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ORIGINAL RESEARCH

Cost-Effectiveness of IncobotulinumtoxinA in the Treatment of Sialorrhea in Patients with Various Neurological Conditions

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ABSTRACT

Introduction: Sialorrhea is a common and debilitating symptom associated with neurological conditions, which can result in considerable physical and psychosocial complications. In Australia, management options are limited and further impeded by the lack of approved treatments. Whilst there is emerging evidence for the efficacy and tolerability of botulinum toxin (BoNT) for the treatment of sialorrhea in patients with neurological conditions, the cost-effectiveness of the treatment is yet to be established.

Objectives: To evaluate the cost-effectiveness of incobotulinumtoxinA for the treatment of chronic troublesome sialorrhea caused by various neurological conditions from the Australian healthcare perspective.

Methods: A Markov state transition model was developed to perform a cost-utility analysis comparing incobotulinumtoxinA with standard of care (SoC). The model consisted of a hypothetical cohort of patients transiting between three severity-based health states, defined according to the Drooling Severity and Frequency Scale (DSFS), in 16-weekly cycles over 5 years. All clinical and utility inputs were sourced from a single placebo-controlled randomised clinical trial. Only direct healthcare costs were considered, and potential indirect costs such as carer's time and lost productivity were ignored. The primary outcome measure was the incremental cost per quality-adjusted life-year (QALY). Univariate and probabilistic sensitivity analyses were conducted.

Results: The model demonstrated that proportionally more patients spent time in less severe sialorrhea health states in the incobotulinumtoxinA arm. For example, over the 5-year period, patients receiving incobotulinumtoxinA were estimated to spend 1.6 years with minimal or no sialorrhea, while no patients achieved this level of improvement under SoC. IncobotulinumtoxinA was shown to have an incremental cost per QALY gained of A$23,445 when compared with SoC.

Conclusions: The quality of life (QoL) of patients with sialorrhea caused by neurological conditions was considerably compromised. IncobotulinumtoxinA was shown to successfully alleviate sialorrhea and it was demonstrated to be a cost-effective intervention when compared with SoC alone.

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Keywords: Botulinum toxin; Cost-effectiveness; Cost-utility; IncobotulinumtoxinA; Neurological disorders; Sialorrhea

Key Summary Points

There are no approved agents for the treatment of sialorrhea in Australia, and any use of pharmacotherapy is currently off-label.

The evidence from a large phase 3 placebo-controlled randomised trial (SIAXI) support incobotulinumtoxinA 100 U as an effective and well-tolerated treatment for chronic sialorrhea in adult patients with neurological conditions.

The cost-effectiveness of incobotulinumtoxinA or BoNT-A in general for the treatment of sialorrhea has not been established in published literature.

The current analysis demonstrates that, from an Australian healthcare system perspective, incobotulinumtoxinA represents a cost-effective intervention for the treatment of sialorrhea when compared with the current best supportive care.

INTRODUCTION

Uncontrolled and/or excessive salivation, known as sialorrhea or drooling, is a common and debilitating symptom associated with several neurological conditions, including Parkinson's disease (PD), atypical Parkinsonism, amyotrophic lateral sclerosis (ALS), cerebral palsy and sequelae of stroke or acquired brain injury [1]. In adults, PD is the most common cause of sialorrhea, although published prevalence estimates are associated with a wide range from 10% [2] to 84% [3]. This is partly due to a lack of uniformity in defining drooling and its diagnostic criteria [4, 5] as well as different disease severities of the study groups.

Saliva is primarily mediated by three major pairs of salivary glands, namely parotid, submandibular and sublingual, which are innervated by the autonomic nervous system via cholinergic nerve fibres [6]. In patients with neurological disorders, the aetiology of sialorrhea is multifactorial and has been attributed to poor coordination between oral and pharyngeal stages of swallowing, open-mouth posture, flexed posture, interruption in normal swallowing reflexes or dysphagia, and limited tongue movement [7, 8].

Sialorrhea can result in a range of physical and psychosocial complications, including perioral chapping, skin maceration, halitosis, dehydration, impaired speech, difficulty eating and aspiration-related lung infections, as well as social embarrassment and stigmatisation, [9, 10] all of which have a detrimental impact on quality of life (QoL) [11].

Traditional approaches to managing sialorrhea consist of speech and behavioural therapy, pharmacotherapy, radiation or surgical interventions [5]. Topical or systemic anticholinergic agents (e.g. atropine, ipratropium or benztropine) block the parasympathetic pathways to the salivary glands and are generally recommended as first-line therapeutic options for sialorrhea [12]; however, the use of systemic agents in particular is impeded by burdensome adverse events such as blurred vision, urinary retention, drowsiness and cognitive impairment [1, 13]. They are also contraindicated in patients with glaucoma, obstructive uropathy, gastrointestinal motility disorders and myasthenia gravis, and are often poorly tolerated in elderly patients who have multiple comorbidities [9]. In addition, as there are currently no approved agents for sialorrhea in Australia, the use of pharmacotherapy is off-label, which highlights the lack of clinical evidence available for these agents in treating sialorrhea. Salivary gland irradiation and surgical ablation are invasive and permanent and can result in an irreversibly dry mouth and exacerbation of dysphagia and dysarthria [14, 15].

The percutaneous injection of botulinum toxin (BoNT) into the salivary glands has been shown to be safe and effective in treating sialorrhea caused by neurological disorders in

several randomised controlled trials (RCTs) [16–24]. The rationale for the use of BoNT is the selective inhibition of presynaptic acetylcholine release from the parasympathetic nerve terminals supplying eccrine salivary glands, thereby reducing saliva production [25, 26]. Clinical studies vary in the type and dose of BoNT used (type A or B), glands injected (parotid, submandibular or both), population and cause of sialorrhea, inclusion of placebo-control arm, and anatomic or ultrasound-guided injections. Meta-analyses have evaluated the efficacy of BoNT type A (BoNT-A) compared with placebo [27] and anticholinergic medications [28].

IncobotulinumtoxinA (Xeomin®; Merz) is currently indicated for a range of conditions including upper limb spasticity, blepharospasm and cervical dystonia. It is approved for sialorrhea in Europe and the United States, but yet to be included as an approved indication in Australia.

SIAXI (Sialorrhea In Adults Xeomin® Investigation; NCT02091739 [29]) is the largest prospective placebo-controlled randomised trial to date investigating the efficacy and safety of BoNT-A (incobotulinumtoxinA) for the treatment of chronic troublesome sialorrhea due to a variety of neurological conditions. A total of 184 patients were randomly assigned in a double-blind manner to receive either incobotulinumtoxinA 75 U (n = 74), 100 U (n = 74) or placebo (n = 36) in a single treatment (main period; 16 weeks) followed by incobotulinumtoxinA doses of 75 U or 100 U in three further treatments (extension period). The study demonstrated a statistically significant reduction in unstimulated salivary flow rate (uSFR) for patients treated with 100 U compared with placebo at 4 weeks post-treatment (p = 0.004). A lower dose of 75 U, also investigated in the trial, was not found to be efficacious (p = 0.542 versus placebo). Dry mouth was among the most frequently reported treatment-related adverse event (occurring in 2.7% of patients in the 100 U group) [29].

The objective of this publication is to present a modelled cost-utility analysis (CUA) of incobotulinumtoxinA for the treatment of chronic troublesome sialorrhea due to a variety of neurological conditions, based on clinical evidence from the SIAXI trial, from the Australian healthcare providers' perspective.

METHODS

Model Structure

A Markov state transition model was developed to perform the CUA. In the current model, a hypothetical cohort of patients transit between health states in 16-weekly cycles over a 5-year model duration. This approach was the preferred modelling methodology due to its simplicity and transparency when compared with other modelling techniques such as microsimulation. The comparison was made versus standard of care (SoC), assuming its effectiveness was represented by the available placebo data.

Figure 1 presents a schematic of the current Markov model. In designing the model structure, the Drooling Severity and Frequency Scale (DSFS; see Table 1) total score was used to define a set of "severity-based" health states. DSFS consists of two subscales: a five-point Likert scale for classifying "drooling severity" from 1 (dry) to 5 (profuse drooling), and a four-point Likert scale for classifying "drooling frequency" from 1 (no drooling) to 4 (constant drooling). The two subscale scores are summed together to

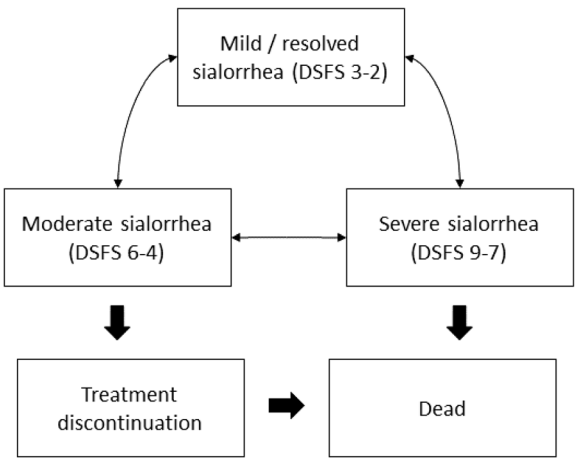

Fig. 1 Model structure showing Markov health states in the treatment of sialorrhea. *DSFS* Drooling Severity and Frequency Scale

Table 1 DSFS

Drooling severity score	Drooling frequency score	Total score
1 = Dry (never drools) 2 = Mild (only lips wet) 3 = Moderate (wet on lips and chin) 4 = Severe (drool extends to clothes wet) 5 = Profuse (hands, tray and objects wet)	1 = Never 2 = Occasionally (not every day) 3 = Frequently (part of every day) 4 = Constantly	Add severity score and frequency score together, providing the sum score range of 2 (least severe) to 9 (most severe)

determine an overall drooling ranking that ranges from 2 to 9 [30]. Three categories of overall sialorrhea severity were established for the purpose of this modelling, including "Severe" (DSFS 9–7), "Moderate" (DSFS 6–4) and "Mild/Resolved" (DSFS 3–2), and they were represented by three severity-based health states in the model. The patients transitioned these health states reflecting improvement/worsening of their sialorrhea severity over time. Categorising the disease severity into three levels was considered adequate from the perspective of providing model transparency without compromising the model's sensitivity in capturing cost/QoL implications associated with changes in the sialorrhea severity.

Patients could also discontinue the treatment they received (transiting to "Treatment discontinuation") or die (transiting to "Dead") at any time during the model horizon (see Fig. 1).

A 16-week model cycle was employed, as this reflected the re-injection intervals implemented within the relevant clinical trial. All patients began in the model by receiving the first injection. Patients then transitioned health states depending on the changes in sialorrhea severity experienced following the injection. This process was continued each 16-week model cycle as long as patients remained on the treatment allocated at baseline. Within this model structure, treatment benefits offered by incobotulinumtoxinA over SoC were represented by a greater proportion of the patient cohort being allocated to health states of less sialorrhea severity over the modelled time horizon.

The sialorrhea severity for patients stopping the allocated treatment, thus transiting to the discontinuation health state described above, was assumed to revert to the mean severity observed at baseline.

The primary outcome measure of the model was the number of quality-adjusted life-years (QALYs), and the incremental cost-effectiveness ratio (ICER) was expressed in terms of incremental cost per QALY gain. The base-case model horizon was set at 5 years. A 5-year horizon was considered sufficiently long to assess the long-term cost-effectiveness of treatment without introducing unnecessary extrapolation-related uncertainties. The perspective of the analysis was the Australian healthcare system, meaning only direct healthcare costs were included. All costs and health outcomes are discounted at 5% as currently required by the Pharmaceutical Benefits Advisory Committee (PBAC) submission guidelines [31]. Costs are expressed in Australian dollars (2018 values).

All clinical and utility inputs for this model were sourced from the placebo-controlled randomised SIAXI trial [29] and its extension study (including individual patient data on file). The current model thus has a strong faithfulness to the available trial data. While extrapolation of the clinical data was necessary for an adequate assessment of cost-effectiveness, the model should provide an RCT-based cost-effectiveness analysis with adequate interval validity. As the anticipated licensed dose for this indication is 100 U in Australia, clinical and utility data pertaining to the 100 U and placebo treatment groups of the SIAXI trial were considered in this analysis (i.e. the lower incobotulinumtoxinA dose of 75 U was not included in the model).

Model Inputs

Patient demographics of the modelled cohort were also based on the aforementioned RCT. The only patient characteristics relevant to the model were age and gender, which both affect the risk of death at each cycle in the model. The baseline age was 65, with 71% being male (Table 2). This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Mortality was based on Australian life tables, and for simplicity, no excess mortality due to the underlying neurological conditions was considered. Of note, most trial participants suffered from sialorrhea associated with PD (70.7%).

All clinical data and utility inputs were based on the SIAXI RCT and its extension phase study (Table 3). A post hoc analysis of DSFS data was performed to estimate transition probabilities that informed the movement of the modelled cohort across the three severity-based health states at each model cycle. During the extension phase study, DSFS was only assessed in the fourth week of each injection cycle (i.e. 4 weeks after injection). To this end, the fourth-week data from each injection cycle were utilised to produce the transition matrix of the respective injection cycle. When combined with the extension phase study, DSFS data were available up to the fourth injection cycle (to 64 weeks) for incobotulinumtoxinA. In contrast, the placebo data from the controlled phase were employed to represent the effectiveness of SoC in the model, offering data only for one injection cycle (to 16 weeks). Extrapolation of the health state transition probabilities (thus the distribution of the patient cohort across the severity-based health states) was conducted on a last-observation-carried-forward (LOCF) basis; therefore no further transitions among these health states occur after these time points in the model. Rates of treatment discontinuation were also informed by the trial (Table 3), and extrapolation was again performed on a LOCF basis. These extrapolation assumptions hence meant that, while no transitions occurred among the three severity-based health states after 64 weeks and 16 weeks (i.e. the fourth and first model cycles) for incobotulinumtoxinA and SoC, respectively, patients could still discontinue in subsequent modelling cycles, prompting transition to the discontinuation health state.

Table 2 Patient characteristics of the modelled cohort-informed by the SIAXI trial Source: [29]

Patient/disease characteristic	Total participants, n = 184
Sex, n (%)	
Male	130 (70.7)
Female	54 (29.3)
Age, years; mean (SD)	65.2 (11.4)
Drooling aetiology, n (%)	
PD	130 (70.7)
Atypical Parkinsonism	16 (8.7)
Stroke	33 (17.9)
Traumatic brain injury	5 (2.7)
DSFS total score, mean (SD)	6.86 (0.93)[a]

DSFS Drooling Severity and Frequency Scale, *PD* Parkinson's disease, *SD* standard deviation

[a] Captured as 54.55% and 45.45% of the cohort being in the "Severe" and "Moderate" health states, respectively, based on the trial data

All cost inputs are presented in Table 3. The drug acquisition cost per treatment was determined according to the current subsidisation list price of incobotulinumtoxinA [32]. Each injection required one 100 U vial of incobotulinumtoxinA at A$375.00, and a pharmacy mark-up and dispensing fee (A$22.29) were also added onto the total drug acquisition cost. The cost of treatment administration was based on equivalent fees currently available on the Australian Medicare Benefits Schedule (MBS). Each administration procedure was assumed to attract an injection fee of A$45.05 (MBS item number 18369; based on the BoNT injection procedure for unilateral blepharospasm) and a specialist consultation fee of A$76.65 (MBS item number 116). In the clinical trial, 55% of

Table 3 Model inputs for the base-case analysis

Model variable	Base-case input	Source
Clinical inputs		
Health state transition probabilities[a]		
IncobotulinumtoxinA	Resulting Markov trace in Fig. 3	Placebo-controlled double-blind SIAXI RCT [29] and extension phase study (data on file), assuming no further severity changes after 64 weeks
SoC	Resulting Markov trace in Fig. 3	Placebo-controlled double-blind SIAXI RCT [29], assuming no further severity changes after 16 weeks
Treatment discontinuation, % (SD)[c]		
IncobotulinumtoxinA, 1st cycle	2.7% (0.02)	Placebo-controlled double-blind SIAXI RCT [29]
IncobotulinumtoxinA, +2nd cycle	3.1% (0.03)	Extension phase of SIAXI study (data on file)
SoC, 1st cycle	11.1% (0.05)	Placebo-controlled double-blind SIAXI RCT [29]
SoC, +2nd cycle	11.1% (0.05)	Assuming the first cycle rate applicable
Cost inputs[b]		
IncobotulinumtoxinA treatment		
Price per 100 U vial	A$375.00	PBS schedule [32]
Number of vials per treatment cycle	1	One vial sufficient to deliver 100 U
Pharmacy mark-up and dispensing fee per treatment cycle	A$22.29	PBS BoNT Program; 4% mark-up + $7.29 dispensing fee
Administration cost per treatment cycle	A$151.70	MBS item 116 for consultation at A$76.65 × 1 (assumption) MBS item 18369 for injection at A$45.05 × 1 (assumption) MBS items 55011 for ultrasound at A$54.55 × 0.55 (% requiring ultrasound-based on RCT)
Total cost per treatment cycle	A$548.99	Calculated
Allied healthcare services for sialorrhea		
Severe sialorrhea/DSFS 9–7	A$124.50	Two allied healthcare services every 16 weeks (assumption) at $62.25 per service (MBS item number 10970)
Moderate sialorrhea/DSFS 6–4	A$62.25	One allied healthcare service every 16 weeks (assumption) at $62.25 per service (MBS item number 10970)
Mild/resolved sialorrhea/DSFS 3–2	A$0.00	No allied healthcare service required (assumption)
Baseline (for discontinuers)	A$62.25	Assumed to be equal to moderate sialorrhea
Utility inputs[c]		
Health state utility values, mean (SD)		

Table 3 continued

Model variable	Base-case input	Source
Severe sialorrhea/DSFS 9–7	0.55 (0.31)	Post-hoc analysis of EQ-5D data from the placebo-controlled double-blind SIAXI RCT [29]
Moderate sialorrhea/DSFS 6–4	0.64 (0.26)	
Mild/resolved sialorrhea/DSFS 3–2	0.74 (0.26)	
Baseline (for discontinuers; calculated according to the baseline severity)	0.59	

BoNT botulinum toxin, *DSFS* Drooling Severity and Frequency Scale, *MBS* Medicare Benefits Schedule, *PBS* Pharmaceutical Benefits Scheme, *PSA* probabilistic sensitivity analysis, *RCT* randomised controlled trial, *SD* standard deviation, *SoC* standard of care

[a] Dirichlet distributions are applied in PSA

[b] All MBS/PBS benefit amounts are as of November 2018

[c] Beta distributions are applied in PSA

patients additionally required ultrasound imaging to guide the identification of injection sites. The model applied an ultrasound fee of A$54.55 (MBS item number 55011) in 55% of all injection procedures, translating to A$30 per injection. The total administration cost was hence $151.70 per injection in the model.

While much of the "background" care for the underlying neurological conditions was assumed to exist equally in both of the treatment arms (thus cancelling out each other), the model accounted for additional sialorrhea-specific resource use for the "Severe" and "Moderate" severity health states. No resource use data were collected in the clinical trials. The model assumes that patients with ongoing severe sialorrhea required two episodes of allied healthcare service (such as speech pathology, physiotherapy or occupational therapy) each 16-week period and that patients with ongoing moderate sialorrhea required only one episode. Each care episode was assumed to cost A$62.25 (MBS item number 10970). Based on the baseline DSFS score of 6.86, patients who discontinued the allocated treatment were assumed to be equivalent to moderate severity in terms of the allied healthcare requirements.

A patient's QoL was entirely dependent on sialorrhea severity as measured by the DSFS. Utility values were derived from EQ-5D data of the placebo-controlled double-blind phase of the SIAXI study (data on file) with Australian preference weights applied [33]. The EQ-5D utility values were stratified by the corresponding DSFS scores (Fig. 2). Pooled data across the treatment arms were then further analysed to determine a mean utility score corresponding to each of the severity-based health states (Table 3). For example, patients in the most severe health state (DSFS 9–7) were associated with a utility value of 0.55, while those in the least severe health state (DSFS 2–3) accrued a utility value of 0.74. For patients who discontinued the treatment, their DSFS sum score was assumed to revert to the baseline level, thus accruing a utility value of 0.59.

Adverse events and their potential cost implications were not explicitly captured in the model. However, these were considered as relatively minor and transient, and unlikely to be associated with meaningful cost implications overall.

A series of univariate deterministic sensitivity analyses were conducted on the base case by altering data inputs for key model variables. Probabilistic sensitivity analysis (PSA) was also conducted on the base case by assigning dirichlet distributions to health state transition probabilities and beta distributions to discontinuation rates and utility values [34]. Cost and resource utilisation variables were fixed in the PSA because all cost inputs were based solely on

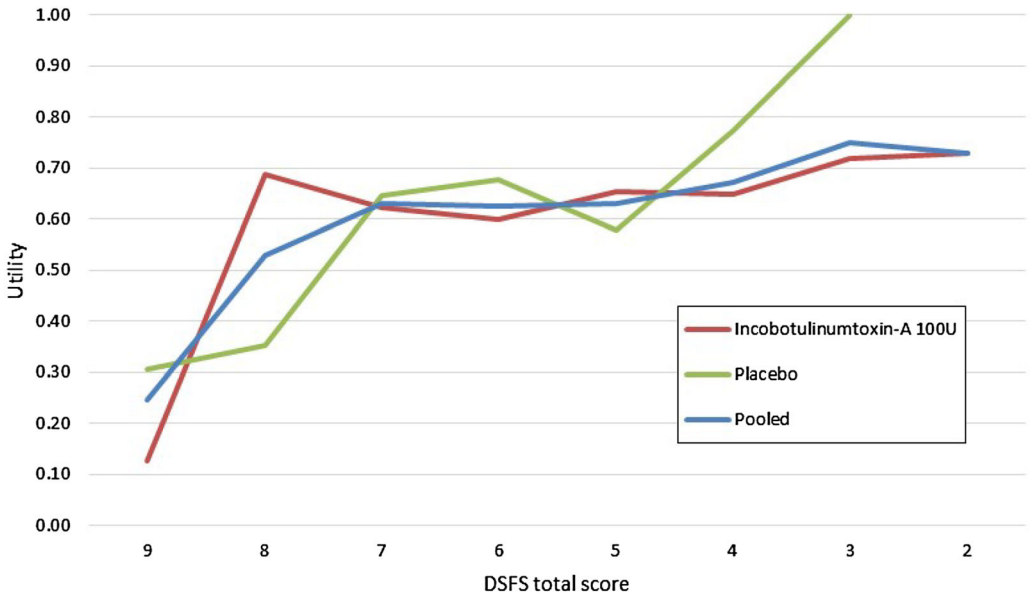

Fig. 2 Mean EQ-5D utility values by DSFS total score. Source: SIAXI trial [29] individual patient data on file. *DSFS* Drooling Severity and Frequency Scale

officially determined fees (MBS or PBS; [35, 36]), and the extent of resource use was a direct function of the health state distributions over time.

RESULTS

Over time, proportionally more patients spent time in less severe health states in the incobotulinumtoxinA arm when compared with the SoC arm of the model (Fig. 3). Patients receiving incobotulinumtoxinA spent on average 1.6 years in the "Mild/Resolved" sialorrhea health state over the 5-year model horizon, while no one reached this health state with SoC. The model estimated incobotulinumtoxinA provided an estimated QALY gain of 0.27 when compared with SoC. The total cost of incobotulinumtoxinA therapy was estimated to be A$6634, but a small cost offset of A$396 was provided by the treatment in terms of other care needs. The incremental cost per QALY gained of incobotulinumtoxinA in the treatment of sialorrhea when compared with SoC was A$23,445 (Table 4).

A series of univariate deterministic sensitivity analyses were performed (Table 5). As expected, utility values were the most influential variable. Altering utility values by using the 95% confidence interval (CI) produced ICERs ranging from A$17,847 to A$34,160. Sensitivity analyses also explored alternative model durations with a 1-year time horizon returning an estimated ICER of A$37,133. Overall, these sensitivity analyses supported the robustness of the base-case results.

A PSA was performed using 1000 iterations of the base-case evaluation (Figs. 4, 5). Across the 1000 iterations, incobotulinumtoxinA was demonstrated to produce a mean QALY gain of 0.27 (95% CI 0.266–0.269) at a mean additional cost of A$6235 (95% CI A$6232 to $A6,238). The cost-effectiveness acceptability curve illustrated that at the willingness-to-pay threshold of A$30,000 per QALY, the probability of the treatment being cost-effective was more than 95%.

DISCUSSION

This modelled CUA examined the cost-effectiveness of incobotulinumtoxinA for the treatment of chronic troublesome sialorrhea caused by various neurological conditions. This

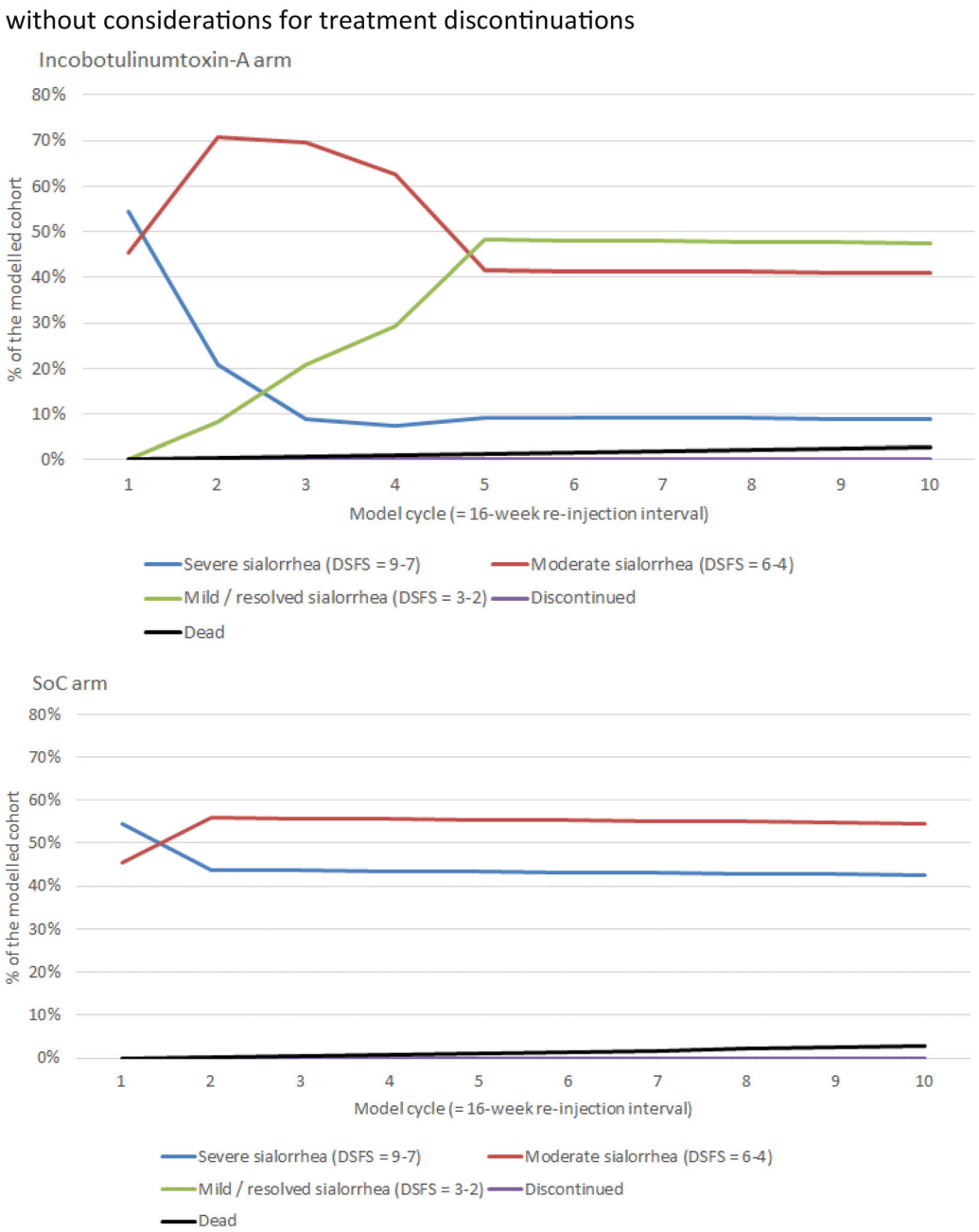

Fig. 3 Distribution of the modelled cohort across health states from Cycle 1 to Cycle 10 (to approximately 3 years): **a** without considerations for treatment discontinuations and **b** with considerations for treatment discontinuations (= the base-case analysis). *DSFS* Drooling Severity and Frequency Scale, *SoC* standard of care

analysis was essentially a trial-based cost-effectiveness evaluation, informed by a 16-week placebo-controlled RCT and its 48-week extension study [29]. To our knowledge, this is the first published cost-effectiveness analysis of incobotulinumtoxinA or BoNT-A in general for this indication.

IncobotulinumtoxinA was shown to successfully alleviate sialorrhea and was demonstrated to be a cost-effective intervention when

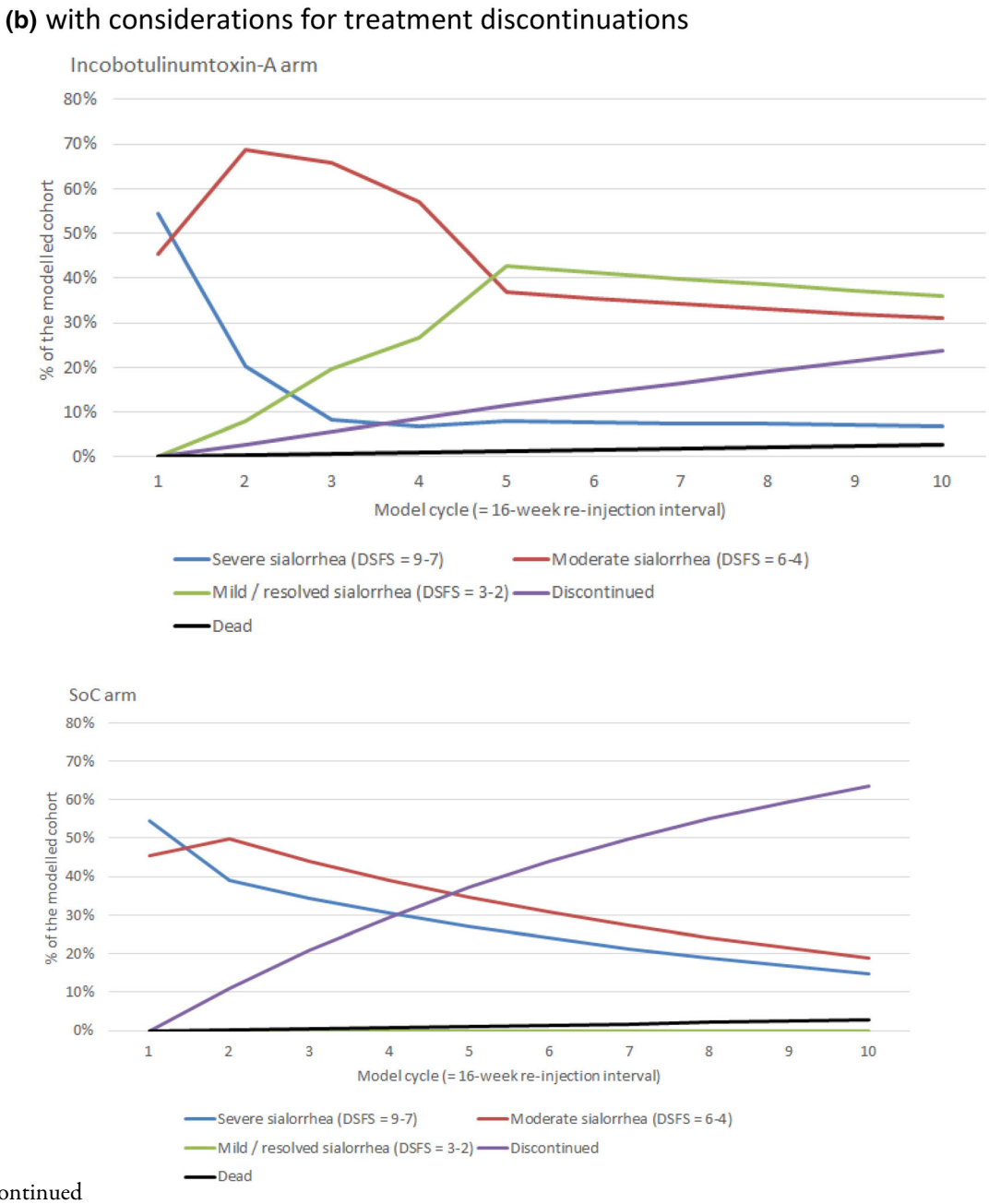

Fig. 3 continued

compared with SoC alone. The current study also highlighted that the QoL of patients living with sialorrhea was considerably compromised. The trial subjects with severe sialorrhea had an estimated utility score of 0.55, and it was 0.64 for those with moderate sialorrhea. Improvement to mild/resolved sialorrhea was estimated to provide a utility score of 0.74.

It is noted that the clinical trial supporting this CUA was conducted in a "mixed" patient population with respect to the aetiology of sialorrhea. The trial comprised predominantly patients suffering from PD (70.7%), followed by stroke (17.9%), atypical Parkinsonism (8.7%) and traumatic brain injury (2.7%). Patients with other secondary causes of sialorrhea such as

Table 4 Results of the CUA of incobotulinumtoxinA compared against SoC alone in the treatment of sialorrhea

Model outputs	IncobotulinumtoxinA	SoC alone	Incremental difference
Total costs (A$)			
IncobotulinumtoxinA therapy	A$6634	–	A$6634
Other care	A$732	A$1128	− A$396
Total	A$7365	A$1128	A$6238
QALYs	3.02	2.75	0.27
ICER			A$23,445

NB. All outputs are discounted at 5% per annum
CUA cost-utility analysis, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year, *SoC* standard of care

motor neuron disease or ALS were excluded from participation. Nevertheless, based on subgroup analyses of the clinical data and also supported by the mechanisms of action of incobotulinumtoxinA, the results are expected to be applicable regardless of the underlying neurological condition. However, the model results should be interpreted in the above context accordingly.

The health states in the current model were defined primarily by sialorrhea severity as measured by DSFS. The primary outcome of the trial was uSFR, which is a direct measurement of saliva flow. Several saliva quantification methods exist, e.g. in the SIAXI trial, it involved placing several absorbent cotton rolls at the orifices of the ducts of glands for 5 min and weighing. While routinely employed in research settings, uSFR can be cumbersome and unpleasant for patients, and thus its application may experience limitations in clinical practice as an efficacy assessment tool for BoNT-A therapy. In particular, patients with neuromuscular conditions may experience difficulties in completing such a method of direct saliva quantification. In contrast, the DSFS is a questionnaire-based assessment tool offering a practical and readily administered alternative for routine clinical application and is also widely used in clinical trials evaluating sialorrhea. Its sensitivity and reliability in clinical decision-making has been tested and well corroborated against another direct measurement method, Drooling Quotient, which involves recording the absence or presence of saliva on the lip in two 10-min observational sessions with a 60-min interval [37]. The implementability of efficacy evaluation was a particularly important consideration in formulating the model approach for this study, because the subsidisation of BoNT-A in Australia is typically associated with a response-based stopping rule whereby only patients satisfactorily responding to the treatment are eligible for ongoing subsidisation. The current model could hence be easily adapted to explore the implementation of such a response-based stopping rule in the future if necessary, without altering the model structure. Nonetheless, the subjective nature of the outcome and other potential weaknesses such as recall error are acknowledged [38].

Another structural feature of the model that may require clarification is that patients can "discontinue" SoC. In a strict sense, this may not happen in actual clinical practice, and instead, the extent and nature of care is altered with the aim of improving effectiveness if a patient is responding poorly to the administered treatment. Applying the baseline sialorrhea severity to all discontinuers could be hence considered as favouring incobotulinumtoxinA in the current model. However, the consistent handling of treatment discontinuation was important because the sialorrhea severity in the treatment arm would have been otherwise unfairly overstated relative to SoC in the model, especially given that the model assumed any treatment benefit achieved was lost upon discontinuation. Here, it is also relevant to note that the improvement in sialorrhea severity in

Table 5 Univariate deterministic sensitivity analyses

Model variable/assumptions tested	Incremental cost	Incremental QALY	ICER
Base-case results	A$6238	0.27	A$23,445
Model duration			
1 year	A$1998	0.05	A$37,133
2 years	A$3226	0.11	A$28,149
10 years	A$8800	0.40	A$22,181
Short injection cycle			
12-weekly cycle[a]	A$7571	0.25	A$30,231
Treatment discontinuation			
Halved in both arms	A$6884	0.30	A$23,214
Doubled in both arms	A$5143	0.21	A$24,280
0% applied to incobotulinumtoxinA	A$7813	0.35	A$22,177
0% applied to SoC	A$6013	0.24	A$24,956
0% in both arms	A$7588	0.33	A$23,192
Cost inputs			
No ultrasound use for injection	A$5875	0.27	A$22,083
Double allied healthcare use	A$5842	0.27	A$21,957
Halve allied healthcare use	A$6436	0.27	A$24,189
Utility inputs			
Upper 95% CI values[b]	A$6238	0.35	A$17,847
Lower 95% CI values[c]	A$6238	0.18	A$34,160
Utility differences vs "Severe" are halved for "Moderate" and "Mild/Resolved"[da]	A$6238	0.20	A$31,117
Discounting rate			
3.5%	A$6388	0.27	A$23,347
No discounting	A$6775	0.29	A$23,118

All outputs discounted at 5% per annum

CI confidence interval, *ICER* incremental cost-effectiveness ratio, *LOCF* last observation carried forward, *QALYs* quality-adjusted life-years, *SoC* standard of care

[a] The same transition probabilities as those employed in the base-case analysis were employed; however, the cost and QALY calculations were done every 12 weeks (instead of 16 weeks in the base-case analysis). The treatment cost is incurred every 12 weeks

[b] 0.59, 0.67, 0.84 and 0.63 for severe, moderate, mild/resolved and discontinued, respectively

[c] 0.50, 0.61, 0.63 and 0.55 for severe, moderate, mild/resolved and discontinued, respectively

[d] 0.55, 0.59, 0.69 and 0.55 for severe, moderate, mild/resolved and discontinued, respectively

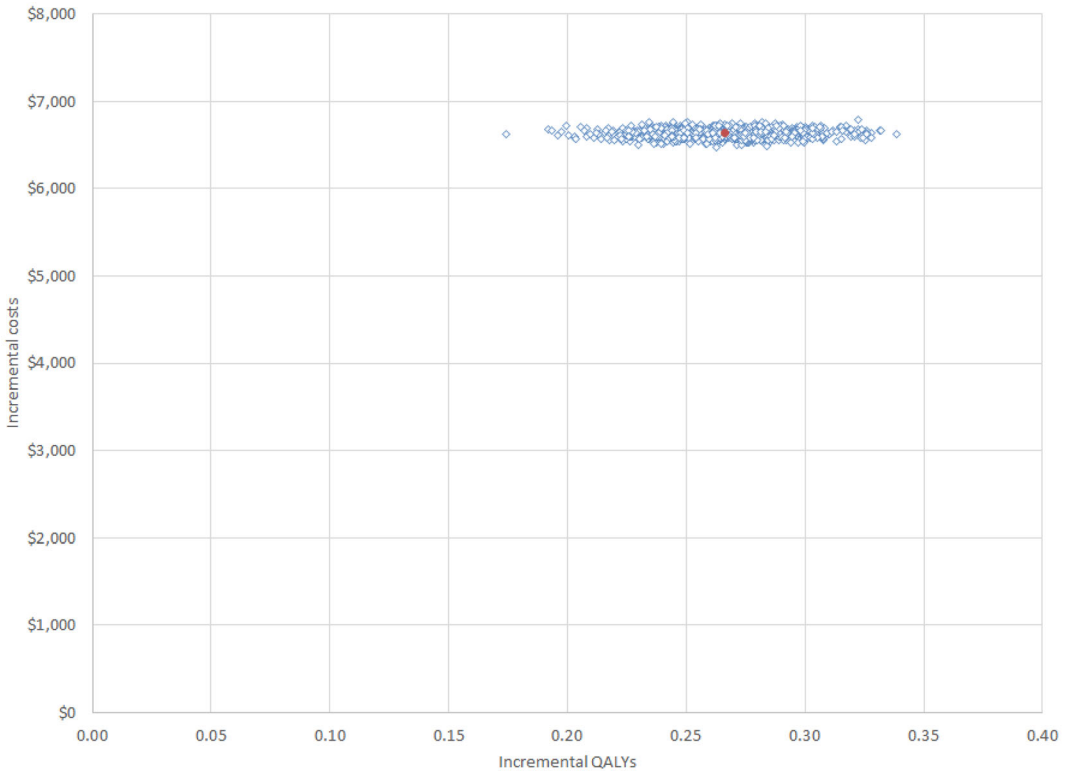

Fig. 4 Scatterplot for PSA for incobotulinumtoxinA regimen versus SoC alone in the treatment of sialorrhea. Red point represents the base case. *PSA* probabilistic sensitivity analysis, *QALYs* quality-adjusted life-years, *SoC* standard of care

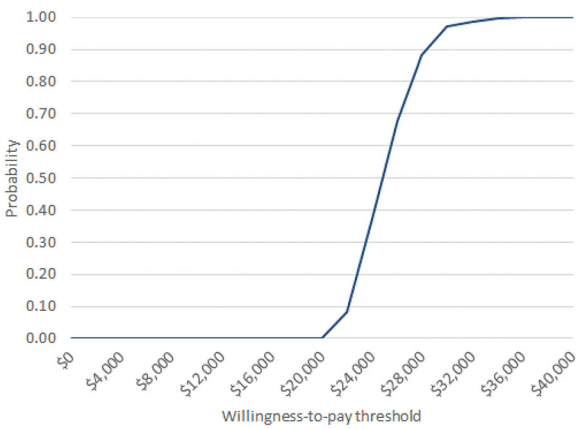

Fig. 5 Cost-effectiveness acceptability curve for incobotulinumtoxinA regimen versus SoC alone in the treatment of sialorrhea. *SoC* standard of care Source: [30]

the SoC arm of the model was at least partly due to placebo effects observed within the RCT. Sensitivity analysis on the rate of discontinuation for SoC also suggested a minor impact on the ICER. This could be explained by the limited improvement in DSFS post-baseline in the placebo arm of the RCT.

Only direct healthcare resource costs were considered in the model. In addition to the costs of incobotulinumtoxinA therapy, the model considered additional allied healthcare services (e.g. speech pathology, physiotherapy and occupational therapy) for patients with ongoing moderate to severe sialorrhea. Due to the lack of relevant evidence, the extent of resource use in relation to these services was based on assumptions, but these assumptions should fall within a reasonable realistic range if not conservative. No indirect costs, most importantly, carer time and other productive opportunities foregone, were considered in this study as per the current PBAC submission guidelines [31]. This was a conservative approach, likely underestimating the cost-effectiveness of incobotulinumtoxinA. Also, carer time would have important direct resource

implications if patients were in residential or in-hospital care. From this perspective, the treatment may have a more favourable cost-effectiveness in these settings.

One potential weakness of the current model was the relatively crude way in which the clinical data were extrapolated beyond the trial duration. The estimated health state distributions in the treatment arm over the first four model cycles, during which time relevant trial data were available, showed that patients continued to improve on the sialorrhea severity (Fig. 3). If this trend were to be sustained, the LOCF-based extrapolation would have biased against incobotulinumtoxinA, and this point is particularly relevant in interpreting the results of sensitivity analyses examining shorter model durations (Table 5). The trial data were only available for the first cycle for the SoC arm. Pragmatically speaking, as also discussed above, the improvement in sialorrhea severity in the SoC arm was at least partly due to placebo effects of the trial. In the absence of placebo injections, a greater proportion of patients than predicted by the model would stay at their baseline sialorrhea severity in reality. This again would mean that the model results were conservative against incobotulinumtoxinA. The extrapolation of treatment discontinuations was also similarly crude; however, relevant sensitivity analyses suggested that the ICER was insensitive to changes in these variables.

The SIAXI trial did not examine the severity of the underlying neurological conditions and its potential impacts on sialorrhea severity or treatment effects. Thus, the utility values employed in the current model could not be controlled for this. The trial included patients suffering from moderate or severe sialorrhea only, with an estimated utility value of 0.59 (Table 3). The current study demonstrated that patients who had achieved mild/resolved sialorrhea (DSFS 3–2) were associated with a utility value of 0.74. While some uncertainties may remain, this is a sizeable gain and should suggest that a reduction in sialorrhea severity provides a meaningful improvement in QoL among these patients. A sensitivity analysis tested a scenario where the extent of utility gain from the "Severe" health state was halved; even under this conservative scenario, the ICER remained acceptable at A$31,117 (Table 5).

The health state transition probabilities were based on the DSFS total scores collected at 4 weeks into each injection cycle in the trial. As discussed above, this reflected the timing of DSFS assessments during the extension phase study. It is acknowledged that some of the incobotulinumtoxinA effects could wane towards the end of each 16-week injection cycle, and similar trends were observed with other applications of BoNT therapies [39–41]. This would mean that the base-case ICER might have been underestimated. In practice, the waning of the treatment effects could be addressed by a shorter re-injection cycle if it becomes problematic. The current Australian Product Information for incobotulinumtoxinA also suggests a 12-week injection treatment interval for various approved indications such as cervical dystonia or blepharospasm, although re-treatment with incobotulinumtoxinA is permitted as early as 6 weeks post-injection if clinically necessitated. When a 12-weekly re-injection cycle was implemented in the current model (impacting the treatment costs upwards whilst applying the same transition probabilities as those employed in the base-case analysis), incobotulinumtoxinA was still cost-effective, with an estimated ICER of A$30,231.

Limitations

This model is primarily informed by a single RCT, and therefore the generalisability of the model results to real-world clinical settings needs due consideration in terms of, for example, patient characteristics and the presence of placebo effect. Extrapolation-related uncertainties may also exist. Severity of the underlying neurological conditions may have compounded the estimated disutility caused by sialorrhea. The scope of costing is limited to direct healthcare resource use, likely underestimating the true economic implications. These limitations were discussed above.

CONCLUSION

The QoL of patients living with chronic neurological conditions such as PD is often already compromised due to other symptoms [42]. For those with troubling sialorrhea, incobotulinumtoxinA should offer a useful and targeted treatment strategy, and it represents a highly cost-effective treatment.

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Authorship Contributions. KM helped design the research question and model structure, developed the economic model and generated the results, and wrote and reviewed drafts of the manuscript. NM provided clinical expert opinion on the disease area of sialorrhea, which helped design the research question and model structure, and reviewed drafts of the manuscript. DT helped design the research question and model structure and wrote and reviewed drafts of the manuscript. LA helped design the research question, extracted and analysed clinical trial data, and wrote and reviewed drafts of the manuscript.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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