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Emerging Trends in Botulinum Neurotoxin A Resistance: An International Multidisciplinary Review and Consensus

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Background: Botulinum neurotoxin A (BoNT-A) injection is the most widely performed aesthetic procedure and a first-line therapeutic option for various medical conditions. The potential for BoNT-A immunoresistance and secondary nonresponse related to neutralizing antibody (NAb) formation warrants attention as the range of BoNT-A aesthetic applications continues to expand.
Methods: An international multidisciplinary panel reviewed published evidence on BoNT-A immunoresistance in aesthetic and therapeutic applications and discussed best practices integrating clinical, ethical, and aesthetic considerations. Consensus statements relating to awareness, assessment, and management of the risk of NAb-related secondary nonresponse in aesthetic practice were developed.
Results: There was a consensus that, as doses used in aesthetic practice become like those in therapeutics, rates of NAb formation may be expected to increase. However, the true extent of NAb formation in aesthetics is likely underestimated due to limitations of published evidence and variability in treatment patterns of aesthetic patients. Since BoNT-A therapy is often lifelong, practitioners need to recognize immunogenicity as a potential complication that might affect future therapeutic use and strive to minimize modifiable risk factors. The selection and use of a BoNT-A product with the least immunogenic potential from the beginning may thus be advantageous, especially when treatment with high doses is planned.
Conclusions: In view of current trends in BoNT-A aesthetic use, it is essential for practitioners to conduct thorough clinical assessments, inform patients of treatment risks, and develop BoNT-A treatment plans to minimize immunogenicity. This can help preserve the option of continued or future BoNT-A treatment with satisfactory outcomes. *(Plast Reconstr Surg Glob Open 2022;XX10X:e4407; doi: 10.1097/GOX.0000000000004407; Published online 20 June 2022.)*

INTRODUCTION

Injection of botulinum neurotoxin A (BoNT-A) has remained the most frequently performed aesthetic procedure since 1999. It accounted for one-third of 13.3 million minimally invasive aesthetic procedures performed in 2020 in the United States.[1,2] Beyond facial rhytid treatment, the range of BoNT-A aesthetic applications has expanded to include cosmetic treatment of masseteric hypertrophy and, more recently, body contouring.[3–7] BoNT-A is also considered a first-line treatment for various therapeutic indications.[8,9]

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BoNT-A, a potent neurotoxin produced by *Clostridium botulinum*, causes muscle paralysis by blocking synaptic neurotransmission.[9,10] Its therapeutic and aesthetic use derives from this ability to selectively weaken or paralyze the injected muscle group.[8–11] Since the effects of BoNT-A diminish over time, repeated injections are required to maintain the treatment effect. However, repeated injections of BoNT-A may stimulate antibody formation, including neutralizing antibodies (NAbs) that counteract its biological activity.[12,13] With NAb formation, the patient may develop partial or complete nonresponse to further BoNT-A treatment. This immunoresistance potentially has direct and long-term implications for future therapeutic options and should be considered in BoNT-A treatment decisions.

Three BoNT-A formulations [onabotulinumtoxinA (ONA), abobotulinumtoxinA (ABO), and incobotulinumtoxinA (INCO)] are currently approved by the US Food and Drug Administration (FDA) for therapeutic and aesthetic use.[11,14] Besides ONA, ABO, and INCO, an increasing number of other formulations are commercially available around the world.[15,16]

To highlight issues surrounding BoNT-A resistance and propose approaches for best practice, a multidisciplinary panel (Aesthetic Council for Ethical use of Neurotoxin Delivery) comprising 14 experts in aesthetic medicine, dermatology, plastic surgery, neurology, immunology, and bioethics was convened. This article reviews emerging concerns related to increasing BoNT-A use and possible immunoresistance due to NAb formation in the current aesthetic treatment landscape and discusses how BoNT-A treatment decision-making can integrate relevant biological, clinical, ethical, and aesthetic considerations.

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Takeaways

Question: How can aesthetic practitioners minimize risks of NAb formation and SNR with BoNT-A treatment?

Findings: An international multidisciplinary panel reviewed published evidence on BoNT-A immunoresistance and established a consensus on the need for awareness, assessment, and management of NAb-related SNR risks. The panel advocates for practitioners to recognize the potential impact of immunogenicity on future treatment options and strive to minimize modifiable risk factors.

Meaning: Since BoNT-A therapy is often lifelong, it is important for practitioners to minimize the risk of immunogenicity by using a highly purified BoNT-A and injecting the lowest dose required at appropriate intervals.

Emerging Trends in BoNT-A Resistance: An Overview of Recent Literature

Globally, BoNT-A usage has increased due to growing numbers of patients seeking treatment and expanding off-label applications.[6] With this growth, concerns have emerged regarding secondary nonresponse (SNR) to BoNT-A aesthetic treatment, initially highlighted in case reports.[17,18] SNR refers to the reduction or absence of therapeutic effects (partial or complete SNR) after initial successful treatments.[12,19,20] BoNT-A SNR may be related to NAb formation or other factors, including disease progression, inadequate dosage, incorrect muscle target, or improper injection technique.[12] Typical signs of SNR include dose or interval creep, wherein higher BoNT-A doses or shorter injection intervals are required to achieve the desired therapeutic effect. However, such signs may be overlooked, resulting in underrecognition of the issue.

For therapeutic BoNT-A use, rates of NAb formation have been estimated using systematic reviews/meta-analyses (SR/MAs) and clinical studies. The reported range is 0.3%–27.6%, highest for therapeutic applications involving high-dose BoNT-A, especially dystonias (1.3%–27.6%) and spasticity (0.3%–13%) (Table 1).[21–24] Reported NAb formation frequency was lowest for patients receiving INCO (0%–1.1%), followed by ONA (0.3%–5.6%) and ABO (0%–13.3%) (Table 2).[21,23,25–28] These overall estimates warrant careful interpretation because patients

Table 1. Reported NAb Formation Frequency by Therapeutic Indication

Indication	NAb Formation Frequency (%)	No. Publications
Dystonias	1.3–27.6	4[21–23,25]
Spasticity	0.3–13	4[21–23,25]
Hyperhidrosis	0.4–14	3[21,22,25]
Bladder disorders	2.6–6.2	2[21,25]
Blepharospasm	5.4	1[25]
Not specified	0.5–17	4[21,22,25,26]

Table 2. Reported NAb Formation Frequency in Therapeutic Indications, by Formulation*

Formulation	NAb Formation Frequency (%)	No. Publications
ABO	0–13.3	6[21,23,25–28]
ONA†	0.9–5.6	3[21,26,28]
ONA (new)	0.3–4.0	3[23,25,27]
ONA (old)	7.2	1[27]
INCO‡	0–1.1	6[21,23,25–28]
Not specified	1.9–2.5	2[21,27]

*Estimates in these studies may be associated with either overall use or exclusive use of the BoNT-A formulations studied.
†This publication did not distinguish between the old and new formulations of ONA.
‡Most patients had previously received ABO and/or ONA.

could have previous exposure to BoNT-A formulations other than those addressed in these studies. However, a similar trend is apparent when considering patients who exclusively used specific formulations: the percentages of patients with NAbs were 0%, 0.6%, and 5.3% with exclusive use of INCO, ONA, and ABO, respectively (Table 3).[22,23,26,28]

Although it is recognized that NAb-related SNR may arise in patients receiving high doses of BoNT-A for chronic medical conditions, the extent and clinical relevance of NAb formation in aesthetic treatment has been questioned, citing reasons such as the lower doses typically used in aesthetics.[29] There may also be a perception that the issue is not of substantive clinical concern because published reports of SNR in aesthetic settings have been relatively rare. However, this overlooks the potential cumulative effects of BoNT-A doses received over an individual's lifetime. Several off-label aesthetic BoNT-A applications involve higher amounts than on-label indications. Examples include masseter reduction (approximately 40–80 units of ONA/INCO per session) or calf contouring treatments where ≥100 units are injected per gastrocnemius.[5–7,17] High-dose intradermal BoNT-A injections are also increasingly popular, and these are believed to be more immunogenic than intramuscular injections due to high concentrations of dendritic cells (DCs) in the dermis.[30,31] Thus, total doses received for aesthetic procedures could easily reach the range used for therapeutic indications.

The real-world extent and implications of NAb formation in aesthetic practice remain unclear. Therefore, we systematically searched the published literature for information on BoNT-A-related NAb formation and SNR in aesthetic indications to complement what is known for therapeutic indications. (**See appendix, Supplemental Digital Content 1,** which displays the literature search for NAb formation and SNR in aesthetic indications, **http://links.lww.com/PRSGO/C78**.) We identified 18 relevant publications with data on NAb-related SNR with aesthetic use (Table 4). SR/MAs reported overall rates of NAb formation with aesthetic BoNT-A use ranging from 0.2% to 0.4%, lower than for therapeutic indications.[21,22,25] Except for one SR/MA focusing on ONA, these estimates represent various BoNT-A formulations and aesthetic applications.

Thirteen cases of NAb-related SNR emerging during aesthetic BoNT-A treatment were identified in case series or case reports, which would have been excluded from SR/MAs (Table 5).[17–19,40–41] Across these cases, we noted a pattern of regular repeated treatments (with the same or different formulations) before detection of SNR, usually with clear signs of dose and/or interval creep. In all cases, patients had initially or exclusively received ABO or ONA; three patients were switched to INCO after partial or complete SNR with previous treatments. Duration of therapy before NAb detection varied considerably (2–72 months). Systematic testing was uncommon, and it was unclear precisely when NAb formation first occurred in most cases. These observations illustrate the difficulty of identifying precisely when and how NAbs/SNR arose. Nevertheless, considering only patients treated exclusively with one formulation, no cases of NAb-related SNR have been reported with exclusive INCO aesthetic use. This is consistent with observations for therapeutic indications, even those requiring high BoNT-A doses.[23,26,28,35,37]

We note certain caveats in interpreting these estimates. First, the summary estimates reported in SR/MAs are based on data aggregated from randomized controlled trials and observational studies, and are limited by the heterogeneity of study designs and measured outcomes. Such estimates are convenient for overall description but may obscure meaningful variation due to differences in the design and intent of studies. For example, one SR/MA noted differences between studies that were or were not primarily designed to detect NAbs.[25] Second, all the published aesthetic studies on NAb formation and SNR evaluated only approved indications, such as glabellar lines,[21,22,25,43] whereas a large proportion of real-world BoNT-A use includes off-label applications involving higher BoNT-A doses. Third, follow-up periods were relatively short, ranging from 4 to 16 months, whereas it is known that NAbs typically develop over a more extended period of years.[24] For a complete view of NAb formation and SNR in clinical practice, one should consider the full range of published literature, including evidence from case reports and case studies. The frequency of BoNT-A NAb formation and SNR in real-world aesthetic practice

Table 3. Reported NAb Formation Frequency in Therapeutic Indications, by Formulation (Exclusive Use*)

Formulation	Patients with NAbs or Who Were Considered Nonresponders (n)	Total Number of Patients (N)	Percentage of Patients with NAbs or Nonresponders (n/N, %)	No. Publications
ABO	21	399	5.3	3[23,26,28]
ONA	19	2839	0.6	4[22,23,26,28]
INCO	0	529	0	3[23,26,28]

*Estimates in these studies were associated with exclusive use of the BoNT-A formulations studied.

Table 4. Identified Publications with Data on BoNT-A NAb-related SNR in Aesthetic Applications

Publication	Type	Application(s)
Borodic[32]	Case report	Facial lines
Borodic[33]	Case report	Facial lines
Cohen and Scuderi[34]	SR	Glabellar lines; crow's feet
Dressler et al[19]	Case series	Facial lines (four cases)
Fabbri et al[21]	SR/MA	Ax: glabellar lines Tx: dystonia, spasticity, urologic conditions, and hyperhidrosis
Fischer et al[35]	Clinical study (interventional)	Facial lines
Helmstaedter[36]	Clinical study (chart review)	Facial lines
Imhof and Kühne[37]	Clinical study (interventional)	Glabellar lines
Lacroix-Desmazes et al[27]	SR	Ax: glabellar lines Tx: dystonia, blepharospasm, spasticity, and urological indications
Lawrence and Moy[38]	Secondary analysis (safety and efficacy) of clinical trial data	Glabellar lines
Lee[17]	Case report	Masseteric hypertrophy
Naumann et al[22]	SR/MA	Ax: glabellar lines Tx: dystonia, urologic conditions, spasticity, and hyperhidrosis
Rahman et al[25]	SR/MA	Ax: glabellar lines and crow's feet Tx: dystonia, urological indications, spasticity, facial hemispasm, blepharospasm, and hyperhidrosis
Srinoulprasert et al[39]	Clinical study (interventional)	Aesthetic indications (various)
Stengel and Bee[18]	Case report	Glabellar lines
Stephan et al[40]	Case report	Facial lines
Torres et al[41]	Case series	Facial rejuvenation (four cases)
Wanitphakdeedecha et al[42]	Clinical study (interventional)	Aesthetic indications (various)

Ax, aesthetic indications; Tx, therapeutic indications.

may be higher than published estimates suggest. Although the reported frequency of NAb-related SNR appears relatively low for aesthetic versus therapeutic use of BoNT-A, the issue warrants further attention because of current aesthetic treatment trends and the potential implications of immunoresistance on access to future therapeutic options.

BoNT-A NAb Formation and Resistance: An Immunological Perspective

Although the true extent of NAb-related SNR in real-world practice remains unclear, the underlying biological process (how the immune system assesses and responds to the presence of BoNT-A or other biologic products) is well understood. This understanding can guide practitioners in evaluating the risk of immunogenicity and taking measures to manage that risk.

Immune system activation by BoNT-A (or any other antigen) is controlled via two key decision points (Fig. 1A, B). Both are necessary to stimulate classical T-helper cell-dependent antibody production. The first decision is made by DCs, which determine whether an antigen is potentially dangerous. Toll-like receptors (TLRs) on DCs recognize characteristic microbial cell surface features (eg, flagellin) as "danger signals." This triggers phagocytosis of the microbe or other "dangerous" particles by the DCs, which migrate to lymph nodes to act as antigen-presenting cells (APCs). APCs process the microbe or other "dangerous" particles and present the "dangerous" peptide antigens to naive T-helper cells while providing costimulatory signals to trigger clonal expansion of antigen-specific T-cells. The second decision involves antigen-specific T-cells that recognize presented peptide antigens as "foreign." Fully activated antigen-specific T-helper cells expand clonally and then support antigen-specific B-cell activation as well as their clonal expansion, finally producing antibodies against the original antigen. These two decisions are strictly hierarchical since naive T-helper cells always require peptide-antigen presentation by a fully activated DC.

The physiological BoNT-A supramolecular complex produced in nature by *C. botulinum* comprises the core 150-kDa neurotoxin and various neurotoxin-associated proteins (NAPs), including hemagglutinins (HAs) and non-HAs.[44] Of the FDA-approved formulations, ONA and ABO are known to include NAPs and/or other unnecessary bacterial proteins, whereas INCO contains only the core 150-kDa neurotoxin[10,45,46] (Fig. 1C). If a highly purified BoNT-A formulation is injected, peptides derived from the BoNT-A core neurotoxin subunits could be identified as "foreign" by naive T-helper cells.[47] However, the pure bioactive 150-kDa core neurotoxin lacks the concomitant "danger signals" required to fully activate DCs to become APCs. Without these signals, the first decision-maker (the DCs) would not register BoNT-A core neurotoxin subunits as "dangerous," escaping the immune cascade.[46] In contrast, NAPs, such as HA-33, and other bacterial contaminants, particularly flagellin, inactive/denatured toxin, and clostridial DNA, can trigger an immune response.[11,13,46] HA-33 is reported to be an immune response stimulator,[48] whereas flagellin and clostridial DNA are adjuvants that bind readily to TLR5 and TLR9 on DCs, respectively, activating the immune cascade.[49,50] In the context of BoNT-A treatment, NAPs have no therapeutic role and merely enhance the immunogenicity of the injected product.[10,11,45,46,51]

It is, thus, clear that antigen-specific immune activation by BoNT-A is not determined by the indication (therapeutic versus aesthetic) for which it is administered. Instead, factors that could influence the risk of NAb formation with a given BoNT-A formulation include its purity, dose administered, and the number and interval between injections. These factors are generally modifiable within a BoNT-A treatment plan. As noted, the purity of

Table 5. Summary of BoNT-A NAb Formation and Secondary Nonresponse Reported in Aesthetic Cases

No.	Publication	Age	Sex	Condition	Treatments	Intervention	Results	Duration of Treatment before NAb Detection
1	Borodic[32]	48	F	Facial lines	1–14 >14	ONA ONA	Cycles 1–14: response lasted for 3–4 mo Cycle >14: no response	Unclear when NAb test was done. Duration (first to last treatment): 72 mo
2	Borodic[33]	44	F	Facial lines	1–14 15	ONA 30–50 U ONA 100 U	Cycle 15: no response, no effect on forced frown	Unclear when NAb test was done. Duration (first to last treatment): 60+ mo
3	Dressler et al[19]	53	F	Facial lines	1–10	ABO 10–180 MU	Cycles 1–5: normal response Cycles 6–9: PSNR Cycle 10: CSNR	NAb detected (7.0 mU/mL) at cycle 10
4	Dressler, 2010[19]	46	F	Facial lines	1–3 4 5–6 7–9	ONA 80 MU BoNT–B ONA 40–136 MU BoNT–B	Cycle 1: normal response Cycle 2: PSNR Cycle 3: CSNR Cycles 5–6: CSNR	NAb detected (2.7 mU/ml) at cycle 6
5	Dressler et al[19]	51	F	Facial lines	1–9 10–13	ABO 30 MU ONA 30 MU	Cycles 1–11: normal response Cycle 12: PSNR Cycle 13: CSNR	NAb detected (1.0 mU/mL) at cycle 12, and (>10.0 mU/mL) at cycle 13
6	Dressler et al[19]	45	F	Facial lines	1–6 7	ABO 25–105 MU INCO 33 MU	Cycle 3: PSNR Cycle 5: CSNR	NAb detected (>10.0 mU/ml) at cycle 7
7	Lee[17]	20	F	Masseteric hypertrophy	1–6 7	ONA 180 U ABO 180 U	Cycles 1–3: response lasted for 4–5 mo Cycles 4–5: response lasted for 1.5 mo Cycles 6–7: no response	>18 mo
8	Stengel and Bee[18]	41	F	Glabellar lines	1–5 6–8 9–11	ABO ONA 9–28 U INCO 20–44 U	Cycles 1–2: response lasted for 4–8 mo Cycles 3–11: response lasted for 3–4 wk	72 mo
9	Stephan et al[40]	51	F	Facial lines	1–3 NR NR	ONA, ABO ONA 75 U INCO	Cycles 1–3: partial response (<2 mo), required high-dose booster injections Cycle >3: partial response with even shorter duration of efficacy	NAb testing was not available
10	Torres et al[41]	55	F	Facial rejuvenation	1 2	ONA 33 U ABO 80 SU	Cycle 1: no response Cycle 2: mild response lasting 3 mo	2 mo
11	Torres et al[41]	54	F	Facial rejuvenation	1–8 9 10 11	ABO 25–180 U ONA 70 U ABO 120 U INCO 69 U	Cycles 1–7: normal response Cycle 8: loss of efficacy Cycle 9: little treatment effect Cycle 10: no effect after 4 wk Cycle 11: no effect after 2 wk	Unclear when NAb test was done.
12	Torres et al[41]	43	F	Facial rejuvenation	1–6	ABO 100–260 U	Initial response lasted for 6–8 mo, decreased to 3 mo at later treatments	Unclear when NAb test was done. Duration (first to last treatment): 96 mo
13	Torres et al[41]	38	M	Facial rejuvenation	1–3	ABO 120–250 U	Cycle 3: CSNR	Unclear when NAb test was done. Duration (first to last treatment): 36 mo

CSNR, complete secondary nonresponse; F, female; M, male; MU, mouse unit; NR, not reported; PSNR, partial secondary nonresponse; SU, speywood unit; U, unit.

each formulation and the presence of potential adjuvants are product-specific features. High doses or repeated injections increase the exposure to potentially "dangerous and foreign" material. Thus, a risk-based approach, such as that outlined by the FDA and European Medicines Agency (EMA),[52,53] seems eminently applicable to evaluate and manage the risk of immunogenicity associated with therapeutic protein products when used for aesthetics.

Navigating the Complex Landscape of BoNT-A Treatment Decision-making

Advances in BoNT-A treatment have engendered new aesthetic enhancement possibilities and challenges for everyday practice, particularly in terms of decision-making. For example, practitioners must carefully consider the patient's treatment history, which could be potentially complex, including extensive prior BoNT-A treatment for multiple indications from different practices, and weigh the implications of specific treatment choices throughout a patient's medical history. Considering the risk of immunoresistance, we suggest that it is clinically prudent to minimize the risk of NAb formation to facilitate continued clinical response over time.

Since aesthetic and medical treatments are associated with distinct contexts and expectations, aesthetic patients' clinical course and behaviors may be expected to differ from therapeutic patients (Fig. 2A). BoNT-A use in both aesthetic and therapeutic contexts becomes "complicated" in cases where injection patterns in one setting have clinical implications within the other. For example,

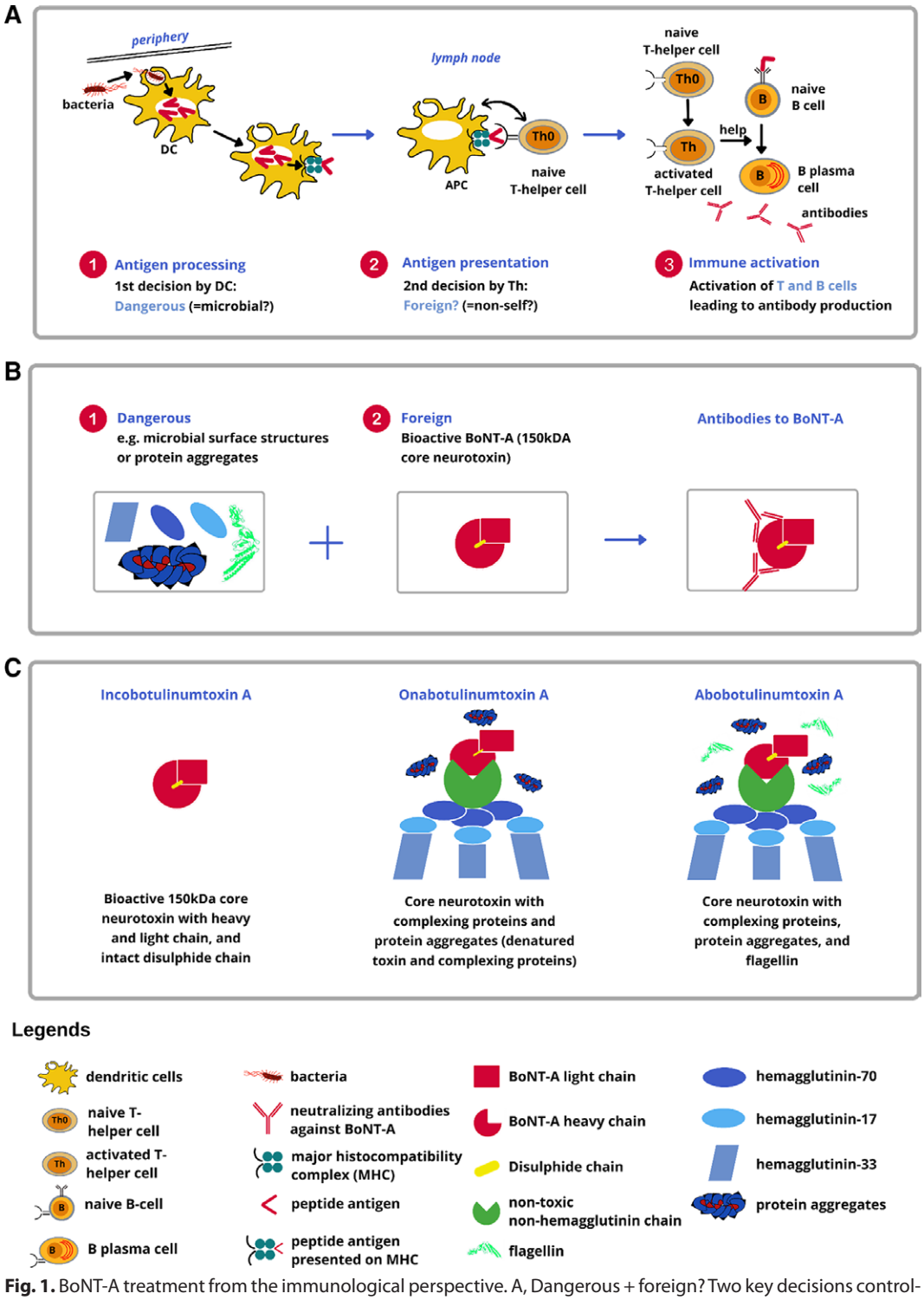

Fig. 1. BoNT-A treatment from the immunological perspective. A, Dangerous + foreign? Two key decisions controlling the immune response to biologics. The first decision involves DCs that determine whether or not a particle (eg, a microbe) is likely to be "dangerous." DCs can recognize microbial surface molecules (eg, flagellin) as "danger signals." Upon recognition of microbial danger signals, DCs will be activated and phagocytose the particle bearing the danger signal. Subsequently, these activated DCs migrate to lymph nodes and become professional APCs. The second decision involves naive T-helper cells that determine whether a particle is self or foreign. Upon encountering foreign antigen peptides presented by APCs along with co-stimulatory signals, naive T-helper cells become activated and undergo clonal expansion, leading to activation and clonal expansion of antigen-specific B cells. These mature into plasma cells that produce antibodies specific to the antigen that triggered the immune response. B, Development of BoNT-A neutralizing antibodies. C, Composition of FDA-approved BoNT-A formulations. Figure credit: Michael Martin.

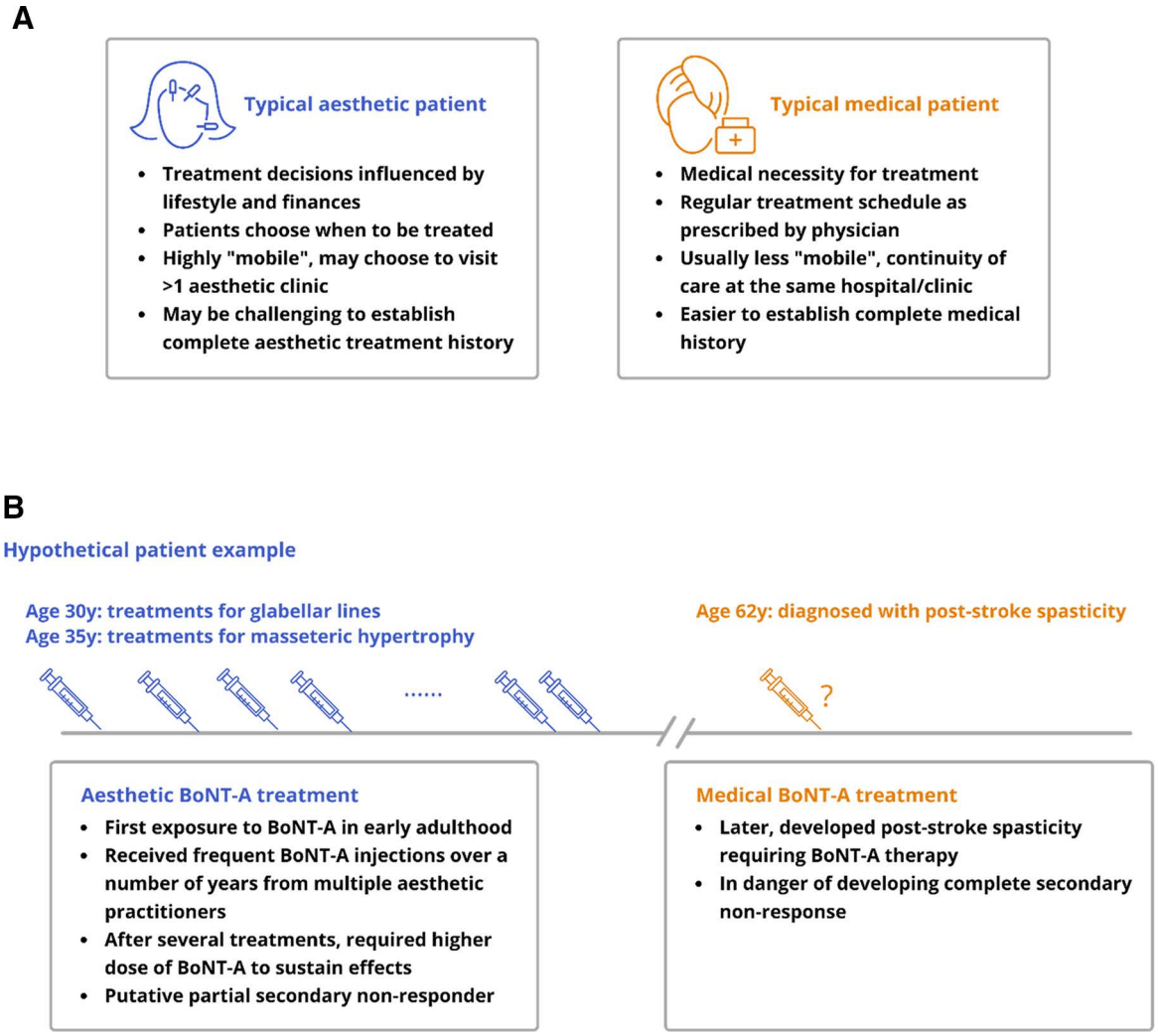

Fig. 2. Patient journey. A, Patient archetypes in aesthetic vs medical practice. B, Hypothetical case example illustrating the potential implications of aesthetic BoNT-A treatment patterns for later therapeutic use in a patient.

extensive aesthetic treatment with high BoNT-A doses, along with frequent retreatments, results in greater exposure to potentially immunogenic material, and could, thus, increase the risk of developing NAb-related SNR. As illustrated in the hypothetical example (Fig. 2B), this potentially leads to suboptimal outcomes if this patient later develops a chronic medical condition that requires BoNT-A treatment. Furthermore, the younger a patient is when beginning aesthetic BoNT-A treatment and the more extensive the use of BoNT-A, the greater the possible lifetime exposure and risk of developing NAb-related SNR. Such cases may have medicolegal implications, especially if risks such as NAb-related SNR were not thoroughly discussed with the patient before treatment. A better understanding of patients' awareness, attitudes, and motivations in relation to their BoNT-A treatment choices is warranted. This could help practitioners to more effectively communicate and work with their patients to manage the risk of BoNT-A resistance.

The ethical principles of medicine underpin therapeutic and aesthetic practice alike. Accordingly, it is often suggested that patient safety and empowerment in decision-making are of prime importance in good aesthetic practice. However, few published guidelines deal with ethics in aesthetic practice. The topic is usually covered only briefly within general guidance for aesthetic practitioners. Nevertheless, the applicability of core medical ethics principles is a recurring theme across the literature,[54] including respect for patient autonomy and obtaining informed consent, comprehensive assessment of expectations within and from clinical encounters (eg, aesthetic enhancement and improved quality of life), and empathic and truthful communication of possible risks and outcomes.[55]

Recognizing the strong influence of patient preference and choice in aesthetic medicine, we suggest that a collaborative patient-centered approach offers a better chance of achieving safe and satisfactory outcomes. In our view, a patient-centered approach in aesthetic practice encompasses not only consideration of patients' individual preferences and circumstances but also individualized assessment, patient education, and informed

decision-making following adequate discussion of possible risks and outcomes.

There are strong clinical and ethical reasons for making thorough pretreatment assessments and informed discussions of risk/benefit integral to the aesthetic consultation process. A comprehensive treatment history (including the BoNT-A products used, number of previous injections, doses, indications, and injection intervals) would help practitioners evaluate and mitigate risks. However, with greater patient choice and "mobility" in aesthetic practice, it may prove challenging to construct a complete history and assess all relevant risk factors (Fig. 2A). Information on concurrent medical conditions or treatment may be highly relevant but may not often be solicited or volunteered. Nevertheless, it is essential to recognize clinical signs of BoNT-A resistance, know the appropriate diagnostic tests to perform, and make informed decisions on options for management.

Consensus on BoNT-A Resistance and Implications for Aesthetic Practice

The panel discussed the above issues surrounding BoNT-A resistance and achieved consensus on a set of recommendations (Table 6). This was achieved through a blinded voting process, in which panel members indicated their position on each statement (agree/disagree). The results were categorized as strong consensus (>95% agreement); consensus (>75%–95% agreement); majority consent (>50%–75% agreement); no majority consent (≤50% agreement).

All panel members agreed that the true extent of BoNT-A antibody-induced SNR in aesthetic applications is likely underestimated within the published literature. They noted that conclusions of SR/MAs are based on data aggregated across studies that may miss clinically relevant observations concerning individual-level data. There was a strong consensus that practitioners should refer to the full range of clinical evidence for a complete picture of antibody-induced SNR and its implications for their practice. There was also consensus that the variability of a typical aesthetic patient's treatment journey may contribute to missed diagnoses or underreporting of BoNT-A resistance.

There was a strong consensus that BoNT-A resistance is a problem that warrants attention. The panel noted that, with expanding off-label applications and doses used in aesthetics becoming more like those in therapeutics, increased rates of NAb formation could be expected. In light of these trends, all panelists agreed that the first step toward preventing BoNT-A NAb formation is for practitioners to acknowledge immunogenicity as a potential complication that might affect future treatment options. Recognizing that BoNT-A therapy is often lifelong, there was a strong consensus that immunogenicity should be considered when making BoNT-A-related treatment decisions. All panelists agreed that using a highly purified BoNT-A formulation with the lowest immunogenicity to minimize the risk of NAb formation may be a prudent clinical decision. Where efficacy and safety are comparable, a lower immunogenicity formulation may offer advantages for further treatment, even though increasing

Table 6. Consensus Statements

Statements	% Agreement*	Consensus*
The true extent of antibody-induced SNR in aesthetic practice is likely to be underestimated/underreported in the medical literature	100	Strong consensus
Clinicians should refer to published literature beyond SRMAs (including single-arm studies and case reports) for real-world evidence and a more complete picture of NAb formation in clinical practice	100	Strong consensus
A typical aesthetic patient's treatment journey, follow-up behavior, and treatment patterns are distinct from that of a medical patient	100	Strong consensus
The aforementioned differences further contribute to the underreporting or missed diagnosis of BoNT-A resistance	93	Consensus
Although the frequency of antibody-induced SNR for BoNT-A is low compared with other therapeutic protein products, it is a real problem that warrants further attention as the clinical applications of BoNT-A continue to expand	100	Strong consensus
As the doses used in aesthetic practice become similar to those in therapeutics owing to the rise in off-label applications, a corresponding increase in the rate of NAb formation can be expected	100	Strong consensus
The first step in preventing NAb formation against BoNT-A is for aesthetic practitioners to acknowledge that immunogenicity is a potential complication that might affect future therapeutic use	100	Strong consensus
The nature of antigen and the presence of adjuvants are modifiable risk factors for immunogenicity that are directly influenced by an injector's choice of BoNT-A formulation	93	Consensus
Aesthetic practitioners are obliged to make treatment decisions in accordance with the key pillars of medical ethics and should strive to minimize modifiable risk factors	100	Strong consensus
As BoNT-A therapy is often lifelong, the risk of immunogenicity should be a key consideration in treatment decisions regarding BoNT-A formulation	100	Strong consensus
Using a highly purified BoNT-A formulation with the lowest immunogenic risk to minimize the risk of NAb formation is a prudent clinical decision	100	Strong consensus
Where efficacy and safety are comparable, a BoNT-A formulation that is less likely to cause antibody-induced SNR should be considered as a first-line therapy	100	Strong consensus
The FDA and EMA recommendations on assessing and mitigating adverse immunologically related responses associated with therapeutic protein products are equally applicable to BoNT-A use in aesthetics	93	Consensus
There is a need to raise public awareness on the risk of immunogenicity associated with BoNT-A therapy via patient education programs supported by health authorities and professional societies	100	Strong consensus

*Cutoffs are as follows: strong, more than 95% agreement; consensus, more than 75%–95% agreement; majority consent, more than 50%–75% agreement; no majority consent, less than 50% agreement.
SRMA, systematic reviews/meta-analyses.

the dose and/or reducing treatment intervals can compensate for partial SNR in some patients. These views are summarized in Figure 3 and are consistent with observations suggesting that using a highly purified BoNT-A formulation and administering the lowest acceptable dose at appropriate intervals may help limit the development of immunoresistance.[11–13,46]

To minimize adverse immunologically related responses, the FDA and EMA have provided recommendations on immunogenicity assessment and risk-based management with therapeutic biologics.[52,53] The panel concluded that these recommendations are also applicable to aesthetic BoNT-A use. In addition, the panelists discussed BoNT-A-specific advisories on NAb formation by the Korean FDA for patients, physicians, and manufacturers as examples of how regulatory bodies could provide leadership in promoting prudent use in aesthetics.[56–58] These Korean Food and Drug Administration advisories provide patient education on risk factors and physician guidance on prevention strategies. Furthermore, manufacturers were recommended to conduct clinical trials assessing the immunological impact of repeated administration for at least 1 year.

As in therapeutic decision-making, the panelists concurred that treatment decisions in aesthetics should be aligned with core medical ethics principles, alongside the relevant clinical and aesthetic considerations. Given the diverse applications of BoNT-A and an increasingly complex aesthetic treatment landscape, practitioners should strive to recognize and minimize modifiable risk factors for future adverse outcomes. Finally, there was strong consensus on the need to raise public awareness of the risk of immunogenicity associated with BoNT-A therapy, as the issue can only be fully addressed with the understanding and cooperation of patients. However, the panel members acknowledged that existing resources for clinicians might be overly technical for use in patient education. Consumer advisories in lay language, such as those issued by the Korean Food and Drug Administration, may be more helpful for highlighting the issue.

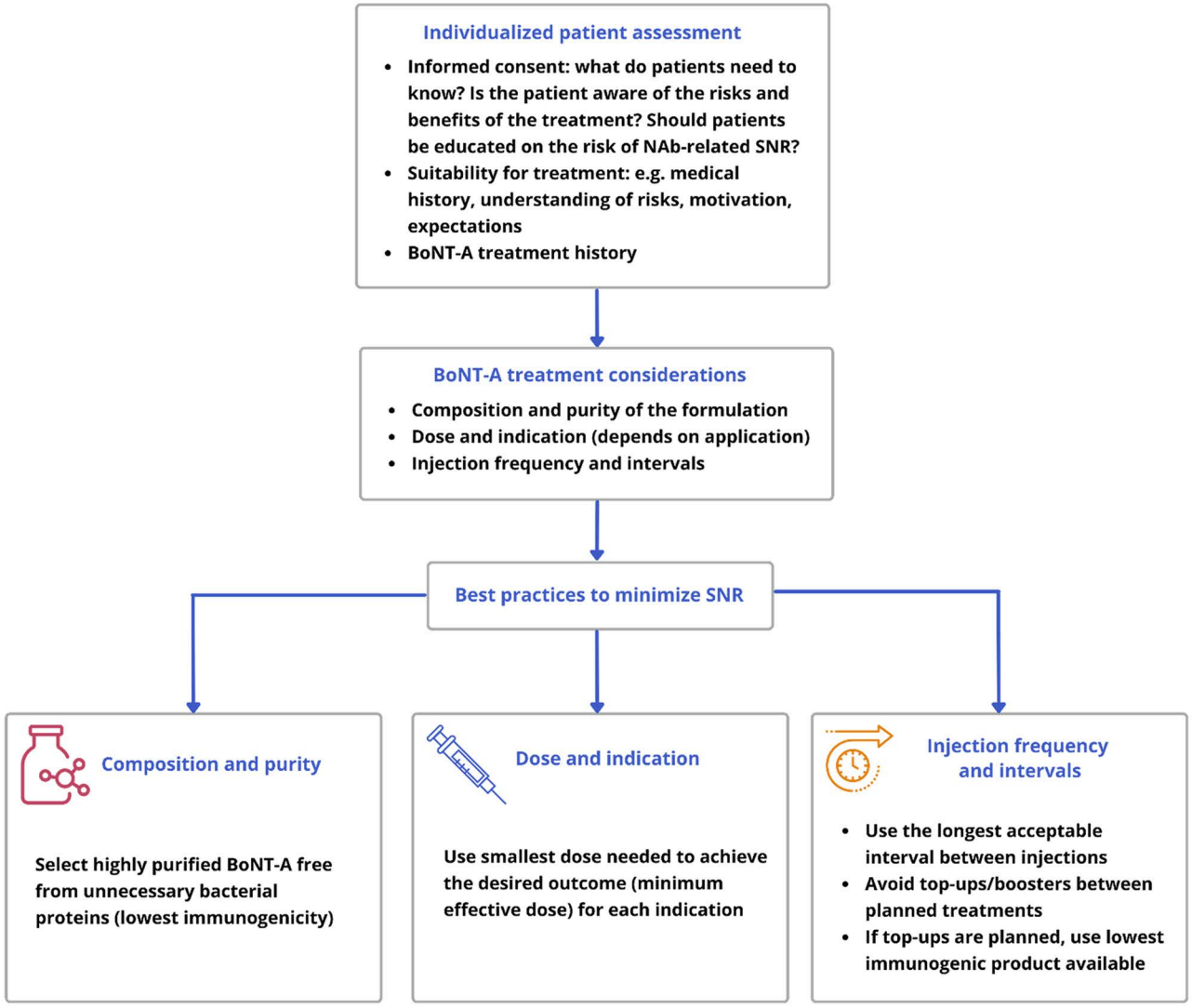

Fig. 3. Key treatment considerations for BoNT-A use in aesthetics.

CONCLUSIONS

With millions of aesthetic BoNT-A treatments performed worldwide, especially off-label applications involving higher doses than traditional on-label indications, more practitioners may expect to encounter possible cases of NAb-related SNR. They will need to make appropriate clinical assessments and design/adjust treatment plans accordingly. A collaborative patient-centered approach and informed decision-making may offer a better chance of achieving safe and satisfactory treatment outcomes. We advocate individualized assessment and thorough discussion of BoNT-A treatment issues and risks, including immunogenicity, with patients from the outset. It may be clinically prudent to minimize immunogenic risk to preserve the option of continued or future BoNT-A treatment. The selection and use of a BoNT-A product with the highest purity and lowest immunogenicity from the beginning may be advantageous, especially when treatment with high doses is planned. We believe that this view is aligned with relevant clinical, ethical, and aesthetic considerations, and with recommendations in the therapeutic space for risk-based management of adverse immunological responses related to biologic drugs, including BoNT-A.

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