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Real-world Implications of Botulinum Neurotoxin A Immunoresistance for Consumers and Aesthetic Practitioners: Insights from ASCEND Multidisciplinary Panel

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Background: As long-term, regular aesthetic botulinum neurotoxin A (BoNT-A) use becomes more commonplace, it is vital to understand real-world risk factors and impact of BoNT-A immunoresistance. The first Aesthetic Council on Ethical Use of Neurotoxin Delivery panel discussed issues relating to BoNT-A immunoresistance from the health care professionals' (HCPs') perspective. Understanding the implications of BoNT-A immunoresistance from the aesthetic patient's viewpoint allows HCPs to better support patients throughout their aesthetic treatment journey.
Methods: A real-world consumer study surveyed 363 experienced aesthetic BoNT-A recipients across six Asia-Pacific territories. The survey mapped participants' BoNT-A aesthetic treatment journey and characterized awareness and attitudes relating to BoNT-A immunoresistance and treatment implications. At the second Aesthetic Council on Ethical use of Neurotoxin Delivery meeting, panelists discussed survey findings and developed consensus statements relating to the impact of BoNT-A immunoresistance on the aesthetic treatment journey.
Results: Aesthetic BoNT-A patients' depth of knowledge about BoNT-A immunoresistance remains low, and risk/benefit communications need to be more lay-friendly. The initial consultation is the most important touchpoint for HCPs to raise awareness of BoNT-A immunoresistance as a potential side effect considering increased risk with repeated high-dose treatments. HCPs should be cognizant of differences across BoNT-A formulations due to the presence of certain excipients and pharmacologically unnecessary components that can increase immunogenicity. Standardized screening for clinical signs of secondary nonresponse and a framework for diagnosing and managing immunoresistance-related secondary nonresponse were proposed.
Conclusion: These insights can help patients and HCPs make informed treatment decisions to achieve desired aesthetic outcomes while preserving future treatment options with BoNT-A. *(Plast Reconstr Surg Glob Open 2024; 12:e5892; doi: 10.1097/GOX.0000000000005892; Published online 20 June 2024.)*

INTRODUCTION

Aesthetic practitioners are increasingly faced with issues relating to botulinum neurotoxin A (BoNT-A) immunoresistance, due to the formation of BoNT-A neutralizing antibodies (NAbs) with repeated treatments.[1–4] NAbs can lead to reduced BoNT-A therapeutic efficacy,

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resulting in partial or complete secondary nonresponse (SNR).[3,5,6] Because BoNT-A has important therapeutic and aesthetic applications, loss of this treatment option has potentially serious consequences for patients. It has been proposed that shared decision-making between aesthetic practitioners and patients is vital to minimize the risk of BoNT-A immunoresistance, thereby preserving future treatment options.[5] Specifically, careful selection of highly purified, low-immunogenicity BoNT-A formulations, the lowest effective dose, and the longest acceptable treatment interval can minimize exposure to immunogenic material.

To meet increased demand for aesthetic BoNT-A treatment worldwide, the range of BoNT-A formulations has expanded well beyond the three established formulations, onabotulinumtoxinA (Botox/Vistabel), abobotulinumtoxinA (Azzalure/Dysport), and incobotulinumtoxinA (INCO, Bocouture/Xeomin).[7–10] All BoNT-A formulations contain the same 150 kDa core neuromodulator (from the *Clostridium botulinum* Hall A strain). However, BoNT-A formulations are known to differ in terms of purity, specific bioactivity and excipient content (Table 1), and consequently in their immunogenic potential. Most available BoNT-A formulations contain pharmacologically unnecessary components (eg, complexing proteins, inactive neurotoxin, clostridial DNA[3]), and/or excipients that could increase the risk of an immune response (Table 1). We refer readers to publications with more in-depth discussion of the role that adjuvants play in the adaptive immune response and the risk of BoNT-A neutralizing antibody formation.[5,14–17] Although the recently introduced daxibotulinumtoxinA (DAXI, Daxxify) and Coretox formulations are described as complexing protein-free, they contain potentially immunogenic excipients, such as polysorbate-20 and RTP004.[18,19] Polysorbates can have direct adjuvant properties (polysorbate-20 is used as an adjuvant in vaccines[20]); or indirect immunogenic effects due to their propensity to auto-oxidize and form free radicals that might chemically alter protein structure and increase the immunogenicity of a BoNT-A formulation.[21,22] RTP004, a highly positively charged synthetic peptide derived from the human immunodeficiency virus-1 TAT protein, is reported to bind strongly to and stabilize the BoNT-A core complex by preventing adsorption to surfaces.[23,24] In DAXI, RTP004 is present in a large molar excess to BoNT-A, and may bind to negatively-charged areas on BoNT-A to create novel structures (neo-epitopes) that could theoretically be targets for an immune response. To date, INCO is the only available formulation known to be free from complexing proteins and to contain only immunologically inert excipients including human serum albumin and sucrose.[15,25,26] Previous studies reported no signs of NAb or SNR in patients exclusively treated with INCO,[14,16] and a recent study reported absence of NAb development in patients with focal dystonia who exclusively received INCO despite long-term treatment.[15]

In a previous publication following the first Aesthetic Council on Ethical Use of Neurotoxin Delivery (ASCEND) meeting,[5] we discussed issues surrounding BoNT-A immunoresistance from the perspective of health care professionals (HCPs), highlighting notable gaps in documenting BoNT-A use in real-world aesthetic practice and understanding patients' treatment-seeking behavior. To support aesthetic patients in optimizing their BoNT-A treatment journey, it is vital to understand the potential impact and implications of BoNT-A immunoresistance from their perspective, particularly in light of recent trends: initiating treatments at a younger age, often involving multiple face/body indications, and off-label indications involving high doses.[10,27,28] A real-world consumer study was commissioned to (1) map the typical treatment journey of experienced aesthetic BoNT-A recipients across the Asia-Pacific region and (2) characterize awareness and attitudes relating to BoNT-A immunoresistance and implications for treatment, including declining efficacy. The study focused on experienced aesthetic patients who receive significant doses of BoNT-A at regular intervals, who may represent a group at higher risk of developing BoNT-A immunoresistance. Here, we highlight key findings and accompanying insights from the second multidisciplinary ASCEND meeting.

Takeaways

Question: What are key implications of botulinum neurotoxin A (BoNT-A) immunoresistance for aesthetic patients?

Findings: The Aesthetic Council on Ethical Use of Neurotoxin Delivery (ASCEND) multidisciplinary panel discussed real-world survey findings in experienced aesthetic BoNT-A recipients, which revealed that experience of declining efficacy is relatively common, but there is limited understanding of BoNT-A immunoresistance risk, causes, and implications for future treatment. ASCEND's consensus emphasizes informed discussion from initial consultation for planning treatment and selecting BoNT-A formulations.

Meaning: Considering increased immunogenic risk with repeated high-dose treatments, it is vital that health care professionals and patients consider BoNT-A immunoresistance as a potential side effect in treatment decision-making to achieve desired outcomes while preserving future treatment options with BoNT-A.

Mapping the Aesthetic BoNT-A Treatment Journey: An Asia-Pacific Survey

This real-world study surveyed 363 participants recruited from online consumer panels across Australia, Hong Kong SAR China, Singapore, South Korea, Taiwan, and Thailand in November 2022. The aim was to assess the real-world impact of BoNT-A immunoresistance and

Disclosure statements are at the end of this article, following the correspondence information.

Related Digital Media are available in the full-text version of the article on www.PRSGlobalOpen.com.

Table 1. Characteristics and Properties of BoNT-A Formulations Currently Available on the Market[1,3,7,11–13]

Generic Name	Trade Name	Manufacturer	Storage Conditions	BoNT-A Neurotoxin	Complexing Proteins Present	Formulation (Excipients)	Mean Concentration of Neurotoxin (pg/100U)	Potency (U/ng Neurotoxin)	Calculated Proportion of Inactive Neurotoxin (%)
OnabotulinumtoxinA	Botox/ Vistabel	Allergan Inc. (Allergan Pharmaceuticals)	2–8°C	900 kDa complex	Yes	0.5 mg I 0.9 mg NaCl	730	137	40
AbobotulinumtoxinA	Dysport/ Azzalure	Ipsen Biopharm Limited	2–8°C	300–500 kDa complex	Yes	0.125 mg I 2.5 mg lactose	650	154	32
IncobotulinumtoxinA	Xeomin/ Bocouture	Merz Pharmaceuticals	Room temperature (20–25°C)	150 kDA purified toxin	No	1 mg I 4.7 mg sucrose	416–440	227–240	Not found
LetibotulinumtoxinA	Botulax/ Letybo	Hugel Inc	2–8°C	Complex*	Yes	0.5 mg I 0.9 mg NaCl	844	118	103
-	Meditoxin/ Neuronox	Medytox Inc	2–8°C	Complex*	Yes	0.5 mg I 0.9 mg NaCl	575	174	38
PrabotulinumtoxinA	Nabota	Daewoong	2–8°C	900 kDa complex	Yes	0.5 mg I 0.9 mg NaCl	754	133	81
-	Relatox	Microgen	2–8°C	900 kDa complex	Yes	6 mg Gelatin 12 mg Maltose	578	173	33
LanbotulinumtoxinA	CBTX-A/ Prosigne/ Lantox	Lanzhou Institute of Biological Products	2–8°C	900 kDa complex	Yes	Gelatin Dextran Sucrose	Unknown	Unknown	Unknown
NivobotulinumtoxinA	Innotox	Medytox Inc	2–8°C	Complex*	Yes	Polysorbate	Unknown	Unknown	Unknown
DaxibotulinumtoxinA-lanm	Daxxify	Revance	Room temperature (20–25°C)	150 kDA core toxin	No	11.7 µg RT004-peptide 0.1 mg Polysorbate-20 0.65 mg L-Histidine-HCl monohydrate 36 mg Trehalosedihydrate	Unknown	Unknown	Unknown
—	Coretox	Medytox Inc	2–8°C	150 kDA core toxin	No	3.0 mg Sucrose 0.9 mg NaCl Polysorbate-20 L-Methionine	Unknown	Unknown	Unknown

*No manufacturer information available.
I, human serum albumin; NaCl, sodium chloride.

explore its implications for patients and HCPs. Only experienced BoNT-A recipients (≥6 treatments for face or body applications in the past 36 mo) were surveyed (Fig. 1). Because most aesthetic BoNT-A recipients are female,[29] only women were enrolled. Eligible participants were 21–55 years, had a middle to high monthly household income, and intended to receive future BoNT-A treatments. Detailed methods and participant selection criteria are described in Supplemental Digital Contents 1–3. (**See figure, Supplemental Digital Content 1**, which describes methods for targeted literature review and consumer study and expert panel discussion and consensus. **http://links.lww.com/PRSGO/D279**.) (**See figure, Supplemental Digital Content 2**, which displays the eligibility flowchart for the targeted literature search. **http://links.lww.com/PRSGO/D280**.) (**See figure, Supplemental Digital Content 3**, which displays the summary of hits from targeted literature search on PubMed database. **http://links.lww.com/PRSGO/D281**.) Participant characteristics are summarized in Table 2.

Understanding of BoNT-A Treatment Concepts

"True/false" questions on BoNT-A treatment (efficacy, safety, and side effects) and formulations were used to explore participants' knowledge and beliefs about aesthetic BoNT-A treatment (Table 3). Although most participants knew that BoNT-A treatments can improve appearance and reduce wrinkles (90%) and relax muscles (86%), fewer participants knew that BoNT-A can be used to treat medical conditions (36%). Participants were generally aware that BoNT-A treatment effects last 3–4 months on average (87%), and that the dose used depends on the areas treated (87%).

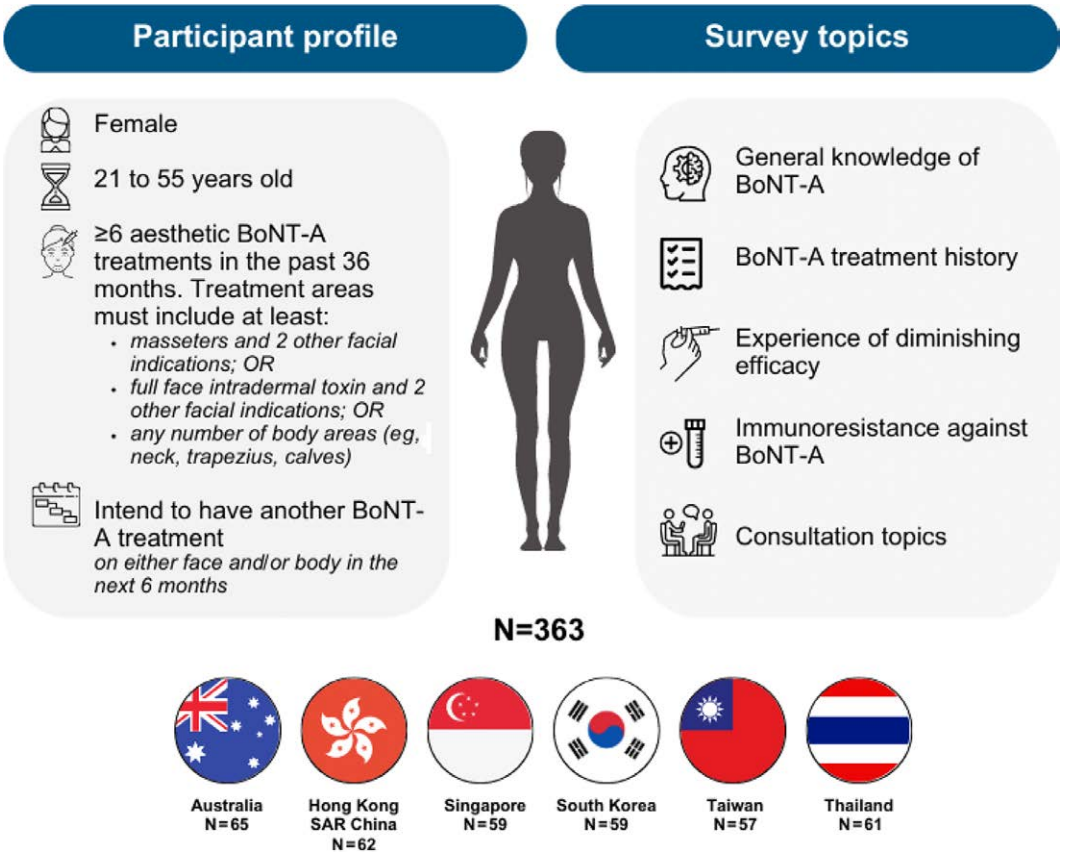

Fig. 1. Overview of Asia-Pacific consumer survey on the aesthetic BoNT-A treatment journey.

Although 75% of participants knew that repeated treatments can lead to development of immunoresistance against BoNT-A, 45% thought that future injections would always be effective if the first injection was effective (Table 3). This suggests that many participants did not perceive links between BoNT-A immunoresistance and its consequences, including weakening/loss of treatment efficacy over time.

Overall, 61% of participants were aware that all BoNT-A formulations have the same mechanism of action. However, 66% thought that all BoNT-A formulations are pure and free of complexing proteins and unnecessary bacterial components (**Table 3**).

Experience of Declining BoNT-A Treatment Efficacy of BoNT-A and Its Impact

Within this sample of experienced BoNT-A recipients, 92% had experienced one or more symptom and 49% had experienced three or more symptoms of declining efficacy (Fig. 2). Participants reported various emotions after experiencing declining treatment efficacy. Although some participants reported feeling in control (37%), others felt uncertain (25%), anxious (23%), distressed (23%), and/or stressed (20%). Besides the direct emotional impact of experiencing declining efficacy, measures taken to manage the issue, such as taking extended treatment breaks, can have an additional impact. [**See figure, Supplemental Digital Content 4,** which displays (a) emotional impact of (A) declining BoNT-A efficacy and (B) extended breaks between treatments on participants. (b) Emotional impact of (A) declining BoNT-A efficacy and (B) extended breaks between treatments on participants. **http://links.lww.com/PRSGO/D282**.]

Most participants who experienced declining BoNT-A efficacy chose to continue treatment but switched to a different BoNT-A formulation and/or a different clinic/aesthetic practitioner (Fig. 3). Over half (57%) switched to a different BoNT-A formulation but continued their treatment with the same clinic/aesthetic practitioner, whereas 33% and 34% continued treatment with a different clinic/aesthetic practitioner using the same or different BoNT-A formulation, respectively. Participants generally waited for no more than 3–6 months before their next BoNT-A treatment (Fig. 3).

Most participants (72%) reported switching BoNT-A formulations at least once, most commonly due to their HCP's recommendation (49%) or wanting to try a new formulation (41%). Notably, some reasons given for switching BoNT-A formulations were potentially immunoresistance-related: dissatisfaction with treatment experience and/or outcomes with the current formulation (38%); treatment effects were not as long-lasting (37%), or weaker/less prominent than before (26%); higher doses or shorter treatment intervals were required to achieve the same effect (12%) (Fig. 4).

Table 2. Sociodemographic Characteristics and Aesthetic BoNT-A Treatment History of Respondents

Variables	Total
No. respondents, %	363 (100.0)
Age (y), average	36.8
Age (y), %	
21–30	21.0
31–40	49.0
41–50	24.0
51–55	6.0
Income, %	
High*	40.0
Middle†	60.0
Type of work, %	
Professional or higher technical work‡	28.0
Manager or senior administrator§	43.0
Clerical¶	16.0
Sales or services‖	4.0
Supervisor or other works**	1.1
Skilled manual work††	0.6
Semi-skilled or unskilled manual work‡‡	0.8
Others§§	6.0
No. treatments in the past 3 y, %	
6–8	53.0
≥9	47.0
Areas ever treated with BoNT-A, %	
Upper face§§	96.0
Lower face¶¶	94.0
Full face‖‖	42.0
Body***	71.0
Administering HCP, %	
Licensed dermatologist	20.0
Licensed plastic surgeon	33.0
Licensed aesthetic physician	45.0
Licensed aesthetic/cosmetic nurse	2.2

*High monthly household income—Australia: >10,000 AUD; Hong Kong: >100,000 HKD; Singapore: >10,000 SGD; South Korea: >7,500,000 SKW; Thailand: >75,000 THB; Taiwan: >150,000 NTD.
†Middle monthly household income–Australia: 7501–10,000 AUD; Hong Kong: 60,001–100,000 HKD; Singapore: 7501–10,000 SGD; South Korea: 4,500,001–7,500,000 SKW; Thailand:45,001–75,000 THB; Taiwan: 90,001–150,000 NTD.
‡Work that requires at least degree-level qualifications (eg, accountant, school teacher, university lecturer, social worker, and systems analyst).
§For example, company director, finance manager, personnel manager, senior sales manager, and senior local government office.
¶For example, clerk, secretary, and administrative assistant.
‖For example, commercial traveler, shop assistant, nursery nurse, care assistant, paramedic, and customer service.
**For example, supervisor of cleaning workers.
††For example, cook and hairdresser.
‡‡For example, machine operator, assembler, waiter, cleaner, bar worker, and call center worker.
§§Upper face: browlift, bunny lines or nasal flare, crow's feet, (horizontal) forehead lines, frown lines, that is, glabellar and under eye.
¶¶Lower face: chin (cobblestone chin)–mentalis, marionette lines, nasal tip elevation, lip lines, masseters, salivary gland reduction, smile lines/gummy smile.
‖‖Full face refers to intradermal lift, skin lifting, or mesotoxin.
***Body comprises shoulder muscles (trapezius), upper arm (deltoid), calf, neck, and hyperhidrosis (excessive sweating).

The survey also confirmed that clinic switching is common in aesthetic practice in the Asia-Pacific region, with 60% of participants switching clinics at least once, and 13% switching three or more times. Most participants received three or more treatments before they first switched clinics. **(See figure, Supplemental Digital Content 5,** which displays the history of clinic switching behavior. **http://links.lww.com/PRSGO/D283**.) Similar reasons were cited for switching clinics as for switching formulations, including reasons potentially related to BoNT-A immunoresistance (Fig. 5). Notably, 33% of consumers switched clinics because they wanted to perform another treatment although their aesthetic practitioner recommended a break from treatment.

Topics Discussed with HCPs during Consultation

Cost (68%), duration of treatment effects (67%), and possible side effects (65%) were most frequently discussed. Available BoNT-A formulations (54%) and immunoresistance to BoNT-A (53%) were also discussed. (**See figure, Supplemental Digital Content 6,** which displays the discussion topics during consultation with HCP for aesthetic BoNT-A treatment. **http://links.lww.com/PRSGO/D284**.) Interestingly, only 8% of participants regarded cost as one of their top three considerations when selecting a BoNT-A formulation. (**See figure, Supplemental Digital Content 7**, which displays top considerations for consumers when choosing a BoNT-A formulation for their aesthetic treatment. **http://links.lww.com/PRSGO/D285**.) The top considerations were expected treatment results (50%), aesthetic practitioner's recommendations (47%), lower risk of side effects (39%), and duration of treatment effects (39%). Notably, issues that participants were most concerned with (ie, effectiveness, duration of treatment results and side effects) can be negatively influenced by BoNT-A immunoresistance. However, only 28% of participants selected lower risk of NAb formation as one of the top three factors influencing their choice of BoNT-A formulation. This suggests many participants remain unaware that BoNT-A immunoresistance is a potential side effect that can influence treatment outcomes and experience. Highlighting this association during consultation could help patients to make informed choices when selecting a BoNT-A formulation.

Panel Discussion and Consensus: Recognizing Real-world Implications of BoNT-A Immunoresistance and Optimizing the Aesthetic Treatment Journey

A summary of consensus statements relating to general knowledge of BoNT-A and immunoresistance, the patient treatment journey, and diagnosis and management of NAb-related SNR are provided in Table 4. Criteria used for determining consensus on statements are described in Supplemental Digital Content 1 (**http://links.lww.com/PRSGO/D279**). When discussing the Asia-Pacific consumer study findings, the panel noted that the study provided valuable quantitative insights into the experiences, motivations, and treatment-seeking behaviors of aesthetic patients across the region, particularly experienced BoNT-A recipients who are likely to continue long-term BoNT-A treatment. Survey participants were receiving high-dose and/or off-label BoNT-A aesthetic treatments, reflecting current trends, and may represent a group at higher risk

Table 3. Knowledge and Beliefs Relating to Aesthetic BoNT-A Treatment

Statement	T/F*	Selected Correct Answer (%)
BoNT-A improves appearance and reduces wrinkles	T	90.0
The dose of BoNT-A is dependent on the areas treated	T	87.0
BoNT-A treatment effect lasts 3–4 mo on average	T	87.0
BoNT-A relaxes muscles	T	86.0
BoNT-A may spread outside the injected muscle	T	60.0
A higher dose of BoNT-A may result in increased effectiveness of the treatment	T	57.0
Side effects cannot be reversed with antitoxin	T	51.0
If the first injection is effective, future injections will always be as effective	F	45.0
You can only use one BoNT-A brand throughout your aesthetic journey	F	44.0
BoNT-A cannot be used to treat medical conditions	F	36.0
You can administer BoNT-A to only one muscle during each session	F	35.0
BoNT-A treatments are generally safe, if injected by a qualified doctor or nurse	T	80.0
All licensed physicians are authorized to administer BoNT-A injection(s)	T	52.0
All licensed nurses are authorized to administer BoNT-A injection(s)	T/F†	55.0
All beauty consultants are authorized to administer BoNT-A injection(s)	F	55.0
BoNT-A is known to be safe during pregnancy	F	45.0
BoNT-A has no drug interactions	F	40.0
BoNT-A treatment(s) may give rise to the development of immunoresistance against BoNT-A	T	75.0
The mechanism of action for all BoNT-A brands is the same	T	61.0
All BoNT-A brands are pure, free of complexing proteins and unnecessary bacterial components	F	34.0

*Participants were asked to indicate whether they believed each statement to be true (T) or false (F). The percentages selecting the correct answer (T or F) are shown.
†Correct answer (T or F) according to applicable local regulations; in certain territories, licensed nurses are authorized to administer BoNT-A injections. For Australia, the regulations vary by state.

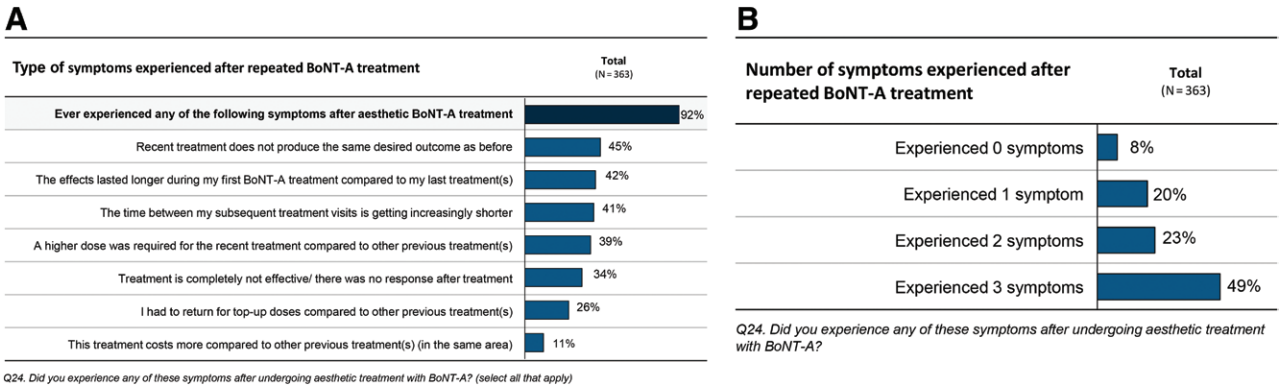

Fig. 2. Participants' experience of symptoms of declining efficacy BoNT-A treatment. A, Type of symptoms experienced. B, Number of symptoms experienced.

of developing BoNT-A immunoresistance. In contrast, published meta-analyses provide data primarily on low-dose approved indications (eg, glabellar lines) with limited follow-up (6–18 mo), representing considerably lower exposure than in typical real-world settings; perhaps unsurprisingly, the estimated incidence of BoNT-A NAb-related SNR in these meta-analyses was low.[5,30] Panelists noted that observations on declining BoNT-A efficacy in the survey sample (nearly 50% with three or more symptoms) corroborate the increasing trend in suspected/confirmed cases of NAb-related SNR that they or their peers have encountered in recent years.[2,10] This provides clear motivation for both practitioners and their patients to carefully consider the potential causes and consequences of BoNT-A immunoresistance when planning treatment.

Consumers' Current Understanding of BoNT-A and Immunoresistance

The findings highlight addressable gaps in communicating the balance of risks and benefits associated with BoNT-A treatment to enhance patient understanding. Although most survey participants reported that they were aware of and informed about "immunoresistance," the responses suggest a lack of in-depth understanding of its implications for their treatment, especially in the long term. Although awareness of the term "immunoresistance" has increased, many patients may not understand the concept, causes, or consequences sufficiently to make informed treatment choices without effective guidance from their aesthetic practitioner.

Thus, the panel concurred that there is a need to improve communication surrounding BoNT-A treatment by using lay-friendly language, and making information

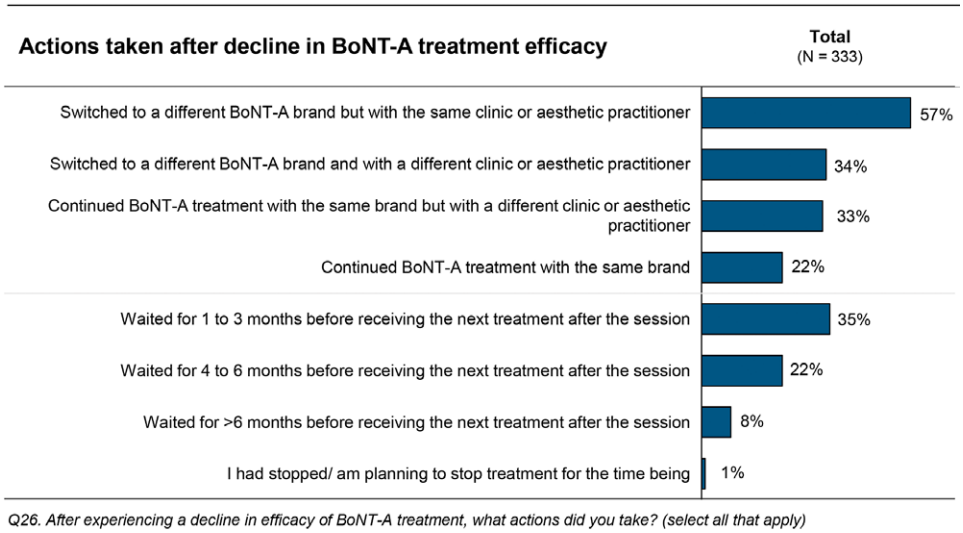

Fig. 3. Actions taken by participants following a decline in BoNT-A efficacy.

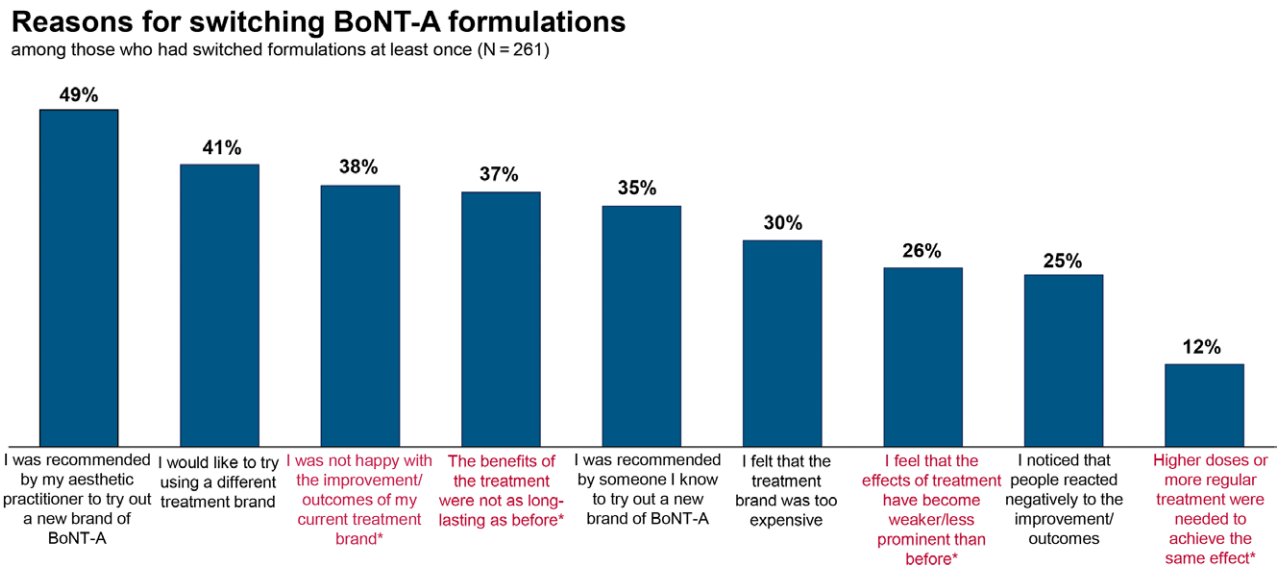

Fig. 4. Reasons for switching BoNT-A formulations (N = 261 who had previously switched formulations). *Attribute potentially related to BoNT-A immunoresistance. Q14. Why did you decide to switch brands of BoNT-A?

more accessible to patients (Table 4). It is especially important to help patients realize that the tangible outcomes they consider important (cost, efficacy, treatment longevity, and safety/side effects) could be compromised by developing BoNT-A immunoresistance. One suggestion to make the concept of BoNT-A immunogenicity more accessible was to draw parallels with vaccination. The panel also recognized that patient-directed communications on immunoresistance may require tailoring for different levels of awareness and willingness to engage in shared decision-making, calling for further research.

With the survey showing only 36% of the participants knew that BoNT-A can be used to treat medical conditions, the panel stressed the importance of recognizing that BoNT-A is ultimately a therapeutic drug and its use is associated with both risks and benefits. Because the immune system cannot discriminate between therapeutic and aesthetic use, the risks of immunoresistance should not be overlooked in either setting.[5]

Enhancing Patient-HCP Consultations to Optimize the Aesthetic Treatment Journey

The panel discussed strategies to minimize the risk of declining treatment efficacy and immunoresistance to BoNT-A at each step of the aesthetic treatment journey. HCPs are the most trusted sources of BoNT-A treatment advice and recommendations and, therefore, have the opportunity and responsibility to offer balanced advice on questions relating to safety (treatment risks and side effects, including immunoresistance), treatment outcomes (ie, efficacy), and

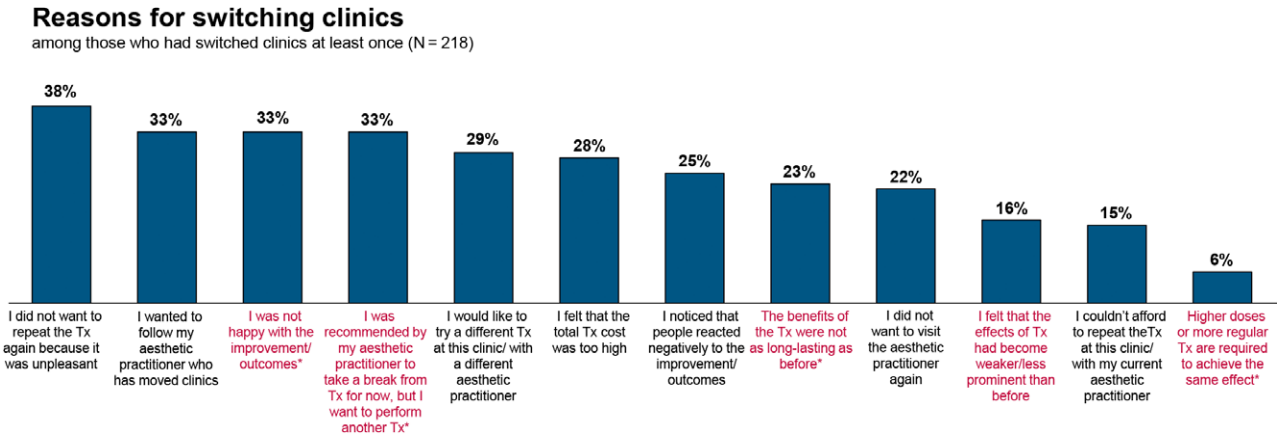

Fig. 5. Reasons for switching clinics (N = 218 who had previously switched clinics). *Attribute potentially related to BoNT-A immunoresistance. Q20. Why did you decide to not repeat treatment with BoNT-A in the same clinic? Tx, treatment.

Table 4. Consensus Statements

Statements	Agreement (%)
General knowledge and immunoresistance	
Awareness of immunoresistance is growing, but consumers' depth of knowledge remains low and they poorly understand its clinical implications	100
Current communications around immunoresistance are not effective and language needs to be more lay-friendly	100
The concept of immunoresistance needs to be linked to tangible clinical outcomes that patients are concerned about (eg, cost, efficacy, treatment longevity, and side effects)	100
Communication strategies on immunoresistance should be tailored to different patient archetypes/profiles (eg, young versus old, higher versus lower income)	83
Patient treatment journey (consultation, treatment, switching) and sources of information	
The initial consultation session is the most important touchpoint to raise awareness of immunoresistance by showing association with treatment longevity and side effects	100
Aesthetic practitioners should actively ask if patients are concurrently receiving BoNT-A for a medical/therapeutic indication	100
Immunoresistance should be included as a potential treatment side effect when taking informed consent and be clearly documented in clinical notes	100
The behavior of clinic hopping poses a challenge to establishing a complete BoNT-A treatment history and contributes to the underreporting of BoNT-A immunoresistance in aesthetic practice	100
All clinic staff involved in patient management should be aware of the issue of immunoresistance and can play a role in patient education	100
Diagnosis and management of NAb-related SNR	
In the absence of MHDA, ELISA and frontalis tests are useful adjuncts that might indicate the presence of NAbs to guide management plans	100
In patients with partial SNR, further treatment or switching to another BoNT-A formulation with pharmacologically unnecessary components increases the risk of immunogenicity	100
In patients with partial SNR, switching to a BoNT-A formulation with lower risk of immunogenicity is a viable option	100
In patients with complete SNR, a treatment holiday (complete cessation of BoNT-A injections) of at least six months is recommended	100
When restarting treatment in complete SNR cases, a highly purified BoNT-A formulation with lowest risk of immunogenicity is recommended	100

cost. (**See figure, Supplemental Digital Content 8**, which displays top channels for consumers for BoNT-A information gathering. **http://links.lww.com/PRSGO/D286**.) Panelists concurred that the initial consultation session is the most important touchpoint to raise awareness of immunoresistance. During this initial touchpoint, HCPs can help patients understand the risk factors for developing BoNT-A immunoresistance and potential impact on their overall treatment experience, including treatment outcomes, side effects, and total cost. Although panelists considered it impractical to schedule a separate pretreatment consultation session for patient education and consent-taking before performing BoNT-A injections (unlike surgical procedures), they unanimously agreed on the importance of adequate, timely discussion of treatment risks and setting expectations. Panelists also agreed that BoNT-A immunoresistance should be mentioned as a potential side effect when taking informed consent for treatment and should be clearly documented in clinical notes.

Panelists noted that aesthetic patients who are receiving BoNT-A treatment for a medical condition (eg, migraine) often do not make their HCPs aware of this. The panel

concurred that aesthetic practitioners should actively ask patients about concurrent medical/therapeutic BoNT-A treatment. If HCPs learn that patients are receiving BoNT-A for multiple conditions, a coordinated treatment plan should be initiated, involving other treating HCPs and the patient, to better manage the extent of BoNT-A exposure and immunogenic risk. Unless a highly purified and lower immunogenicity BoNT-A formulation is used for all the treatments, the panel advised selecting the longest justifiable treatment interval, regardless of the indication. However, the panel acknowledged that follow-up and coordination can be very challenging, especially where several clinics/practitioners are involved. Furthermore, as the consumer study illustrates, the practice of switching clinics/aesthetic practitioners is common among experienced aesthetic BoNT-A recipients. As noted previously, this practice may hinder adequate follow-up and BoNT-A treatment history-taking, contributing to underreporting and/or missed diagnosis of immunoresistance.[5] Switching formulations may also be underreported as patients may not recall which formulation(s) they have received. This is particularly important, as having frequent formulation switches and the use of high initial doses are associated with higher risk of SNR development.[31]

The panel also highlighted that many aesthetic practitioners are still not aware or fully convinced of the risks and relevance of BoNT-A immunoresistance in aesthetic practice. In a recent survey of Asia-Pacific physicians, 24% of respondents believed that none of their patients had experienced treatment failure due to NAb formation.[2] The panel agreed that awareness of immunoresistance is important not only for HCPs but also for all clinic staff involved in patient management, as they can play a role in patient education.

Tailoring communication approaches to the needs of different groups and stakeholders is crucial. For HCPs, it is important to emphasize that BoNT-A formulations are not "all the same" although they have similar efficacy when used as indicated. The presence of certain excipients and pharmacologically unnecessary components can increase the immunogenicity of a formulation. With long-term and high-dose off-label use of BoNT-A becoming more common, using a highly purified BoNT-A formulation with the lowest immunogenic risk is the most cost-effective and clinically prudent option. Patient educational material should frame the implications of BoNT-A immunoresistance in terms of issues considered important (safety, efficacy, and cost). Causes of immunoresistance should also be explained in accessible language, to support and motivate choices that patients can make to retain the possibility of continued and/or future BoNT-A use. Most panelists shared the view that regulatory authorities could have a valuable positive influence in promoting recognition of BoNT-A immunogenicity as an issue warranting attention. Panelists also highlighted the importance of ensuring that highly purified, low-immunogenicity BoNT-A formulations are approved and available for both therapeutic and aesthetic indications, which would benefit the wider population of BoNT-A recipients.

Diagnosis and Management of NAb-related SNR

Next, the panel discussed current challenges with diagnosing and managing BoNT-A NAb-related SNR in aesthetic practice. To support SNR assessment and risk mitigation, simple screening tools and standardized tests should be made available to aesthetic practitioners in the Asia-Pacific region. Such tools should be as convenient/accessible and cost-effective as possible. The panel agreed that a standardized screening checklist for clinical signs/symptoms of SNR could be created and provided to HCPs for use during consultation and proposed a framework for diagnosing and managing NAb-related SNR (Fig. 6).

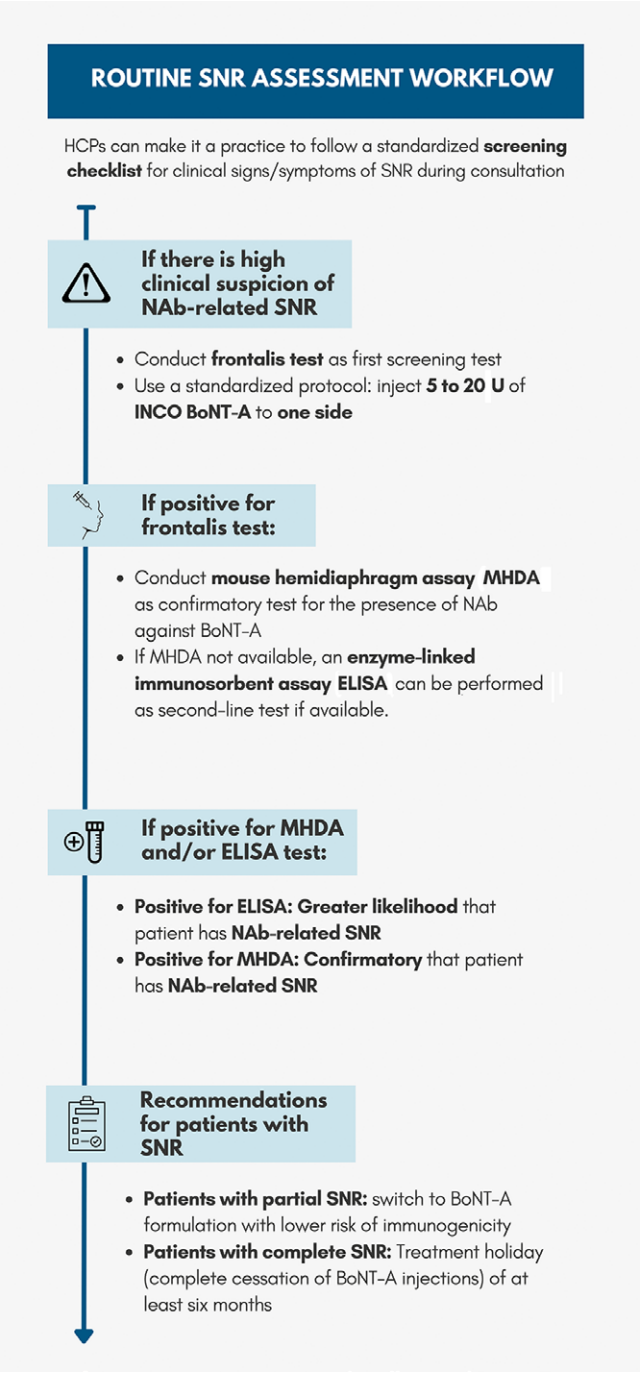

Fig. 6. Proposed workflow for diagnosis and managing NAb-related SNR. MHDA, mouse hemidiaphragm assay.

The panel also discussed standardizing the tests that HCPs can administer when they suspect NAb-related SNR, and the merits of the frontalis test for initial screening. The advantages of this test are ease of administration and clinical relevance,[32] the disadvantages being inability to detect early partial SNR and patient acceptability because correction may be needed to restore symmetry.[17] Some panelists suggested a "test" treatment with INCO to the frontalis muscle on both sides or other facial muscles (eg, orbicularis oculi muscle for crow's feet) to confirm clinical suspicion of SNR. The importance of using INCO for test treatments was emphasized, as repeated injection with BoNT-A formulations containing pharmacologically unnecessary components will increase the risk of an immune response, and should be avoided in patients with suspected partial SNR. Panelists proposed standardizing the frontalis test to injecting 5–20 U of BoNT-A (INCO) to one side. In patients with a positive frontalis test, confirmatory mouse hemidiaphragm assays (MHDAs[33]) can be performed. However, if the MHDA is not readily available/accessible, enzyme-linked immunosorbent assays (ELISAs[34–37]), where available, can be performed as a second-line test.[35,36] If a patient is positive for both frontalis and ELISA tests, there is a high likelihood of NAb-related SNR (Fig. 6). There was strong consensus that, in the absence of MHDA, ELISA and frontalis tests are useful adjuncts that might indicate the presence of NAbs to guide management plans.

In patients with partial SNR, the panel concurred that switching to a BoNT-A formulation with lower risk of immunogenicity is a viable option.[38–40] For complete SNR, complete cessation of BoNT-A injections for at least 6 months is recommended. For patients who had complete SNR and are considering restarting treatment, there was strong consensus that a highly purified BoNT-A formulation with lowest risk of immunogenicity should be recommended to minimize the risk of reactivating the immune system.[41]

CONCLUSIONS AND FUTURE DIRECTIONS

Long-term and regular BoNT-A use has become part of the contemporary aesthetic treatment landscape, along with widespread off-label applications with BoNT-A doses approaching those used in therapeutics. There is now a wider selection of BoNT-A formulations that differ in purity, bioactivity, and potential immunogenicity, which may be overlooked by many consumers and HCPs. With new insights into BoNT-A recipients' experiences and treatment-seeking motivations/behaviors, we have elaborated on measures previously proposed for optimizing the aesthetic treatment journey through effective shared decision-making (Fig. 7). It is important to optimize initial patient consultations to adequately communicate treatment risks and benefits, and gather important history details. This supports prudent treatment decisions,

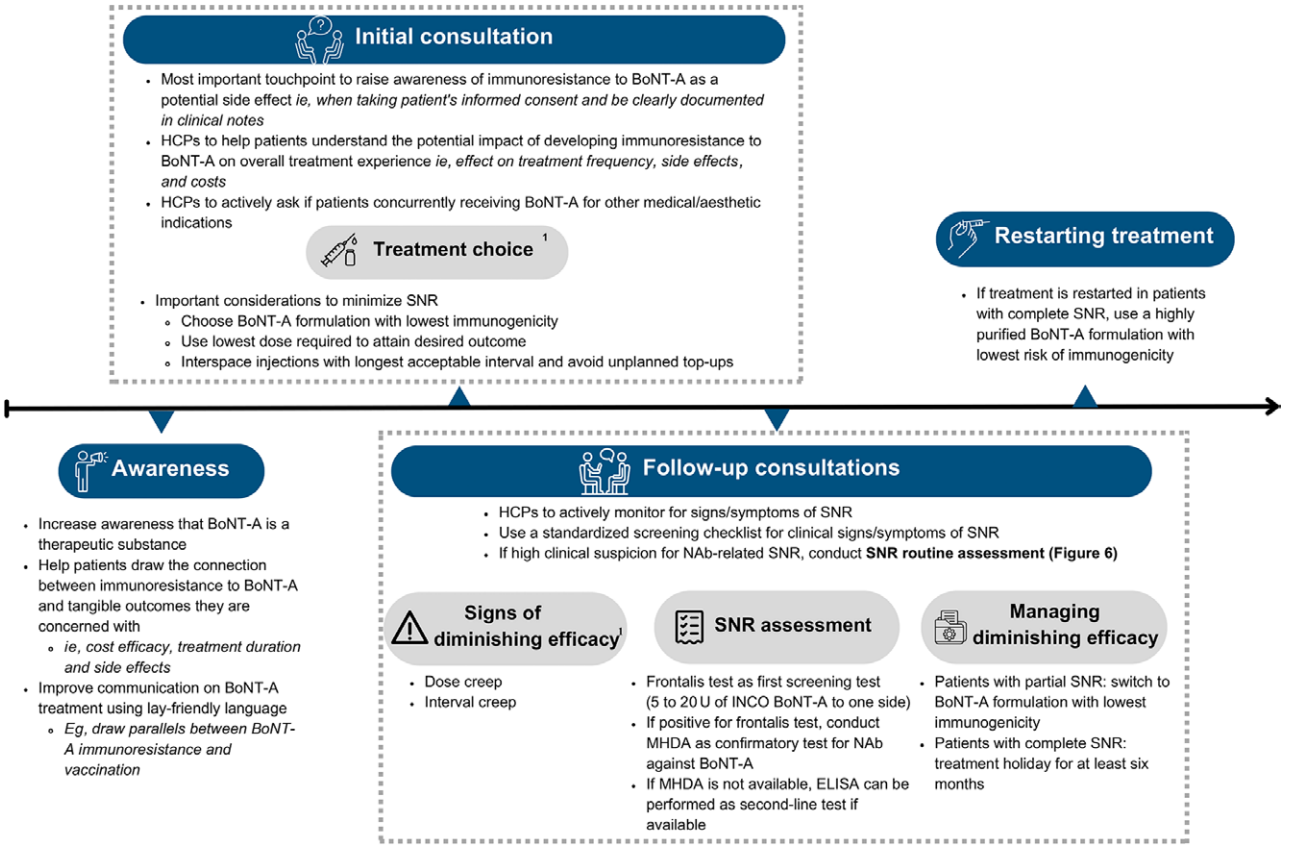

Fig. 7. Optimizing the BoNT-A aesthetic treatment journey. 1: Ho et al.[5]

including choice of BoNT-A formulations, doses, and treatment intervals. Follow-up consultations provide valuable opportunities to elicit information on signs of declining efficacy, and assess/manage SNR in a timely manner if it occurs. Taken together, these measures can help aesthetic patients and their HCPs to achieve the desired outcomes while preserving the possibility of future aesthetic or therapeutic BoNT-A use.

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DISCLOSURES

Dr. Corduff serves as a clinical advisor and speaker for Merz Aesthetics. Dr. Park serves as a consultant of Merz Aesthetics. Dr. Ho served as an advisory board member and consultant for Merz Aesthetics. Prof. Martin serve(d) as an ad-hoc consultant and speaker for Merz. Dr. Tseng serve(d) as a speaker, trainer, and advisory board member for Merz Aesthetics, AbbVie, Bausch & Lomb, Cynosure, Galderma, and Solta. Dr. Vachiramon serves as a speaker for Merz Aesthetics, LG Chem, Leo Pharma, Beiersdorf, L'Oreal, and as an advisory board member for Merz Aesthetics, AbbVie, and L'Oreal. Dr. Yu serves as a key opinion leader for Merz Aesthetic Philippines. Dr. Dingley is/was a speaker and advisor for and has received funding from Merz Aesthetics, Galderma, and Allergan. All authors have received honoraria from Merz Aesthetics for their contributions during the ASCEND panel meeting and subsequent manuscript preparation. The other authors have no financial interest to declare.

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