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Original Research

Exploring the Relationship Between Clinical Presentation in Hallux Valgus and Response to AbobotulinumtoxinA Treatment

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ABSTRACT

The relationship between pain/disability and angular deviation of the hallux valgus (HV), and the impact of orthotic use, laterality, and pain variability on treatment outcomes remain unclear. This was explored in post hoc analyses of a placebo-controlled trial of abobotulinumtoxinA (aboBoNT-A; Dysport®) for HV-associated pain (NCT03569098). The primary endpoint was not met in this study (change from baseline Numeric Pain Rating Scale [NPRS] score vs placebo at week 8); however, there was a greater reduction from baseline in mean NPRS score at week 12 with aboBoNT-A 500U versus placebo ($p = .06$). Adults with painful HV without surgery were randomized (1:1:1) to aboBoNT-A 300U, aboBoNT-A 500U, or placebo. NPRS was completed for 7 days before baseline and weeks 4, 8, and 12. Over-the-counter orthoses were permitted. Participants ($N = 186$) had a mean [standard deviation, SD] age of 48.2 [13.1] years, 18% (33/186) used orthotics, and 67% (124/186) had bilateral HV. No associations between baseline pain severity and angular deviation were identified. Participants with high pain variability at baseline (SD > 2) had a poorer response to aboBoNT-A treatment than those with less variability. In conclusion, no relationship between HV-related pain/disability and angular deviation was observed.

Plain language summary: A bunion (medical term: hallux valgus) is a common adult foot problem in which the big toe points inward toward the other toes, and this can be painful. How much the big toe points inward (how deformed the foot is) has been linked to the amount of pain the patient experiences. A better understanding of this foot deformity and bunion pain will help doctors and patients to make the right treatment decisions.
A study was completed looking at how injections of a type of botulinum toxin (abobotulinumtoxinA) into specific muscles in the foot may help to reduce bunion pain in patients without surgery. This subsequent analysis of the study data looked at the amount of foot deformity in patients, the bunion pain they experienced, and which factors affected how well abobotulinumtoxinA worked to reduce bunion pain.
The results of this study showed that the amount of foot deformity was not linked to the level of bunion pain. When deciding the best treatment option to relieve bunion pain, it is important that doctors not only consider how deformed the foot is, but also other important factors such as foot pain levels.

Hallux valgus (HV; bunion) is a progressive foot deformity affecting approximately 23% of adults of 18 to 65 years of age globally. Symptoms include pain, morphological changes to the foot, and impaired gait and balance (1-3). In HV, the activity of the abductor hallucis muscle of the foot is decreased compared with adductor muscles, and flexor activity of the abductor hallucis increases with severity (4). Hypertonia of the adductor hallucis muscle may result in lateral deviation of the hallux and osseous changes, and development of a pressure-sensitive prominence on the medial side of the first metatarsal that can limit mobility (5,6). Mechanical pressure on this prominence and loss of normal hallux involvement in gait and weight distribution lead to forefoot pain and pain in the lesser toes due to transfer metatarsalgia (7). There is

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Conflict of Interest: B.B. and D.G.A. are investigators for the current study and report consultancy (advisory board) for Ipsen. L.A.D. is an investigator for the current study. M.V. is an Ipsen employee. R.S. was an Ipsen employee during the study and manuscript preparation.

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substantial evidence that pain avoidance in HV induces compensatory musculoskeletal dysfunction (8,9). Increased severity of HV angle has been correlated with pathomechanical changes in the rear foot and increased pain (10), and knee pain can develop concomitantly in patients with severe HV deformity (11). Compensation also takes place in the contralateral lower limb to accommodate for the presence of HV (8). Given that pathomechanical changes occur secondary to pain avoidance, adequate pain control is a key aspect of HV management.

Physicians, patients, and payors alike need a deeper understanding of how patient and disease characteristics may influence treatment decisions and the response to treatment in HV. Currently, referral for treatment and payor considerations are based on HV angle, pain, and degree of functional impairment (7,12,13). However, there is a general lack of agreement in the HV community regarding the relationship between angular deviation and the degree of foot pain or disability experienced by the patient (14). Indeed, the degree of lateral deviation can overshadow other presenting features, most notably pain severity, but also pain variability, chronicity, and laterality of HV. HV often presents as a bilateral rather than unilateral disease (11), and is often initially managed using orthoses, such as splints, inserts, or braces, to correct foot biomechanics, which are now understood to be largely ineffective (15-17). However, there is little evidence of the impact of these factors on self-reported pain severity and treatment outcomes.

Evidence suggests that HV-associated pain and angular deviation can be reduced following botulinum toxin (BoNT) injections to the affected foot (18-20). BoNTs block the release of presynaptic acetylcholine at the neuromuscular junction to reduce localized muscle tone (21) and block pain signaling, both locally and centrally, via the dorsal root ganglia and spinal cord, to reduce pain sensitization (22,23). A phase 2 trial of abobotulinumtoxinA (aboBoNT-A; Dysport®, Ipsen, Paris, France; NCT03569098 [ClinicalTrials.gov]) in adults with HV, who had not undergone surgery, reported Numeric Pain Rating Scale (NPRS) scores that were reduced from baseline 12 weeks after intramuscular injection of aboBoNT-A 500 units (U) (24,25). However, this did not reach statistical significance (p = .061) and the primary endpoint (change in least-squares [LS] mean NPRS score from baseline) was not met at 8 weeks. Despite this, the proportion of participants with an at least 20% reduction from their baseline NPRS score was greater with aboBoNT-A 500U than with placebo at week 12 (p = .006). Furthermore, a post hoc analysis revealed that participants in the aboBoNT-A 500U group spent more days with lower NPRS scores than their lowest baseline score (meaningful response), and with NPRS scores ≥2 points lower than their mean baseline NPRS score at weeks 8 and 12 compared with placebo (all p <.05) (24,25).

Whereas the aforementioned analysis focused on centrally mediated pain state changes that occur following treatment, the current post hoc analyses of data from this phase 2 trial aimed to determine whether angular deviation in HV affected disability or HV-related pain and what factors affected the response to aboBoNT-A treatment. The hypotheses were that there is a relationship between angular deviation and disability or pain, and that orthotic use, bilateral HV, and pain severity would affect the response to aboBoNT-A treatment.

Materials and Methods

Study Design, Participants, and Treatment

Full study design, eligibility criteria, and treatment administration have been described previously (24). Briefly, the phase 2, parallel-group, multicenter trial had a double-blind phase lasting at least 12 weeks (cycle 1), followed by an open-label phase of up to 24 weeks (cycles 2 and 3) (Fig. 1). Participants had a diagnosis of HV; had not undergone surgery; had no pre-existing medical conditions; had an HV angle of <30° and an intermetatarsal (IM) angle of <18° in the great toe; had an NPRS score of ≥4; and had total scores of >27 on the modified Foot Function Index (mFFI) subscales for pain and disability in the study foot, with pain refractory to shoe modifications, nonsteroidal anti-inflammatory medications, and modification of activities. The use of orthoses on the study foot (except over-the-counter shoe inserts, if used for at least 30 days prior to screening) was not permitted. At the start of cycle 1, participants were randomized 1:1:1 to receive aboBoNT-A 300U, aboBoNT-A 500U, or placebo divided equally into 4 injections guided by electrical stimulation to the oblique and transverse heads of the adductor hallucis muscle, the flexor hallucis brevis muscle, and the extensor hallucis brevis muscle. After 12 weeks, participants who met retreatment criteria entered the open-label phase and received aboBoNT-A 300U (cycle 2); eligible participants were further retreated with either aboBoNT-A 300U or aboBoNT-A 500U (investigator's judgment) at least 12 weeks later (cycle 3). Retreatment criteria were participant consent, investigator's clinical judgment, clinically significant foot pain (NPRS score ≥3) in the preceding 24 hours, and no unacceptable risk to the participant (investigator's judgment). Participants ineligible for retreatment at week 12 were assessed every 4 weeks until retreatment or study end. This study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice, and all local regulatory guidelines. Written informed consent was provided by participants prior to study enrollment.

Assessments

Participants, who were blinded to treatment allocation, recorded their pain severity with the NPRS and the mFFI on the 7 consecutive days prior to baseline and at weeks 4, 8, and 12, and the 36-item Short-Form Health Survey (SF-36) at baseline and at weeks 4 and 8 (26-28). At least 4 of the 7 days prior to each time point must have been completed for an assessment to be considered valid for inclusion in analyses. HV angle and IM angle were measured with weightbearing anterior-posterior radiographs, as previously described (24).

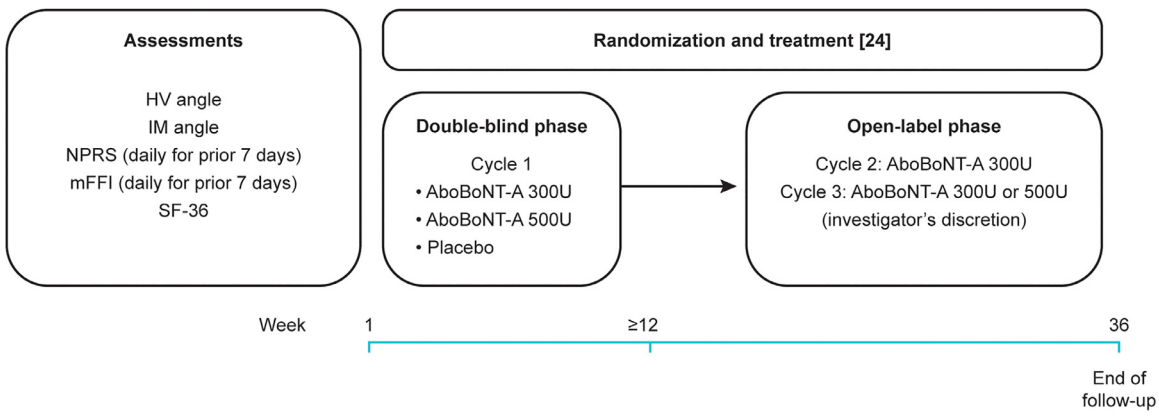

Fig. 1. Study design. Retreatment with aboBoNT-A from week 12 was dependent on eligibility determined by the investigator. AboBoNT-A, abobotulinumtoxinA; HV, hallux valgus; IM, intermetatarsal; mFFI, modified Foot Function Index; NPRS, Numeric Pain Rating Scale; SF-36, 36-item Short-Form Health Survey.

Analyses

All analyses in this manuscript were conducted in a post hoc manner based on a large, placebo-controlled trial for which the power of the trial was determined by the primary endpoint (change from baseline in foot pain as measured by the NPRS). These analyses were intended to generate further hypotheses regarding the underlying causes, contributing factors and other details related to the clinical presentation in HV. The relationships between baseline HV or IM angle, and pain, as measured in the intention-to-treat population (all randomized participants) by NPRS, mFFI, and SF-36, were assessed using Pearson's correlation coefficient. Subgroup analyses used a mixed model for repeated measures on change from baseline in the daily scores averaged over the 7 consecutive days prior to a given study visit. Visit (weeks 4, 8, and 12), treatment-group-by-visit interaction, the stratification parameter (laterality [unilateral vs bilateral HV] at baseline), the subgroup, the subgroup by treatment and/or visit interaction, and the baseline value were included in the model. The proportion of participants experiencing clinically meaningful pain relief was assessed post hoc, defined as the proportion who reported an NPRS score in the 7 days prior to each study time point that was lower than their lowest baseline daily NPRS score.

Results

Participant Disposition and Baseline Characteristics

Full participant disposition was described previously (24). A total of 531 participants were screened and 186 were enrolled between June 2018 and May 2020. Mean (standard deviation [SD]) age was 48.2 (13.1) years and 91.9% (171/186) of participants were female (Table 1). Most participants (66.7%; 124/186) had bilateral HV and 17.7% (33/186) used orthotics. Mean (SD) time from diagnosis to first assessment was 6.4 (8.7) years. Mean (SD) HV and IM angles were 20.7° (5.2°) and 11.9° (2.4°), respectively. Mean (SD) baseline pain scores were 6.9 (1.6) using the NPRS, 63.8 (16.0) on the mFFI pain subscale, and 52.6 (23.1) using the SF-36 bodily pain domain. Mean (SD) mFFI baseline disability and activity scores were 56.8 (18.9) and 23.7 (23.1), respectively.

Pain and Angular Deviation

No relationship was observed between foot pain (n = 185 observations in each correlation) and HV angle (NPRS: r = 0.09, p = .23; mFFI: r = 0.09, p = .20; Fig. 2*A, B*), or IM angle (NPRS: r = 0.03, p = .64; mFFI: r = 0.04, p = .57). Furthermore, no relationship was observed between baseline SF-36 bodily pain domain score (n = 181 observations) and HV (r = −0.19, $p < .05$; Fig. 2*C*) or IM angle (r = −0.07, p = .36).

Disability/Activity Limitation and Angular Deviation

At baseline, no relationships (n = 185 observations in each correlation) were observed between HV or IM angle, and disability (HV angle r = 0.12, p = .12; IM angle r = 0.04, p = .59) or activity limitation scores (HV angle r = 0.14, p = .06; IM angle r = 0.05, p = .47). SF-36 subscales, including physical functioning, did not correlate with either HV or IM angle (data not shown).

Impact of Orthotic Use on Pain Relief

Participants who did (n = 33) and did not (n = 153) use orthotics during the trial reported similar mean (SD) NPRS scores at baseline (placebo: 6.3 [1.6] and 6.6 [1.4]; aboBoNT-A 300U: 6.7 [1.8] and 7.3 [1.6]; aboBoNT-A 500U: 6.5 [1.0] and 6.9 [1.7]; respectively). In the placebo and aboBoNT-A 300U groups, mean (standard error [SE]) changes from baseline in NPRS scores were also similar between participants who did and did not use orthotics, with the greatest changes observed at week 8 (placebo: −2.06 [0.69] and −2.03 [0.35]; aboBoNT-A 300U: −1.80 [0.70] and −1.70 [0.35]; respectively; Table 2). With aboBoNT-A 500U, the greatest changes from baseline were observed at week 8 for participants using orthotics (−2.50 [0.94]) and at week 12 for those who did not use orthotics (−2.53 [0.35]). With numbers available, no statistically significant differences were observed with aboBoNT-A 300U or 500U compared with placebo with or without orthotics at any time point; a trend toward improved efficacy was observed at week 12 with aboBoNT-A 500U compared with placebo in participants who did not use orthotics (p = .0746; Table 2).

The impact of orthotic use was also evaluated using a different measure of treatment benefit in which clinically meaningful pain relief was assessed. The proportion of participants treated with aboBoNT-A 500U who achieved a meaningful response at week 12 was greater in the subgroup of participants who did not use orthoses (51.3% [20/39]) than those who did (16.7% [1/6]; Fig. 3*A*), with no difference between subgroups observed in the placebo group (21.1% [8/38] no orthoses vs 22.2% [2/9] orthotic use).

Impact of Laterality on NPRS Score and Pain Relief

Baseline NPRS scores (mean [SD]) were similar between participants with unilateral (n = 62) and bilateral (n = 124) HV (aboBoNT-A 500U: 6.57 [1.68] vs 6.98 [1.67]; aboBoNT-A 300U: 7.14 [1.54] vs 7.16 [1.70]; placebo: 6.80 [1.48] vs 6.43 [1.36]; respectively). LS mean (SE) change from baseline to week 12 in NPRS score was considerably greater in the

Table 1
Participant demographic and disease characteristics

Characteristic	All Participants (N = 186)
Age, mean (SD), years	48.2 (13.1)
Female, *n* (%)	171 (91.9)
Time since diagnosis, mean (SD), years	6.4 (8.7)
0 days, *n* (%)	29 (15.6)
>0-2 years, *n* (%)	48 (25.8)
>2-5 years, *n* (%)	28 (15.1)
>5 years, *n* (%)	71 (38.2)
Missing	10 (5.4)
NPRS score, mean (SD)	6.9 (1.6)
<7, *n* (%)	94 (50.5)
≥7-9, *n* (%)	69 (37.1)
>9, *n* (%)	22 (11.8)
Missing	1 (0.5)
mFFI subscales, mean (SD)	
Pain	63.8 (16.0)
Disability	56.8 (18.9)
Activity	23.7 (23.1)
SF-36, mean (SD)	
Bodily pain	52.6 (23.1)
General health	79.8 (14.4)
Mental health	78.2 (17.1)
Physical functioning	68.1 (24.8)
Role emotional	83.3 (23.9)
Role physical	67.9 (28.0)
Social functioning	79.4 (23.8)
Vitality	64.2 (18.8)
Mental component	53.6 (9.3)
Physical component	45.6 (8.7)
HV angle, mean (SD), °	20.7 (5.2)
≤20°, *n* (%)	89 (47.8)
>20°, *n* (%)	97 (52.2)
IM angle, mean (SD), °	11.9 (2.4)
≤12°, *n* (%)	114 (61.3)
>12°, *n* (%)	72 (38.7)
Orthotic use	
Yes	33 (17.7)
No	153 (82.3)
HV status, *n* (%)	
Unilateral	62 (33.3)
Bilateral	124 (66.7)

Data for the ITT population are presented.
Abbreviations: HV, hallux valgus; IM, intermetatarsal; ITT, intention-to-treat; mFFI, modified Foot Function Index; NPRS, Numeric Pain Rating Scale; SD, standard deviation; SF-36, 36-item Short-Form Health Survey.

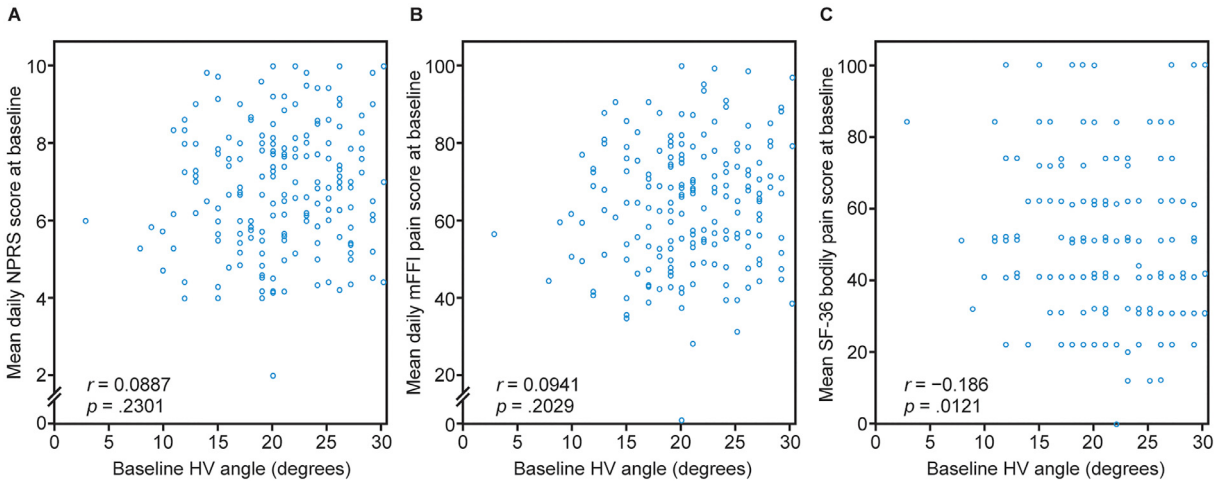

Fig. 2. Lack of relationship between HV angle and participant-reported pain measured with (*A*) NPRS, (*B*) mFFI pain subscale, and (*C*) SF-36 bodily pain domain. Pearson's correlation coefficient was used. (*A*) and (*B*) *N* = 185 observations. (*C*) *N* = 181 observations. HV, hallux valgus; mFFI, modified Foot Function Index; NPRS, Numeric Pain Rating Scale; SF-36, 36-item Short-Form Health Survey.

Table 2
Impact of orthotic use on change from baseline in NPRS score

Time Point	Orthotic Use			No Orthotic Use		
	Placebo (*n* = 13)	AboBoNT-A 300U (*n* = 13)	AboBoNT-A 500U (*n* = 7)	Placebo (*n* = 50)	AboBoNT-A 300U (*n* = 50)	AboBoNT-A 500U (*n* = 53)
Week 4						
LS mean change from baseline (SE)	−1.12 (0.63)	−1.06 (0.67)	−2.46 (0.84)	−1.83 (0.33)	−1.43 (0.33)	−1.74 (0.32)
p value vs placebo	-	.5266	.1008	-	.8086	.5785
Week 8						
LS mean change from baseline (SE)	−2.06 (0.69)	−1.80 (0.70)	−2.50 (0.94)	−2.03 (0.35)	−1.70 (0.35)	−2.38 (0.34)
p value vs placebo	-	.6041	.3501	-	.7448	.2369
Week 12						
LS mean change from baseline (SE)	−1.36 (0.70)	−1.42 (0.70)	−1.73 (0.94)	−1.81 (0.36)	−1.67 (0.35)	−2.53 (0.35)
p value vs placebo	-	.4756	.3752	-	.6087	.0746

Abbreviations: AboBoNT-A, abobotulinumtoxinA; LS, least-squares; NPRS, Numeric Pain Rating Scale; SE, standard error.

aboBoNT-A 500U and placebo groups for participants with unilateral HV than with bilateral HV (aboBoNT-A 500U: −3.06 [0.58] vs −1.99 [0.39]; placebo: −2.45 [0.53] vs −1.19 [0.39]; respectively). Results in the aboBoNT-A 300U group were similar between participants with unilateral and bilateral HV (−1.74 [0.54] and −1.48 [0.38], respectively).

When the proportion of participants achieving a meaningful response was considered by laterality of HV, the placebo effect was similar in participants with unilateral HV compared with bilateral HV (26.3% [5/19] vs 17.9% [5/28], respectively; Fig. 3*B*). However, in the aboBoNT-A 500U arm, a considerably greater proportion of participants with unilateral HV achieved a meaningful response than participants with bilateral HV (73.3% [11/15] vs 33.3% [10/30], respectively; Fig. 3*B*).

Impact of Individual Pain Reporting on Treatment Outcomes

The day-to-day variability of pain severity as reported by individual participants at baseline was assessed for impact on pain reduction 12 weeks after treatment. An SD of >2 for baseline NPRS scores was considered indicative of high pain variability, and a minimal clinically important difference (MCID) of 1.5 was calculated based on MCID values reported via NPRS in postbunionectomy trials (29,30). Variable pain reporting during the 7-day baseline period was observed in a total of 14 participants (placebo, *n* = 5; aboBoNT-A 300U, *n* = 7; aboBoNT-A 500U, *n* = 2), and, of these, 11 (placebo, *n* = 4; aboBoNT-A 300U, *n* = 6; aboBoNT-A 500U, *n* = 1) did not show improvements in NPRS score beyond an MCID at week 12 (Fig. 3*C*).

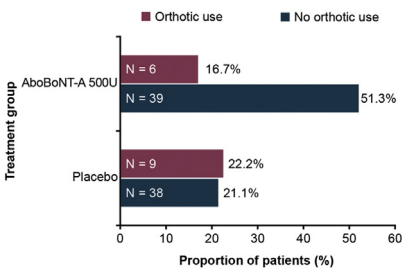

Fig. 3A. Proportion of participants achieving clinically meaningful pain relief at week 12, by orthotic use.[a]

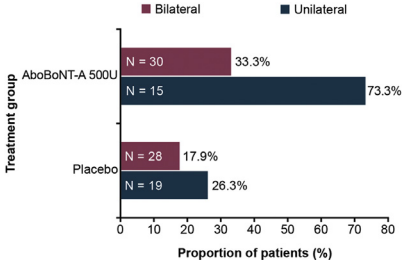

Fig. 3B. Proportion of participants reaching a clinically meaningful pain relief at week 12, by laterality.[a]

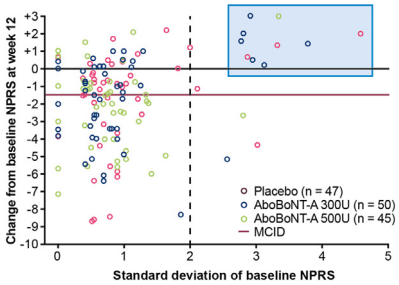

Fig. 3C. Individual NPRS score reporting at week 12 for participants with at least 4 NPRS score values at both baseline and week 12.[b]

[a]Data are presented for the percentage of participants in each subgroup with an NPRS score lower than the minimum NPRS score recorded in the 7 days prior to baseline for all 7 days prior to week 12.

[b]Boxed data indicate variable reporters that are insensitive to change. Dashed line indicates a cut-off of 2 for standard deviation. Solid purple lines indicate the MCID interval.

AboBoNT-A, abobotulinumtoxinA; MCID, minimal clinically important difference; NPRS, Numeric Pain Rating Scale.

Impact of Angle Severity and Chronicity of HV on NPRS Score

No impact on treatment outcome was observed based on the severity of HV or IM angle at baseline. LS mean (SE) change from baseline NPRS score to week 12 in participants receiving aboBoNT-A 500U with an HV angle of ≤20° was −2.33 (0.44) compared with −2.52 (0.48) in participants with an HV angle >20° (placebo: −1.92 [0.45] and −1.52 [0.45], respectively). LS mean (SE) change from baseline NPRS score to week 12 in participants receiving aboBoNT-A 500U with an IM angle of ≤12° was −2.27 (0.42) compared with −2.62 (0.52) in participants with an IM angle of >12° (placebo: −1.80 [0.40] and −1.55 [0.54], respectively). No statistically significant differences between mean NPRS scores were observed with aboBoNT-A 500U compared with placebo at any time point regardless of HV or IM angle, although a trend toward efficacy was observed at week 12 in participants with an HV angle of >20° or an IM angle of >12° (p = .0653 and p = .0773, respectively).

Further to this, baseline pain severity (NPRS) did not impact treatment outcome. However, there was a numerical trend for greater improvement in participants with more severe baseline NPRS scores in the aboBoNT-A 500U group; this trend was mirrored in the placebo group. LS mean (SE) change from baseline to week 12 in participants receiving aboBoNT-A 500U was −1.67 (0.47), −2.71 (0.53), and −4.02 (0.89) in participants with an NPRS score of <7, ≥7-9, or >9 at baseline, respectively (placebo: −0.81 [0.41], −2.47 [0.55], and −4.67 [1.39], respectively). No statistical difference was observed with aboBoNT-A 500U compared with placebo at any time point, although a trend toward efficacy was observed with aboBoNT-A 500U compared with placebo at week 12 in participants with a baseline NPRS score of <7 (p = .0815).

Chronicity (i.e., the amount of time participants have lived with an HV diagnosis) was also found to have no impact on change in pain severity following treatment. LS mean (SE) change from baseline NPRS score to week 12 in participants receiving aboBoNT-A 500U was −2.34 (0.87), −2.16 (0.64), −2.47 (0.96), and −2.74 (0.49) in participants who received a diagnosis at 0 days (n = 8), 0 to 2 years (n = 15), 2 to 5 years (n = 8), and >5 years (n = 26) prior to study enrollment, respectively (placebo: −1.34 [0.68], −1.86 [0.66], −1.67 [0.76], and −2.29 (0.56); n = 14, 15, 11, and 20; respectively). With numbers available, no significant differences were observed with aboBoNT-A 500U compared with placebo at any time point.

Discussion

Emphasis on angular deviation in HV as a determinant of intervention and prognosis has increased in recent years among foot and ankle specialists, in part owing to payor considerations that often require radiographic evidence of minimum angular deviations to approve treatments (12-14). Basing these access decisions on angular deviation alone obviates the impact of the chronic underlying forefoot pain associated with HV even in patients with angular deviations which do not yet warrant surgical correction. There remains a general lack of consensus (based on available data) regarding the relationship between angular deviation in HV and pain or disability associated with the deformity. Other disease factors, such as the extent of bilateral disease, the day-to-day variability of pain severity, concomitant use of orthotic devices, severity of HV and IM angular deviation, pain severity, and chronicity, may impact the efficacy of treatments for pain. We conducted post hoc analyses of data from a large study that evaluated the efficacy and safety of aboBoNT-A compared with placebo as treatment for HV-associated pain in patients who had not yet undergone surgical correction, specifically to explore these factors. These presenting factors may be less clinically apparent than the centrally mediated pain state changes that occur following treatment, but may be important to consider when determining prognosis.

In this study, there was a near complete absence of a relationship between baseline HV or IM angle and participant-reported pain at baseline when measured using the NPRS, which was corroborated using 2 alternative pain measures. This suggests that a relationship between pain and angular deviation in HV is not a universal clinical reality, and that angular deviation alone should not be used to make prognostic and treatment decisions. To our knowledge, this is the first evidence from a large, randomized trial showing no correlation between HV or IM angular deviation and severity of pain using a numeric rating scale. These data add to evidence from previous studies that showed no relationship between HV or IM angle and foot pain as measured using a foot and ankle outcome instrument, SF-36, or a visual analog scale (2,14,31,32). Together, these data indicate that pain status should be an important clinical consideration complementary to the angle of deviation when making treatment decisions related to HV. Conversely, a recent large (N = 512) study of HV measuring pain using a visual analog scale reported a positive correlation between HV angle severity and pain, with the second and third metatarsal bones reported being the main regions of pain, regardless of HV severity (33).

In other studies, an association was reported between HV angle and pain when using the Manchester Foot Pain and Disability Index, a foot health status questionnaire and/or the SF-36 “Bodily Pain” subscale (10,34,35). A study in participants with HV found a strong correlation between physical ability and pain, as recorded with the Foot and Ankle Ability Measure and the Patient-Reported Outcome Measurement Information System (36). In the present study, in addition to assessing the relationship between pain and angular deviation, the relationship between the degree of disability and angular deviation, as well as the degree of activity limitation and angular deviation was evaluated. HV and IM angle showed no correlation with disability scores. Activity limitation scores also did not show an association with HV or IM angle in the present study. This was in line with previous studies using the Foot and Ankle Outcome Score or foot health functional status questionnaire (14,31), but in contrast with another study that utilized the Foot Function Index to measure activity limitation (10). We believe these numerous discordant studies highlight the complex interplay between structural deformity in HV, and shoe gear, pain, and perceived functional limitation, and we look forward to further efforts that explore this domain.

In these post hoc analyses, more participants in the aboBoNT-A 500U group who did not use orthoses reported clinically meaningful pain relief than those who did use orthotics, and than participants in the placebo and aboBoNT-A 300U groups regardless of orthotic use. It is feasible that participants who used orthoses had, historically, more severe pain than participants who did not use them, which was reduced

by orthotic use (because these subgroups had similar baseline NPRS scores) and dampened the subsequent response to aboBoNT-A treatment. More participants with unilateral HV reported improvements in pain than participants with a bilateral HV diagnosis, with almost a full-point difference in mean NPRS score change from baseline between groups. Participants with less variable pain scores at baseline were more likely to report marked pain relief following aboBoNT-A treatment than those with more variable baseline scores, suggesting that patients with high pain variability are not likely to benefit from treatment for pain, though participant numbers were small. In the present study, the majority of highly variable pain reporters were randomized to receive placebo or aboBoNT-A 300U, which may have resulted in more pronounced placebo and nonspecific pain relief responses in these treatment groups as reported in other studies (37,38), leading to a dampening of the pain relief effect observed with aboBoNT-A 500U. Chronicity of HV and the severity of angular deviation did not impact treatment outcome in this study.

Together, these data suggest that HV-associated pain and disability are key presenting factors that should be considered and clinically evaluated independently of angular deviation, and should not be inferred from radiographic results because they do not appear to correlate with HV or IM angle. Consequently, our results support evidence that a lack of correlation between pain and angle may have implications for HV treatment and reimbursement. Some insurance providers require a minimum angle of deviation for corrective HV surgery (12); and may need to focus less on HV/IM angle, and instead prioritize the severity of patient pain and disability as critical factors for either conservative or operative treatment of HV. Laterality, pain variability, and orthotic use should also be taken into account, and may be more important factors to consider than chronicity, or severity of HV/IM angle and pain in determining prognosis. However, further research is required to assess the impact of these factors on presentation of HV and treatment outcome to determine the clinical characteristics of patients who are most likely to experience pain relief with pharmacological treatments such as aboBoNT-A (5).

Although this study was not powered to formally analyze the impact of laterality, pain variability, and orthotic use on pain reporting and treatment outcomes, in these post hoc analyses, potentially clinically relevant differences in sensitivity to treatment effects were observed between subgroups, particularly following aboBoNT-A 500U treatment (for which the greatest pain relief effect was observed in this phase 2 study), and warrant further investigation. Over-the-counter orthotics were permissible only if used for the 30 days prior to screening, resulting in low participant numbers for this subgroup. Additionally, custom-made and dynamic orthotics have been shown to reduce pain in HV more effectively than over-the-counter or static products (39,40), and their inclusion in this study may have further pronounced the separation between the “with” and “without” orthotics groups in terms of treatment response. There are also a number of negative sequelae associated with HV in addition to pain that are important components of the patient experience that were not part of the present analyses, including impact on sleep and the psychological impact of visual deformity.

In conclusion, the results of these post hoc analyses of a large clinical trial in participants with HV who had not undergone surgery suggest that there is little rationale to exclusively consider HV or IM angles to make treatment decisions, particularly surgical correction, because the results of these analyses showed a lack of association between pain and angular deviation in patients with HV and mild to moderate severity forefoot pain. Pain status and its confounding factors should be considered equally relevant to the degree of angular deviation in clinical decision-making for the treatment of HV. This has substantial implications for the standard of care diagnosis and treatment of HV in terms of medical training, acceptable standards of the timing of medical intervention, and how payors consider coverage of HV-related pain and disability in clinical practice and the impact of their sequelae, to address the individualized needs of patients with HV better.

Data Sharing

Anonymized patient-level study data that underlie the results reported in this publication may be made available to researchers who provide a research proposal. Additional relevant study documentation such as the clinical study report, study protocol with any amendments, statistical analysis plan may also be made available. Patient level data will be anonymized, and study documents will be redacted to protect the privacy of study participants. Where applicable, data from eligible studies are available 6 months after the studied medicine and indication have been approved in the USA and EU or after the primary manuscript describing the results has been accepted for publication, whichever is later. Further details on Ipsen’s sharing criteria, eligible studies, and process for sharing are available at https://vivli.org/members/ourmembers. Any requests should be submitted to www.vivli.org for assessment by an independent scientific review board.

Authors’ Contributions

Substantial contributions to study design and data acquisition: B.B., L.A.D., M.V., D.G.A., and R.S. Data analysis or interpretation: M.V. Drafting of the publication or revising it critically for important intellectual content: all authors. Final approval of the publication: all authors.

Ethics Statement

The study was approved by appropriate health authorities and by independent ethics committees/institutional review boards, and was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Consolidated Guideline on Good Clinical Practice and all local regulatory guidelines. Written informed consent was provided by all participants prior to enrollment.

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