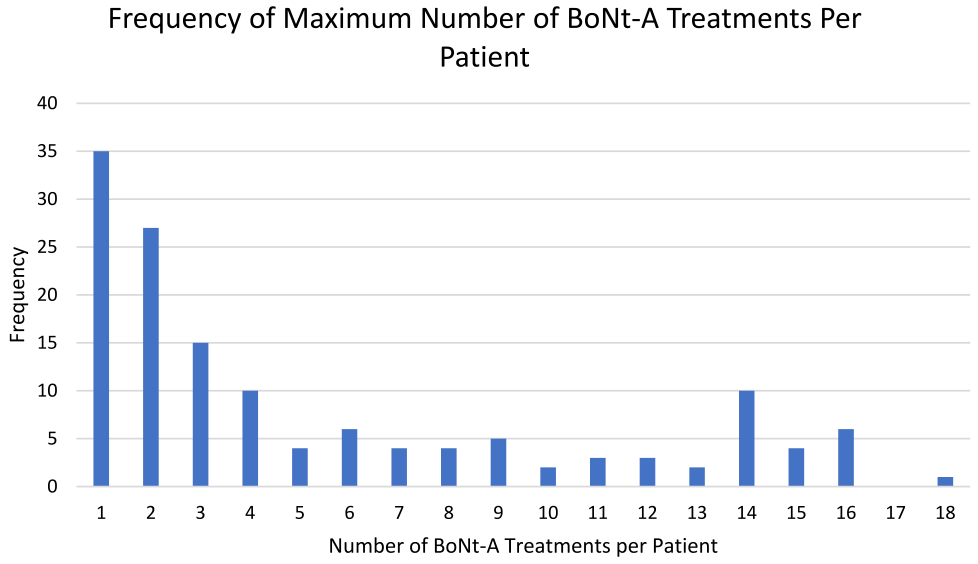

Fig. 2. Total number of BoNt-A treatments given per patient.

3.6. Long term complications

23% of women (n = 31) developed recurrent UTIs. A UTI was defined as a positive urine culture with or without dysuria. Recurrent UTI was defined as three or more UTIs in 12 months, or two or more UTIs in 6 months [17]. Development of recurrent UTIs was found with women who needed to perform CISC, both prior to and following BoNt-A treatment, and those who developed a UTI after their first treatment. The p values are demonstrated in Table 2.

3.7. Discontinuation rates

In our cohort, 30% (n = 39) are continuing with BoNt-A treatment for their OAB. 52% (n = 69) have been lost to follow up and 5% (n = 7) were referred for ongoing management of OAB including sacral nerve stimulation (SNS), percutaneous posterior tibial nerve stimulation (PTNS) or urinary diversion. 8% (n = 10) reverted to medical management, 2% (n = 2) became pregnant and 4% (n = 5) died due to unrelated causes. These rates are illustrated in Fig. 4.

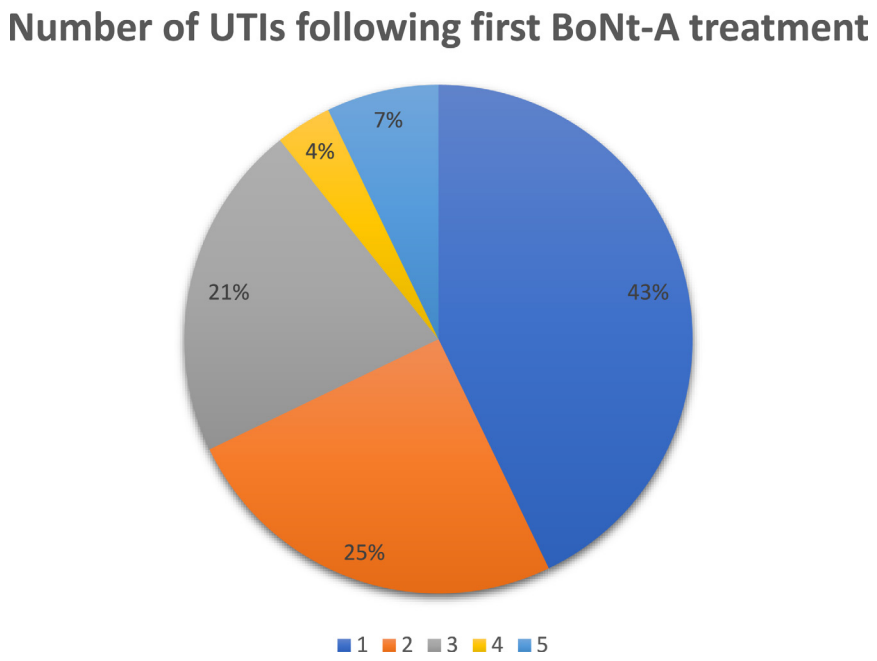

Fig. 3. Number of UTIs following first BoNt-A injection.

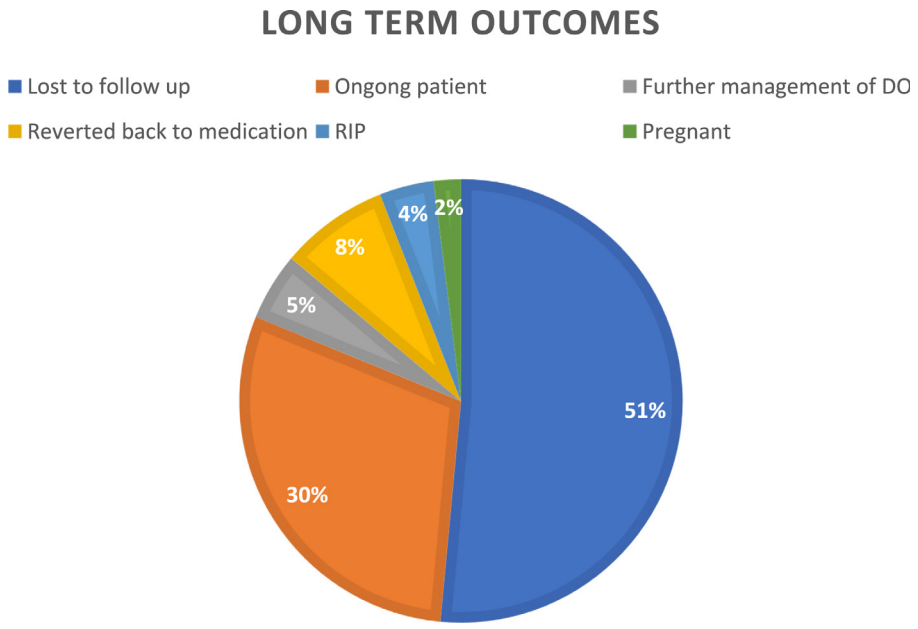

Fig. 4. Long term outcomes following Botox treatment.

4. Discussion

In women who suffer from refractory OAB and are willing to perform CISC, BoNt-A is the recommended first line treatment after two drugs have failed, due to lack of efficacy or side effects [6].

To our knowledge, this study reports on the largest cohort of patients with the highest individual numbers of repeated BoNt-A injections. A prospective cohort study by Dowson et al. on 100 patients had only one patient receiving their tenth treatment [18]. Our data highlight the safety of repeated injections with a median of 58 month follow up.

In this cohort, only 30% of patients over a 16-year period continued with repeated BoNt-A injections for their OAB. In a retrospective cohort study by Mohee et al. 56% of patients discontinued their treatment with BoNt-A due to tolerability issues, including the need to perform CISC, recurrent UTIs or worsening symptoms [19]. The majority of patients that did not continue with BoNt-A treatment, were lost to follow up. We did not collect data on subjective or objective improvement in symptoms after BoNt-A treatment and therefore are unable to comment whether these are contributing factors to the attrition rate. It is important to note that as our department is a tertiary Urogynaecology unit, many patients were referred from other units during the initial introduction of BoNt-A treatment for OAB. It is therefore plausible that some of those who were lost to follow up in our department may have then continued with their ongoing care in units closer to them, once BoNt-A treatment had been established UK wide. A previous study investigating patients lost to follow up who were undergoing glaucoma treatment found that 42% of patients had self-referred to other units for their ongoing treatment [20].

Table 2
Risk factors associated with rUTIs.

	rUTIs	No rUTIs	P value
Age[a] (mean)	72.4	64.5	0.32
Low capacity[b] n(%)	3 (12)	28 (26)	0.13
Low compliance[b] n(%)	3 (20)	28 (24)	0.74
Voiding dysfunction[b] n(%)	3 (33)	28 (23)	0.47
High pressure DO[b] n(%)	5 (14)	26 (27)	0.13
Neurogenic DO[b] n(%)	5 (30)	26 (23)	0.54
CISC[b] n(%)	**19 (43)**	**12 (14)**	**<0.001**
UTI after 1st BoNt-A treatment[b] n(%)	**17 (61)**	**14 (13)**	**<0.001**
Higher dose of BoNt-A[b] n(%)	14 (48)	43 (45)	0.90

[a] Mann-Whitney U.
[b] Chi-squared.

When comparing adherence of BoNt-A treatment to other treatments for OAB, a recent meta-analysis has shown a continuation rate with anticholinergics of 22%, secondary to ineffectiveness and unpleasant side effects [9]. A retrospective cohort study by Chapple et al. reported a continuation rate of 38% with mirabegron at one year [14]. Rates of continuation with treatments for refractory OAB such as PTNS have been reported at 19% [21].

The rate of CISC in our cohort was 22%. All women that were performing CISC prior to BoNt-A treatment for incomplete bladder emptying continued to do so following treatment. The ICS defines female voiding dysfunction as 'abnormally slow and/or incomplete micturition, based on abnormally slow urine flow rates or abnormally high post-void residuals, ideally on repeated measurements'. There were no associations between age, pre-treatment urodynamic parameters or dosage of BoNt-A administered and those women who developed new voiding dysfunction i.e. incomplete bladder emptying and therefore needed to perform CISC. The published literature has reported rates of CISC from as low as 1.9% to higher rates of up to 45% [22–24]. This could be secondary to varying definitions of what constitutes as a significant PVR with some institutions only recommending CISC in women who are symptomatic of a PVR [25]. For example, in the EMBARK studies, CISC was initiated in symptomatic patients with a PVR between 200–350 mls, or asymptomatic patients with a PVR >350 mls, hence their lower CISC rate of just over 6% [26].

The most common adverse effect secondary to intravesical BoNt-A injections are UTIs and the published literature has reported this at rates between 0.4% to 44% [25,27]. Our data show a rate of 21% for a UTI following first treatment and 23% of women developing recurrent UTIs with ongoing treatment. There remains a large discrepancy between published figures of these complications due to the different definitions of UTIs, with some studies including asymptomatic women with positive cultures and others including symptomatic women with negative cultures. There is also varying practice in antibiotic prophylaxis at the time of intravesical BoNt-A treatment. A retrospective cohort study performed by Houman et al. assessed UTI rate in patients who received a single dose of IM ceftriaxone versus those that received three days of oral fluoroquinolones. They found the rate of UTI, defined on either symptoms or positive urine culture, as 36% and 20.8% respectively ($p = 0.04$) [28]. However, a retrospective cohort study performed by Martin et al. found no difference in UTI diagnosis in patients treated with one day versus multiple days of antibiotics, with an OR of 1.38 (CI 0.80–2.38, $p = 0.249$) [29]. Reassuringly, there is no evidence to suggest that developing a UTI following BoNt-A injections causes a worsening in efficacy [30].

The strengths of this study include the large numbers in the cohort as well as the long term follow up, allowing generalisability of the results. The data are from a homogenous surgical team, which decreases variation of practice between operators.

The study's limitations include its retrospective nature, which can introduce bias. The results are from a single centre; data from multiple centres would increase generalisability. A large proportion of the women were ultimately lost to follow up, which can impact the validity of the long-term outcomes. We have not assessed the reasons why patients were lost to follow up, and this therefore cannot be attributed purely to inefficacy. We have not assessed the patients who were taking combination therapy with BoNt-A and oral medication and this may influence the intervals at which patients have their repeated treatments.

5. Conclusion

Repeated BoNt-A injections appear to be a safe form of treatment for refractory OAB. In our cohort, one in three women continued with long term treatment, one in four women developed recurrent UTIs and one in five women developed new voiding dysfunction, for which they now require CISC. There were no demographic or urodynamic parameters to predict the women that will require CISC. Recurrent UTIs were more prevalent in women who developed an initial UTI following first BoNt-A treatment and women that perform CISC. This information can be used to improve patient counselling, allowing them to make a more informed decision regarding their choice for ongoing management of refractory DO.

This study highlights the need for consensus regarding what constitutes a 'significant' PVR. Establishing clear protocol on when to initiate CISC in patients undergoing BoNt-A treatment may improve tolerability of treatment and therefore patient satisfaction, as well as decreasing adverse effects from CISC including pain and UTIs. There is also a requirement to unify guidance regarding antibiotic prophylaxis at the time of or prior to intravesical BoNt-A injections.

CRediT authorship contribution statement

R. Mohamed-Ahmed: Data collection/analysis, Manuscript writing/editing. **C. Tomlinson:** Data collection, Manuscript writing. **A. Taithongchai:** Data collection, Manuscript writing/editing. **A. Rantell:** Manuscript editing. **G. Araklitis:** Project development, Manuscript editing. **D. Robinson:** Manuscript editing. **L. Cardozo:** Manuscript editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Angie Rantell reports a relationship with AbbVie Inc that includes: speaking and lecture fees. Dudley Robinson reports a relationship with AbbVie Inc that includes: speaking and lecture fees.

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