Translations

Cosmetic Medicine

Efficacy and Safety of DaxibotulinumtoxinA for Injection in the Treatment of Glabellar Lines by Age and Race: Subgroup Analysis of the SAKURA Clinical Trials

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Abstract

Background: DaxibotulinumtoxinA for Injection (DAXI) is a novel botulinum toxin type A formulation approved for the treatment of glabellar lines. The efficacy, safety, and extended duration of response of DAXI 40 U for glabellar lines were demonstrated in 2 Phase 3, randomized, double-blind studies (SAKURA 1 and 2) and a Phase 3 open-label trial (SAKURA 3).

Objectives: The aim of this study was to evaluate the efficacy and safety of the first DAXI 40 U treatment received in SAKURA 1, 2, or 3 across age and race subgroups.

Methods: Adults with moderate-to-severe glabellar lines (Investigator Global Assessment–Frown Wrinkle Severity [IGA-FWS] and Patient FWS [PFWS] scales) were evaluated for glabellar line severity for ≤36 weeks after the first DAXI treatment. Efficacy and safety were analyzed by age (18-45, >45-55, and >55 years) and race (Asian, Black and African American, and White).

Results: Overall, 2785 patients were included in the efficacy analysis. The proportion of patients achieving none or mild glabellar line severity at maximum frown (IGA-FWS) after DAXI treatment was high in all age and race subgroups (>96% at Week 4). Glabellar line severity of none or mild by composite IGA-FWS and PFWS rating was maintained for a median of 24.0 weeks in all age subgroups, and for 27.0, 25.3, and 24.0 weeks in the Asian, Black and African American, and White subgroups, respectively. Treatment-emergent adverse events were similar across all subgroups.

Conclusions: Consistent with the overall study population, DAXI 40 U demonstrated a high response rate and duration of effect of ≥24 weeks across all age and race subgroups.

초록

배경: DAXI (DaxibotulinumtoxinA for Injection) 는 미간 주름 치료용으로 승인된 새로운 보툴리눔 독소 A형 제제입니다. 미간 주름에 대한 DAXI 40 U의 효능, 안전성 및 늘어난 반응 기간은 2개의 3상, 무작위 이중 맹검 연구 (SAKURA 1 및 2) 및 3상 개방 표지 시험 (SAKURA 3) 에서 입증되었습니다.

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목표: 본 연구의 목적은 연령 및 인종 하위군에 걸쳐 SAKURA 1, 2 또는 3에서 받은 첫 번째 DAXI 40 U 치료의 효능과 안전성을 평가하는 것이었습니다.
방법: 중등도 이상의 미간 주름이 있는 성인 (Investigator Global Assessment–Frown Wrinkle Severity [IGA-FWS] 및 Patient FWS [PFWS] 척도)을 대상으로 첫 번째 DAXI 치료를 받은 날로부터 36주 이하 동안 미간 주름 심각도를 평가했습니다. 효능 및 안전성은 연령 (18~45세, 46~55세 및 56세 이상) 및 인종(아시아인, 흑인 및 아프리카계 미국인 및 백인)별로 분석했습니다.
결과: 효능 분석에 포함된 환자는 총 2,785명이었습니다. DAXI 치료 후 얼굴을 최대한 찡그린 상태(IGA-FWS)에서 미간 주름 심각도가 '없음' 또는 '경미함'에 해당한 환자의 비율은 모든 연령 및 인종 하위군에서 높았습니다(4주차에 96% 이상). 복합 IGA-FWS 및 PFWS 등급에 따른 미간 주름 심각도 '없음' 또는 '경미함'은 모든 연령 하위군에서 24.0주(중앙값) 동안 유지되었으며, 아시아인, 흑인 및 아프리카계 미국인, 백인 하위군에서는 각각 27.0주, 25.3주 및 24.0주 동안 유지되었습니다. 치료 관련 부작용은 모든 하위군에서 유사하게 나타났습니다.
결론: DAXI 40 U는 전체 연구 모집단과 일관되게 모든 연령 및 인종 하위군에서 높은 반응률과 24주 이상 효과가 지속되는 결과를 보여주었습니다.

Level of Evidence: 1

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Botulinum toxin type A (BoNTA) formulations are established as an effective and well-tolerated approach to the aesthetic treatment of facial lines such as glabellar frown lines. BoNTA injection is the most common cosmetic procedure globally, and the patient population seeking aesthetic BoNTA treatment is increasingly diverse in terms of age, race, and ethnicity.[1,2]

Despite limited data, it is generally accepted that, as patient age increases, responsiveness to aesthetic BoNTA treatment decreases due to greater line severity resulting from years of repetitive contraction coupled with age-related changes in skin quality, including a loss of elasticity and thinning skin.[3] Race differences in facial structure and skin aging, as well as differing aesthetic ideals, may also affect treatment outcomes with BoNTA.[4,5] However, there have been few analyses of the efficacy and safety of BoNTA treatments across age and race subgroups.[6–8]

DaxibotulinumtoxinA for Injection (DAXI) is a novel BoNTA formulation approved for the treatment of glabellar lines. The efficacy, extended duration of response, and safety of DAXI for glabellar lines, in patients with and without prior BoNTA treatment, have been demonstrated in the 3 SAKURA clinical trials, which comprise the largest Phase 3 clinical program conducted to date in aesthetics.[9–13]

Owing to its sample size and robust study designs, the large body of data produced by the SAKURA clinical program provides an excellent opportunity to evaluate differences between patient demographic categories. The objective of this subgroup analysis of the SAKURA trial dataset was to assess the efficacy and safety profile of DAXI across multiple age and race subgroups.

METHODS

Study Design

Details of the SAKURA 1, 2, and 3 study designs have been published previously.[9–11] SAKURA 1 and SAKURA 2 were Phase 3, multicenter, randomized, double-blind, parallel-group studies that assessed the efficacy and safety of DAXI 40 U vs placebo for the treatment of glabellar lines (December 2016-November 2017; ClinicalTrials.gov identifiers NCT03014622 and NCT03014635, respectively).[9,10] SAKURA 3 was a Phase 3, open-label, multicenter trial that evaluated single and repeat treatments of DAXI 40 U, with posttreatment follow-up of up to 84 weeks (December 2016-October 2018; ClinicalTrials.gov identifier NCT03004248).[11,12] All 3 studies were approved by the appointed IRB (Advarra, formerly Quorum Review IRB), and all patients provided written informed consent. The 3 trials were conducted in compliance with Good Clinical Practice and the Declaration of Helsinki. The current analysis included patients from SAKURA 1, 2, and 3 who were treated with DAXI. Pooling of data across the randomized and open-label studies increases the sample size in each of the demographic subgroups and is justified based on the identical treatment and assessment methods used across the studies.

Study Population

All 3 trials enrolled similar study populations, which included patients aged ≥18 years, in good health, with moderate or severe glabellar lines based on the Investigator Global Assessment–Frown Wrinkle Severity (IGA-FWS) and Patient

FWS (PFWS) scales. Key exclusion criteria have been previously reported.[9–11] SAKURA 3 study patients were either patients who had completed the SAKURA 1 or 2 trials and rolled over into SAKURA 3 or were newly enrolled patients.[11]

Treatment and Procedures

As previously reported, SAKURA 1 and 2 study patients were randomly assigned 2:1 to receive a single dose of DAXI 40 U or placebo.[9,10] The randomization schedule was prepared by an independent statistician with PROC Plan, SAS version 9.4 statistical software (SAS Institute, Inc., Cary, NC). Patients in SAKURA 3, whether rolled over or newly enrolled, all received DAXI 40 U. The first 400 patients enrolled in SAKURA 3 were to receive up to 3 treatments and the remaining patients were eligible to receive only 1 treatment.[11] This subgroup analysis included only the first DAXI treatment received by each patient, whether treatment was received in SAKURA 1, 2, or 3.

A trained physician administered 0.5 mL DAXI in a standardized pattern. Guidance for injection technique was provided to the investigators, as follows: "(1) Inject the medial corrugators near the medial brow. Medial corrugator injections should be at least 1 cm above the bony supraorbital ridge; (2) When injecting the lateral corrugators, inject at least 1 cm above the bony orbital rim and do not inject lateral to the mid-pupillary line; (3) To inject botulinum toxin, apply finger pressure on the superior medial orbital rim while advancing the needle through the skin into the underlying muscle; (4) Inject a dose of 0.1 mL into each 5 injection sites: 2 injections into each corrugator muscle and 1 injection in the procerus muscle." All patients included in this analysis were followed for up to 36 weeks after treatment.[9–11]

Outcomes

The severity of glabellar lines at maximum frown was evaluated by the IGA-FWS and PFWS, both of which grade severity as none, mild, moderate, or severe. In SAKURA 1 and 2, glabellar lines were assessed at Weeks 1, 2, and 4 and then every 4 weeks until both scores had returned to baseline, or up to a maximum of 36 weeks, whichever occurred earlier. In SAKURA 3, evaluation after the first treatment followed the same schedule as in SAKURA 1 and 2.[11]

For the current analysis, efficacy outcomes included the proportion of patients with glabellar line severity of none or mild at maximum frown by investigator ratings (IGA-FWS), as well as the duration of response. Duration of response was the time from treatment until loss of none or mild glabellar line severity by composite investigator and patient ratings (ie, by both IGA-FWS and PFWS). The safety of DAXI following the first treatment was evaluated by the incidence, severity, and relationship to DAXI of treatment-emergent adverse events (TEAEs).[9–12]

Statistical Analyses

Data for the first DAXI treatment of each patient across the 3 SAKURA studies were pooled for this subgroup analysis. Efficacy analyses were performed using the intent-to-treat population and safety analyses were performed with the safety population; 1 patient randomized to placebo in SAKURA 2 received DAXI. Descriptive statistics—including means, standard deviations (SDs), ranges for quantitative variables, and counts and percentages for categorical variables—were used to examine the efficacy and safety of DAXI across 3 age subgroups (18-45, >45-55, and >55 years) and 3 self-reported race subgroups (Asian, Black or African American, and White). Efficacy was also analyzed for the subgroup of elderly patients ≥65 years of age to allow comparison with publicly available data for approved BoNTA products. Point estimates of the median duration of response (ie, time to event) and 2-sided 95% CIs within each subgroup were estimated from Kaplan-Meier survival curves, performed with SAS version 9.4 or higher statistical software.

RESULTS

Demographic and Baseline Clinical Characteristics

This subgroup analysis included 2785 patients who received their first dose of DAXI in SAKURA 1, 2, or 3 for moderate-to-severe glabellar lines (Table 1). Mean [SD] follow-up time for these patients was 33.3 [15.3] weeks (range, 0-86 weeks). Most patients were female (88.5%) and White (89.2%), with a mean age of 50 years (range, 21-86 years). Overall, 40.1% of patients had previously received BoNTA in the glabella; the mean time since the last treatment was 32 months. In all 3 studies, baseline glabellar line ratings by patients tended be higher than ratings by investigators; overall, 44% of patients rated their glabellar lines as severe, whereas 38% of investigators rated them as severe.

At baseline, the percentage of patients with an investigator rating of severe at maximum frown ranged from 35.7% in the 18- to 45-year subgroup to 40.9% in the >55-year subgroup, with similar variation in the patient ratings (Table 2). In the race subgroups, the percentage of patients with a severe investigator rating was lowest in the White subgroup (37.4%) and highest in the Asian subgroup (53.9%); patient ratings of severity showed less variation (43.6%-51.3%; Table 2).

Efficacy by Age

Consistent with the overall populations of the SAKURA clinical trials, the proportion of patients achieving glabellar line

Table 1. Demographic and Baseline Characteristics (Intent-to-Treat Population)

Variable	SAKURA 1, 2, and 3 pooled population (n = 2785)
Female, n (%)	2465 (88.5)
Age (years)	
Mean [SD] (min, max)	49.5 [11.27] (21, 86)
Age group	
18-45 years	968 (34.8)
>45-55 years	953 (34.2)
>55 years	864 (31.0)
≥65 years	241 (8.7)
Race, n (%)	
Asian	76 (2.7)
Black or African American	138 (5.0)
White	2483 (89.2)
Other[a]	88 (3.2)
Ethnicity, n (%)	
Hispanic/Latino	531 (19.1)
Not Hispanic/Latino	2254 (80.9)
Prior BoNTA treatment, n (%)	1118 (40.1)
Time since prioir BoNTA treatment (months)	
Mean [SD] (min, max)	32.2 [38.7] (0.2, 319.9)
IGA-FWS at maximum frown, n (%)	
Moderate	1721 (61.8)
Severe	1064 (38.2)
PFWS at maximum frown, n (%)	
Moderate	1557 (55.9)
Severe	1228 (44.1)

BoNTA, botulinum toxin type A; IGA-FWS, Investigator Global Assessment–Frown Wrinkle Severity; max, maximum; min, minimum; PFWS, Patient Frown Wrinkle Severity; SD, standard deviation. [a]Includes Native Hawaiian or Other Pacific Islander (n = 7), American Indian or Alaska Native (n = 4); Multiple (n = 19), and Other (n = 58).

severity of none or mild at maximum frown according to investigator ratings was high regardless of age subgroup (18-45, >45-55, and >55 years; Figure 1A). The none or mild response rate peaked at >96% at Weeks 2 and 4 in these subgroups, and 12% to 16% of patients maintained a none or mild response at Week 32. The response curves generally overlapped for the 3 age subgroups. The median time to loss of none or mild glabellar line severity at maximum frown with DAXI treatment according to composite investigator and patient assessments was 24.0 weeks in the 3 subgroups (Figure 1B).

The proportion of patients achieving none or mild glabellar lines was similar across the age groups (Figure 1A), despite a higher baseline rate of severe glabellar lines in the older (>55 years) subgroup (Figure 2). However, a breakdown of the investigator-assessed glabellar line severity scores (Figure 2) showed that more patients in the youngest subgroup (18-45 years; Figure 2A) achieved no glabellar lines than in the older subgroup (>55 years: Figure 2C).

The analysis of patients ≥65 years old showed similar none or mild response rates to the >55-year subgroup (Supplemental Table 1). The median time to loss of none or mild glabellar line severity was 24.0 weeks, and was consistent between the 3 subgroups (Supplemental Figure 1).

Efficacy by Race

Treatment with DAXI showed consistent efficacy across all 3 race subgroups (Figure 3A). The proportion of patients achieving glabellar line severity of none or mild at maximum frown according to investigator ratings was similar among the Asian, Black or African American, and White subgroups, with peak response rates of >96% observed at Weeks 2 and 4. The response rates remained consistent across the 3 race subgroups throughout the duration of follow-up. At Week 32, 13% of White patients, 20% of Black or African American patients, and 22% of Asian patients retained a none or mild rating. The median time to loss of none or mild glabellar line severity at maximum frown with DAXI treatment according to composite investigator and patient assessments was 27.0, 25.3, and 24.0 weeks in the Asian, Black or African American, and White subgroups, respectively (Figure 3B). The proportion of patients achieving no glabellar lines was high from Weeks 1 to 8 and was similar in all race subgroups, despite a higher rate of severe glabellar lines at baseline in the Asian subgroup (Figure 4).

Safety

The overall incidence of TEAEs after a single dose of DAXI 40 U was similar across all age subgroups included in the safety analysis (18-45, >45-55, and >55 years; Table 3). Headache was the most commonly reported treatment-related TEAE in all age and race subgroups (4%-5%), except for the Black or African American subgroup, which reported injection site pain at a higher incidence (8.7%). However, 75% (9/12) of the cases of injection site pain in the Black or African American subgroup were reported at 2 of the 66 study sites. The incidence of eyelid ptosis was 0.5%, 1.3%, and 1.7% in the 18- to 45-, >45- to 55-, and >55-year subgroups, respectively, and 0%, 1.4%, and 1.1% in the Asian, Black or African American, and White subgroups, respectively.

Table 2. Baseline Frown Severity Scores

Variable by age group, n (%)	18-45 years (n = 968)	>45-55 years (n = 953)	>55 years (n = 864)
IGA-FWS at maximum frown			
Moderate	622 (64.3)	588 (61.7)	511 (59.1)
Severe	346 (35.7)	365 (38.3)	353 (40.9)
PFWS at maximum frown			
Moderate	587 (60.6)	518 (54.4)	452 (52.3)
Severe	381 (39.4)	435 (45.6)	412 (47.7)
Variable by race, n (%)	Asian (n = 76)	Black or African American (n = 138)	White (n = 2483)
IGA-FWS at maximum frown			
Moderate	35 (46.1)	90 (65.2)	1554 (62.6)
Severe	41 (53.9)	48 (34.8)	929 (37.4)
PFWS at maximum frown			
Moderate	37 (48.7)	77 (55.8)	1400 (56.4)
Severe	39 (51.3)	61 (44.2)	1083 (43.6)

IGA-FWS, Investigator Global Assessment–Frown Wrinkle Severity; PFWS, Patient Frown Wrinkle Severity.

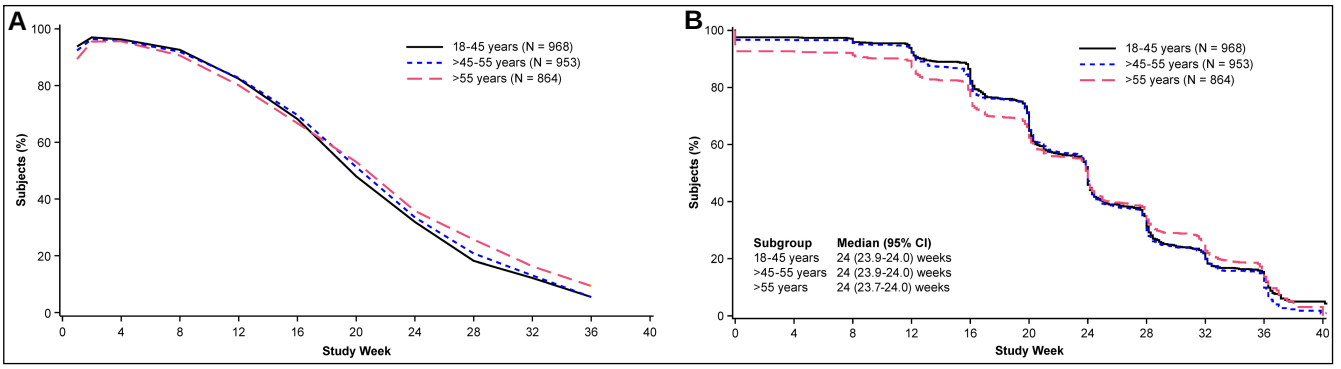

Figure 1. (A) Proportion of patients in each age subgroup with a glabellar line severity rating of none or mild at maximum frown (investigator rating by IGA-FWS) after DAXI treatment. (B) Time to loss of none or mild glabellar line severity by composite investigator (IGA-FWS) and patient (PFWS) assessments after DAXI treatment in each age subgroup. CI, confidence interval; DAXI, DaxibotulinumtoxinA for Injection; IGA-FWS, Investigator Global Assessment–Frown Wrinkle Severity; PFWS, Patient Frown Wrinkle Severity.

DISCUSSION

In this subgroup analysis of an extensive dataset pooled from 3 Phase 3 trials, DAXI demonstrated efficacy and was well tolerated across the age and race subgroups for the treatment of glabellar lines. The results for the age and race subgroups were consistent with the results for the overall populations of the 3 SAKURA trials.[9–12] Rates of achieving none or mild glabellar lines with DAXI were high, regardless of age and race, and the duration of response was consistent across all subgroups. No loss of efficacy was observed in any of the subgroups. The safety profile of DAXI was similar across all subgroups.

As shown in our analysis, aging is associated with increasing severity of dynamic wrinkles. Nevertheless, the efficacy of DAXI in the treatment of glabellar lines in our study was similarly robust across the 3 age subgroups (18-45, >45-55, and >55 years). Patients in the >55-year subgroup had more severe glabellar lines at baseline and were more likely to achieve mild rather than no glabellar lines when compared with younger patients; however, there was no reduction in the combined none or mild response rate

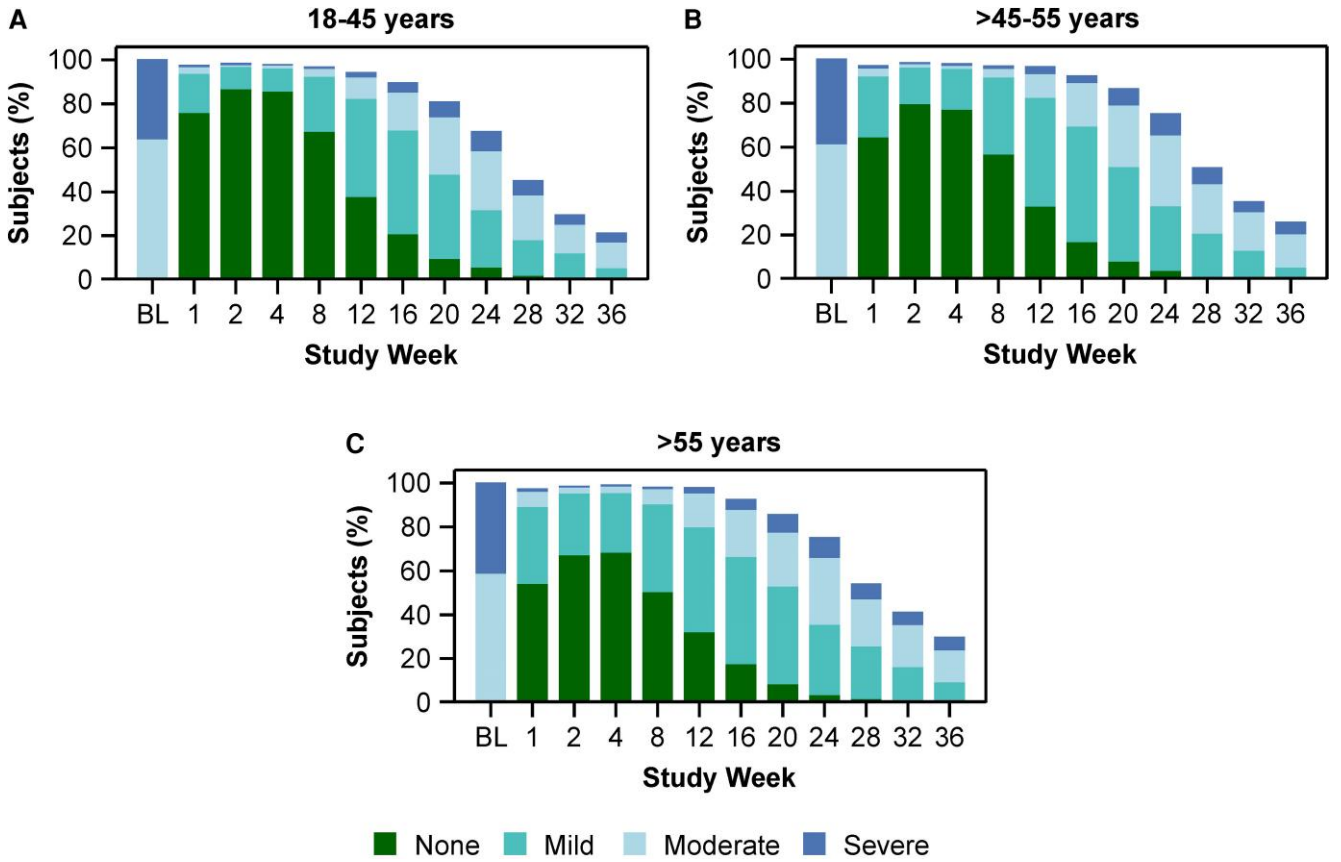

Figure 2. Proportion of patients in each age subgroup—(A) 18 to 45 years, (B) >45 to 55 years, and (C) >55 years—with glabellar line severity ratings of none, mild, moderate, or severe at maximum frown (investigator rating by IGA-FWS) at each time point after DAXI treatment. BL, baseline; DAXI, DaxibotulinumtoxinA for Injection; IGA-FWS, Investigator Global Assessment–Frown Wrinkle Severity.

and no reduction in the duration of effect. Similarly, an analysis of efficacy data from 4 Phase 3 studies of abobotulinumtoxinA for the treatment of glabellar lines found that abobotulinumtoxinA was effective for older patients (aged >50 to <65 years) as well as younger patients (≤50 years).[8] Similarly, in a trial of incobotulinumtoxinA for glabellar lines in Korean patients aged 18 to 65 years, the extent of improvement was unaffected by age.[14] Although other studies have suggested reduced BoNTA efficacy in patients aged ≥65 years,[15] no reduction in efficacy was observed in the current study in the >55-year subgroup (n = 864), or in the patients who were aged ≥65 years (n = 241). Nevertheless, in clinical practice, the age of the patient should still inform outcome expectations at an individual level.

Race and ethnicity are also important factors considered by the clinician when assessing a patient with skin of color for BoNTA treatment. Patients with skin of color may differ in terms of dermal thickness, elasticity, and subcutaneous fat, and often have less photodamage compared with patients of White race.[4,16] Black and Asian populations generally display fewer fine lines, wrinkles, and skin laxity, partly due to a thicker dermis, more collagen fiber, and a firmer attachment of the skin to underlying tissues.[16–18] All of these factors may influence a clinician's decision on dose and injection pattern/depth of treatment with BoNTA in patients with skin of color. In addition, treatment goals and aesthetic ideals for non-White patients are incompletely defined in the literature, and it should be noted that Asian populations are heterogeneous in appearance and culture.[19] Despite these potential differences in skin features and aesthetics, rates of achieving none or mild glabellar lines with DAXI over time in our analysis were similar across the Asian, Black or African American, and White subgroups. In an open-label study of incobotulinumtoxinA for the treatment of glabellar lines, 100% of patients with Fitzpatrick skin types IV to VI (n = 29; of African American, Hispanic, and West Indian ethnicities) improved their glabellar line severity rating at maximum frown by ≥1 level at Day 30.[6] This response was similar to patients with fairer skin.[6] Post hoc analyses of 2 Phase 3 trials of prabotulinumtoxinA for treatment of glabellar lines also showed similar response rates in patients

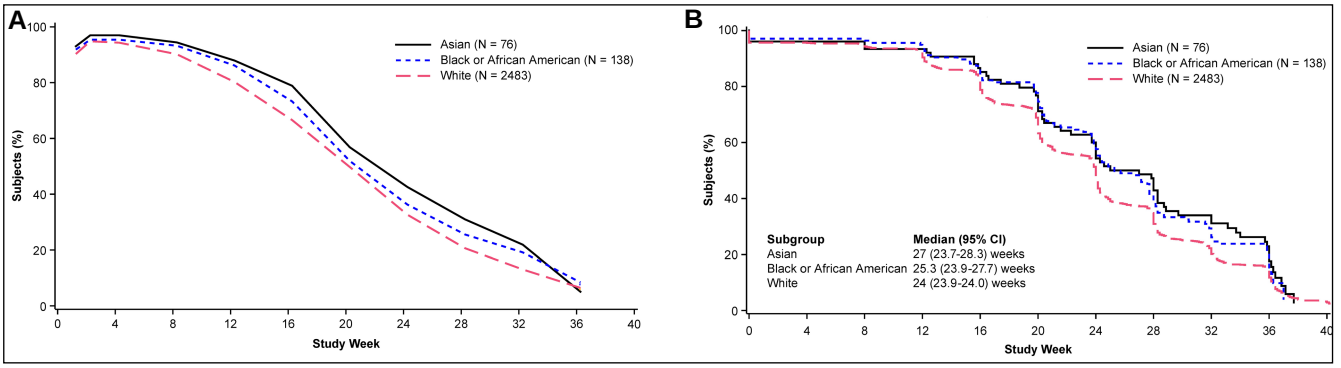

Figure 3. (A) Proportion of patients in each race subgroup with a glabellar line severity rating of none or mild at maximum frown (IGA-FWS) after DAXI treatment. (B) Time to loss of none or mild glabellar line severity by composite investigator (IGA-FWS) and patient (PFWS) assessments after DAXI treatment in each race subgroup. CI, confidence interval; DAXI, DaxibotulinumtoxinA for Injection; IGA-FWS, Investigator Global Assessment–Frown Wrinkle Severity; PFWS, Patient Frown Wrinkle Severity.

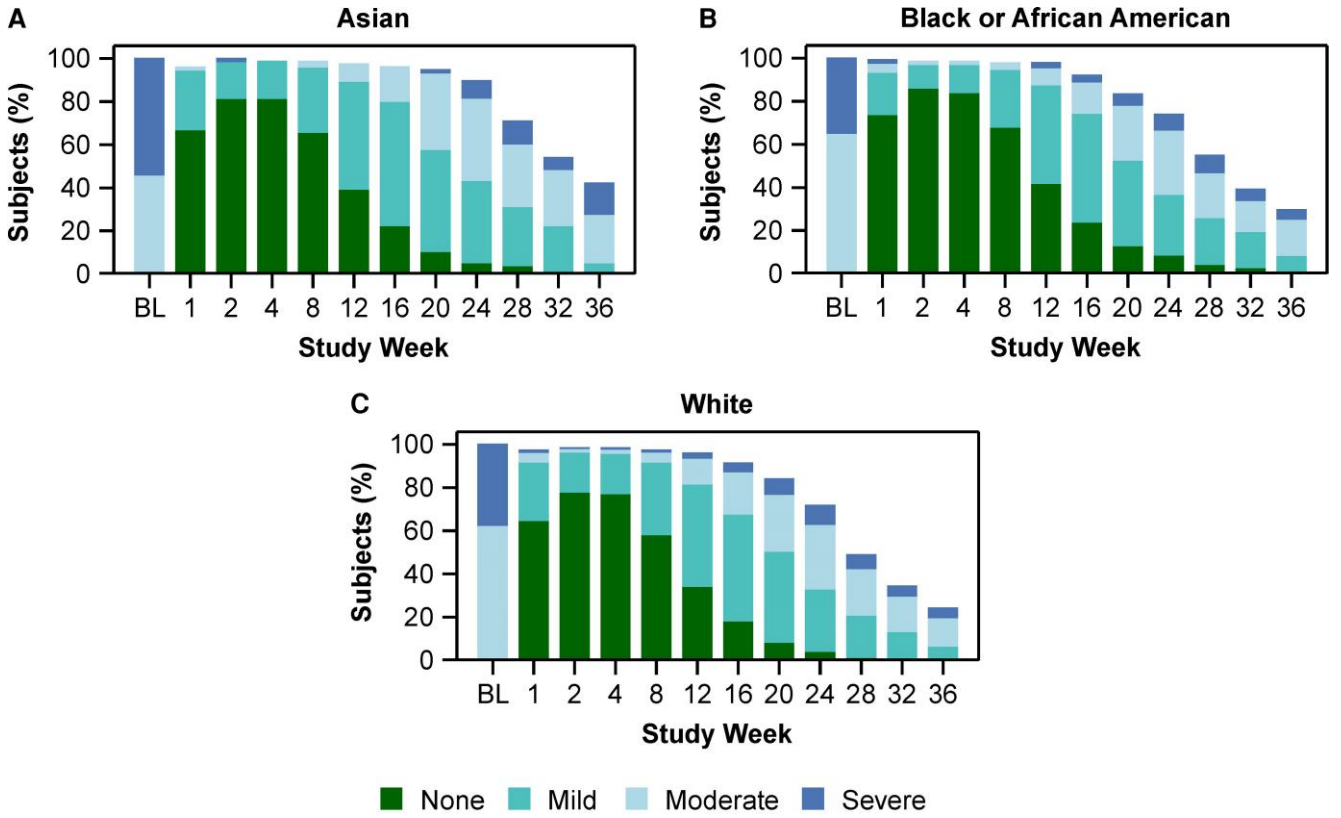

Figure 4. Proportion of patients in each race subgroup—(A) Asian, (B) Black or African American, and (C) White—with glabellar line severity ratings of none, mild, moderate, or severe at maximum frown (IGA-FWS) at each time point after DAXI treatment. BL, baseline; DAXI, DaxibotulinumtoxinA for Injection; IGA-FWS, Investigator Global Assessment–Frown Wrinkle Severity.

with skin of color (Fitzpatrick skin types IV-VI; n = 140) and without skin of color (Fitzpatrick skin types I-III; n = 352) (94% and 96%, respectively, of each group improved their glabellar line severity rating at maximum frown by ≥1 level at Day 30).[20] In contrast, differences between race subgroups in response rate over time were reported in a pooled analysis of 6 clinical trials of abobotulinumtoxinA for treatment of glabellar lines.[7] In this analysis, the onset of effect was similar between patients with skin of color (n = 117) and White (n = 216) patients, but, after 30 days, the response rate was greater for patients with skin of color.[7] In a pooled analysis of 4 clinical trials of incobotulinumtoxinA that included a small subgroup of Asian patients (n = 19), 100% of the Asian subgroup were responders (1 point improvement on the Facial Wrinkle Scale) at Day 30, compared with 87% of non-Asians. However, by Day 120, 37%

Table 3. Summary of AEs by Age and Race (Safety Population)

AEs by age, n (%)	18-45 years (N = 969)	>45-55 years (N = 953)	>55 years (N = 864)	Total (N = 2786)
Patients with ≥1 TEAE	338 (34.9)	317 (33.3)	342 (39.6)	997 (35.8)
Patients with ≥1 treatment-related TEAE	165 (17.0)	153 (16.1)	160 (18.5)	478 (17.2)
Most common treatment-related TEAEs[a]				
Headache	51 (5.3)	42 (4.4)	35 (4.1)	128 (4.6)
Injection site pain	46 (4.8)	26 (2.7)	24 (2.8)	96 (3.5)
Injection site erythema	15 (1.6)	21 (2.2)	33 (3.8)	69 (2.5)
Injection site edema	20 (2.1)	12 (1.3)	29 (3.4)	61 (2.2)
AEs by race, n (%)	Asian (N = 76)	Black or African American (N = 138)	White (N = 2484)	Total (N = 2698)
Patients with ≥1 TEAE	25 (32.9)	55 (39.9)	889 (35.8)	969 (35.9)
Patients with ≥1 treatment-related TEAE	11 (14.5)	37 (26.8)	418 (16.8)	466 (17.3)
Most common treatment-related TEAEs[a]				
Headache	4 (5.3)	7 (5.1)	115 (4.6)	126 (4.7)
Injection site pain	3 (3.9)	12 (8.7)	79 (3.2)	94 (3.5)
Injection site erythema	0	3 (2.2)	65 (2.6)	68 (2.5)
Injection site edema	1 (1.3)	4 (2.9)	56 (2.3)	61 (2.3)
Erythema	0	5 (3.6)	41 (1.7)	46 (1.7)
Edema	0	5 (3.6)	37 (1.5)	42 (1.6)
Injection site pruritis	2 (2.6)	0	15 (0.6)	17 (0.6)
Facial paresis[b]	0	6[c] (4.3)	5 (0.2)	11 (0.4)

AE, adverse event; TEAE, treatment-emergent adverse event. [a]Treatment-related TEAEs occurring in ≥2% of patients in any subgroup. [b]Verbatim terms were "forehead muscle weakness" (n = 7), "forehead left/right side paresis" (n = 3), and "left frontalis weakness" (n = 1). [c]All facial paresis events in the Black and African American subgroup were reported at a single study site.

of the Asian subgroup and 40% of the non-Asian subgroup were responders.[21] Overall, based on the findings from our study and published literature, differences in skin features between racial or ethnic groups do not result in consistent differences in response to BoNTA treatment.

DAXI demonstrated long-lasting efficacy in all subgroups, consistent with the overall population results of the SAKURA clinical trials.[9–12] The median duration of response to DAXI was 24 weeks for all age subgroups and for White patients, and ranged from 25 to 27 weeks for Asian and Black or African American patients. This is consistent with the overall SAKURA population, in which the median duration of response to DAXI was 24 weeks.[9–11] A duration of effect beyond 24 weeks, as observed in the Asian and Black or African American subgroups, is notable for any BoNTA formulation.[22] For example, in a study of abobotulinumtoxinA for treatment of glabellar lines, the duration of effect in African American patients was 1 to 3 weeks longer than in the overall population.[23] However, the duration of effect of abobotulinumtoxinA was shorter than observed with DAXI (17-18 weeks in the African American patients).[23]

The safety profile of DAXI was consistent across the 3 main age and race subgroups, with headache and injection site reactions being the most commonly reported treatment-related TEAEs and treatment-related eyelid ptosis being reported in <2% of patients. In general, the incidences for individual treatment-related TEAEs in the subgroups were similar to the incidences reported in the overall SAKURA populations.[9,12] Exceptions included treatment-related erythema and edema that were not specifically noted by the investigator as being related to the injection site in the Black or African American subgroup (3.6% for both) and treatment-related injection site pruritis in the Asian subgroup (2.6%); these events were reported at higher rates than in the overall SAKURA population (SAKURA 1 and 2: all <2%;[9] SAKURA 3: erythema, 1.8%; edema, 1.6%; injection site pruritis, <1%[12]). Similarly,

treatment-related injection site pain and treatment-related facial paresis were more common in the Black or African American subgroups (8.7% and 4.3%, respectively) than in the general SAKURA population (SAKURA 1, 5.0% and <2%; SAKURA 2, 2.4% and <2%;[9] SAKURA 3, 3.6% and <1%, respectively[12]). The higher incidence of pain may be related to differences among Black or African American patients and the SAKURA population, although a literature search did not reveal any data describing heightened sensitivity to injection site pain among Black or African American individuals. Site-to-site differences in AE reporting may partially explain the pattern, as there were 12 cases of injection site pain in Black or African American patients, of which 75% (9 cases) were reported at 2 of the 66 study sites. Similarly, all Black or African American patients with AEs of facial paresis were from a single site. At this site, the verbatim term reported by the investigator was "forehead muscle weakness" and the investigator's observation and subsequent categorization of the observed AE was likely to be a result of the toxin effect being observed in the lower third of the frontalis muscle. In previous studies of other BoNTA formulations, higher incidences of these specific AEs in Black or African American and Asian patients have not been reported,[20,21,23] although an overall greater incidence of ocular TEAEs, including eyelid edema, was reported in African American patients treated with abobotulinumtoxinA compared with other ethnicities (6% vs 4%, respectively).[23] Together with the findings from this study, these data suggest that there does not appear to be any consistently reported AE profile of BoNTA treatment that is associated with racial or ethnic differences in skin features or structure.

A key strength of this analysis was the large dataset of DAXI-treated patients provided by pooling trials from the SAKURA clinical program, the largest Phase 3 clinical program conducted in aesthetics to date.[9–12] An additional strength was the use of IGA-FWS as an efficacy outcome, as this allowed a trained investigator to provide an objective assessment of response to DAXI treatment. Investigator ratings also provide a more objective assessment of response in the case of differences between race subgroups in aesthetic ideals or expectations of treatment outcomes.

Despite the large dataset from the SAKURA clinical program, the study population was primarily female and White, and some of the race subgroups of interest were relatively small (eg, 76 patients self-identified as Asian and 138 as Black or African American), which may limit the interpretation of the results. In addition, no statistical comparisons between subgroups were conducted. However, the primary purpose of this analysis was to establish that DAXI is effective in each of the subgroups, not to determine if the small differences between subgroups are statistically significant. Furthermore, any statistical comparison would have been limited by the small sample sizes in some of the subgroups. Given the increasing diversity of patients seeking BoNTA treatment, there is a need to increase the patient diversity in future studies to allow for robust statistical analyses across subgroups. It is also noted that the same 40-U dose was used for all patients, which may not reflect clinical practice, where doses for individual patients may be adjusted to suit individual needs.

CONCLUSIONS

DAXI demonstrated a high response rate and extended duration of effect across age and race subgroups that was consistent with the overall study population. As the patient population for facial aesthetic treatment continues to diversify, DAXI provides an effective, well-tolerated, and long-lasting approach for the treatment of glabellar lines.

Supplemental Material

This article contains supplemental material located online at www.aestheticsurgeryjournal.com.

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