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Research Submission

Long-Term Outcome of Patients With Intractable Chronic Cluster Headache Treated With Injection of Onabotulinum Toxin A Toward the Sphenopalatine Ganglion – An Observational Study

Irina Aschehoug, MSc; Daniel Fossum Bratbak, MD, PhD; Erling Andreas Tronvik, MD, PhD

Objectives.—To investigate long-term outcomes in per-protocol chronic cluster headache patients (n = 7), 18 and 24 months after participation in "Pilot study of sphenopalatine injection of onabotulinumtoxinA for the treatment of intractable chronic cluster headache."

Methods.—Data were collected prospectively through headache diaries, HIT-6, and open questionnaire forms at 18 and 24 months after the first treatment. Patients had access to repeated injections when needed.

Results.—An overall significant reduction in cluster headache attack frequency per month (57.3 ± 35.6 at baseline vs 12.4 ± 15.2 at month 18 and 24.6 ± 19.2 at month 24) was found. In addition, there was a reduction in attacks with severe and unbearably intensity (50.0 ± 38.3 at baseline vs 10.1 ± 14.7 at month 18 and 16.6 ± 13.7 at month 24) and an increase in attack free days (4.2 ± 5.9 at baseline vs 19.1 ± 9.4 at month 18 and 12.9 ± 8.8 at month 24).

Conclusions.—Our findings suggest sustained headache relief after repeated onabotulinumtoxinA injections toward the sphenopalatine ganglion in intractable chronic cluster headache. A placebo-controlled trial with long-term follow-up is warranted.

Key words: chronic cluster headache, cluster headache, sphenopalatine ganglion, botulinum toxin, headache

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From the Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway (I. Aschehoug, D.F. Bratbak, E.A. Tronvik); Department of Neurosurgery, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway (D.F. Bratbak); Department of Neurology, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway (E.A. Tronvik); Norwegian Advisory Unit on Headaches, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway (E.A. Tronvik).

Address all correspondence to Irina Aschehoug, MSc, Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Edvard Griegs gate 8, 7030, Trondheim, Norway, email: irina.aschehoug@ntnu.no

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INTRODUCTION

Cluster headache (CH) is considered to be one of the most painful primary headache disorders. A sufficient reduction of attack frequency can be achieved with prophylactic medication in some patients with episodic CH. However, chronic CH (CCH) is often refractory to standard drug therapy. CH has a substantial impact on health-related quality of life (HRQoL).[1] Interventional procedures may be necessary when drug therapy fails, but the procedures available today are resource demanding and have the potential for serious adverse events (AEs) that may limit the use of these techniques.[2,3] Less invasive and more tolerable procedures are warranted.

The sphenopalatine ganglion (SPG) is a large extracranial parasympathetic ganglion located in the pterygopalatine fossa and is thought to play a key role in CH pathogenesis.[4,5] In a prospective, open-label pilot study, our research group (Bratbak et al) performed blockade of the SPG with 25 to 50 IU onabotulinumtoxin type A (BTA) in 10 patients with CCH.[6] The treatment was performed with a transnasal technique in 9 out of 10 subjects; in one subject a percutaneous infrazygomatic (lateral) approach was preferred due to anatomical anomalies. A novel surgical navigation device (MultiGuide, Trondheim, Norway; Fig. 1) was used to perform the injection. In this pilot study, a significant reduction (≥50%) in CH attack frequency was observed in 5 out of 7 per-protocol (PP) patients.[6] After the pilot study, patients experiencing recurring attacks had access to repeated injections with minimal intervals of 3 months using the lateral injection technique (Fig. 2) in an outpatient, office-based setting.

To assess long-term outcomes for the PP patients that participated in the pilot study,[6] a follow-up study was conducted. The primary objective of the follow-up study was to evaluate changes in CH attack frequency 18 and 24 months after the initial BTA injection. Secondary aims were to evaluate CH attack duration and intensity, triptan use, patient experience with the lateral injection technique in those receiving repeated injections, AEs after repeated injections, and quality of life parameters.

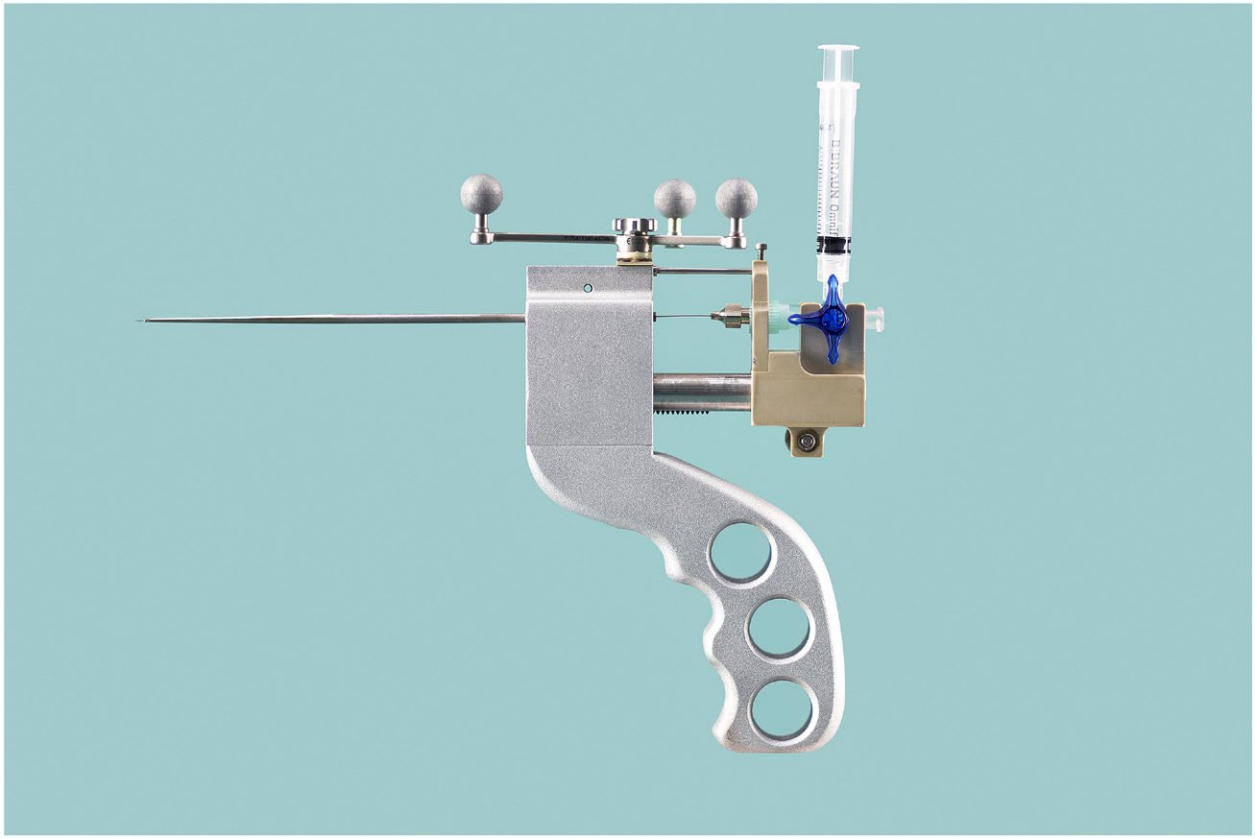

Fig. 1.—MultiGuide – a novel surgical navigation device to perform the injections. [Color figure can be viewed at wileyonlinelibrary.com]

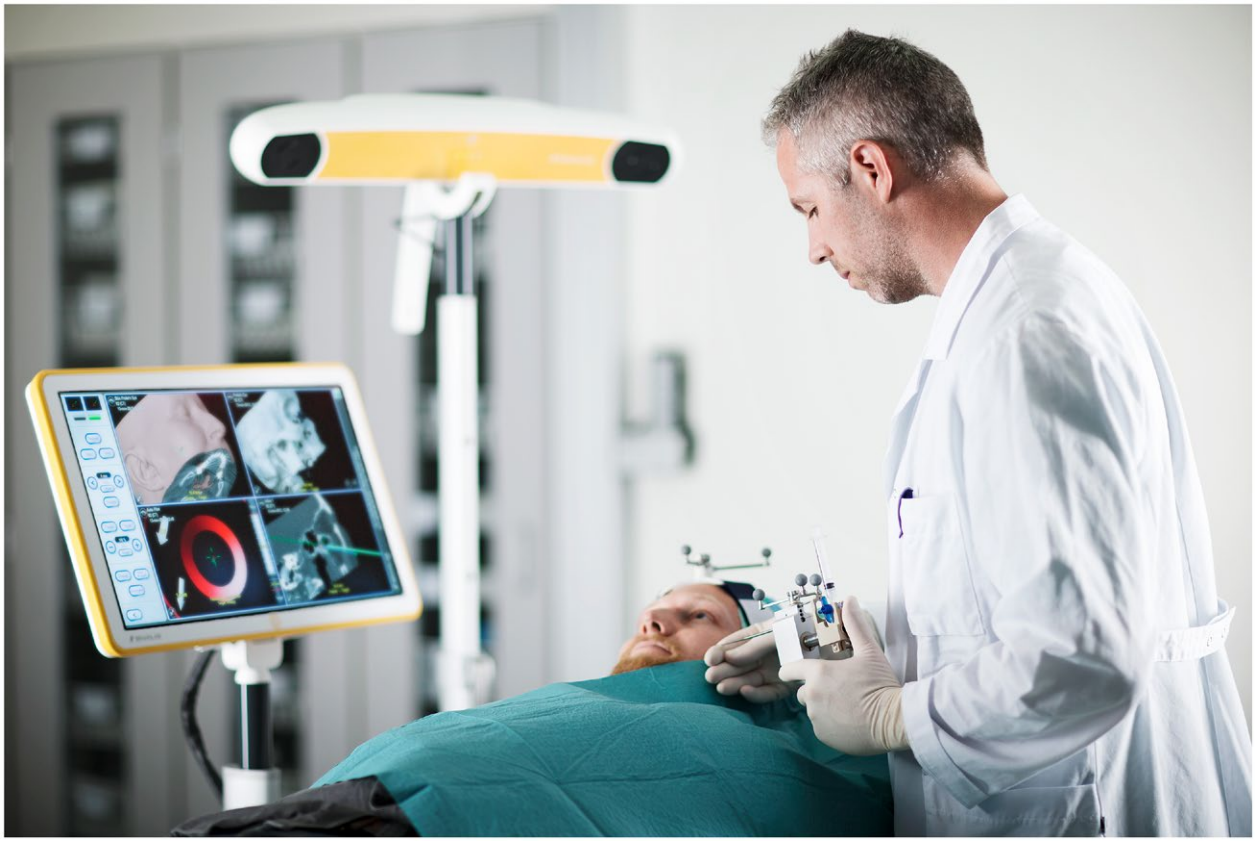

Fig. 2.—An illustration of sphenopalatine ganglion block with botulinum toxin type A with lateral injection technique in an outpatient, office-based setting. [Color figure can be viewed at wileyonlinelibrary.com]

METHODS

Study Design.—This is a prospective observational study. The investigators conducted a follow-up 18 and 24 months after the initial BTA injection against SPG, using headache diaries and questionnaires at month 18 and 24. Data were collected between February 2015 and January 2016. After completing the pilot study, patients had access to repeated injections at timepoints as needed by patients (minimum 3 months between injections). The study protocol was approved by the regional ethics committee (ref. 2015/1194).

Participants.—Per-protocol patients (n = 7) from the pilot study[6] were invited to participate in the follow-up study, and all were included. Patients (n = 3) who were lost to follow-up after the initial injection[6] were not invited to participate in this follow-up study. Written informed consent was obtained from each participant prior to the inclusion and participation in the study was voluntary.

Data Collection.—The follow-up data (Tables 1–3) were collected prospectively using headache diaries and questionnaires. Outcome data for post injection months 18 and 24 were obtained using headache diaries. Each month was defined as 28 calendar days and the 18th and 24th post injection months were calculated individually for each participant. The participants were asked to keep headache diaries during this time period, recording headache attack frequency, duration, and intensity (using categorical intensity scale: 1 = mild, 2 = moderate, 3 = severe, 4 = unbearable intensity), in addition to use of triptans. These time periods were compared to the baseline period (before the initial BTA injection) obtained from the original pilot study.[6]

In addition, 2 general questionnaire forms with open questions about satisfaction with the treatment, changes in life situation after treatment, prophylactic medication use, experience with lateral injection (for subjects receiving repeated treatments during this 24

Table 1.—Primary and Secondary Outcome Measurements for Baseline and After 18 and 24 Months After Initial Injection With OnabotulinumtoxinA Toward the Sphenopalatine Ganglion (n = 7)

	Baseline	Month 18	*P* value	Month 24	*P* value
Number of attacks of all intensities per week	14.3 ± 8.9	3.1 ± 3.8	**(.018)**	6.1 ± 4.8	**(.018)**
Number of attacks, intensity 3 or 4[a] per month	50.0 ± 38.3	10.1 ± 14.7	**(.018)**	16.6 ± 13.7	**(.028)**
Number of attacks of all intensities per month	57.3 ± 35.6	12.4 ± 15.2	**(.018)**	24.6 ± 19.2	**(.018)**
Intensity per attack[a]	3.50 ± 1.05	2.4 ± 1.8	(.237)	2.7 ± 1.5	(.063)
Duration per month[b]	1345.0 ± 793.9	380.7 ± 370.2	(.075)	552.0 ± 537.2	(.249)
Duration per attack[b]	35.6 ± 24.8	28.2 ± 40.7	(.753)	30.9 ± 44.0	(.917)
CH-free days per month	4.2 ± 5.9	19.1 ± 9.4	**(.027)**	12.9 ± 8.8	**(.018)**
Triptan doses per month[c]	91.3 ± 49.1	19.5 ± 22.0	(.068)	53.5 ± 42.4	(.068)
HIT-6	65.1 ± 2.7	N/A		59.9 ± 11.3	(.207)

Results are presented as mean ± SD. *P* values ≤ .05 are depicted in bold.

CH = cluster headache; HIT-6 = Headache Impact Test.

[a]Categorical intensity scale: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = unbearable.

[b]Minutes.

[c]Four of 7 patients used triptan as acute cluster headache attack treatment.

Table 2.—Point Estimate (Median Difference with 95% CI) Between Baseline and Month 18 and Month 24 for All Significant Results

	Baseline vs Month 18	*P* value	Baseline vs Month 24	*P* value
Number of attacks of all intensities per week	−9.7 (−22.6; −1.8)	(.018)	−8.1 (−15.5; −1.3)	(.018)
Number of attacks, intensity 3 or 4[a] per month	−31.9 (−82.4; −4.1)	(.018)	−28.8 (−63.2; −8.0)	(.028)
Number of attacks of all intensities per month	−38.9 (−90.2; −7.5)	(.018)	−32.5 (−61.8; −5.0)	(.018)
CH-free days per month	14.6 (4.0; 28.0)	(.027)	6.5 (2.1; 17.7)	(.018)

CH = cluster headache; CI = confidence interval.

[a]Categorical intensity scale: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = unbearable.

month period) and occurrence of AEs after repeated treatment were used. Assessment of headache related disability was measured using the Headache Impact Test-6 (HIT-6). The pain/discomfort during injections with a percutaneous infrazygomatic approach was assessed using a visual analog scale for pain (VAS Pain), from 0 to 10, where 0 indicates no pain/discomfort and 10 indicates unbearable pain.

Repeated Treatment (With a Percutaneous Infrazygomatic Approach).—After the initial BTA injection against SPG, patients experiencing recurring attacks had access to repeated injections with minimal intervals of 3 months. Repeated treatment was performed using percutaneous infrazygomatic (lateral) approach under local anesthesia on awake patients in an outpatient, office-based setting (Fig. 2). A novel injection device (MultiGuide; Fig. 1), aided by surgical navigation (Brainlab Kick version 1, Brainlab AG, Feldkirchen, Germany), was used to perform the injections. Surgical navigation displays the tip of the needle relative to the pre-acquired medical image. MultiGuide enables the use of surgical navigation for high-precision procedures on awake individuals. Computed tomography (CT) of paranasal sinuses and magnetic resonance

Table 3.—Cluster Headache Attack Frequency per Week in Each Patient at Baseline (Before the Initial OnobotulinumtoxinA Injection Toward the Sphenopalatine Ganglion) and Percentage Change 18 and 24 Months Post-Treatment

	Attack Frequency per Week			
		Percentage Reduction from Baseline		
Patient	BL	M18 (%)	M24 (%)	Number of Repeated Injections
1	30.2	**−100**	**−51**	× 2 (M12 and M21)
2	15.0	**−65**	**−63**	× 2 (M18 and M24)
3	15.2	**−98**	**−51**	× 6 (M7, M10, M13, M16, M19, M21)
4	17.5	**−100**	**−100**	—
5	3.5	**−50**	−7	× 6 (M7, M10, M13, M16, M19, M23)
6	4.5	−6	−28	× 1 (M13)
7	14.3	−28	−39	—

Responders (≥50% reduction from baseline) are depicted in bold.
BL = baseline; M = month.

imaging (MRI) of head scans made prior the initial injection were used. Pre-treatment planning of CT and MRI was performed with Brainlab iPlan 3.0 (Brainlab AG). The SPG on the side of the pain was localized visually and marked on fused MRI and CT scans and the trajectory was calculated.

The patient was placed in supine position. First, the skin and deep structures toward the sphenopalatine fossa were anesthetized with 3–5 mL Marcaine-Adrenaline (5 mg/mL, 5 µg/mL, AstraZeneca, Oslo, Norway) and then a 1–2 mm skin incision was made. BTA (Botox, Allergan Inc, Irvine, CA, USA) was injected toward the SPG using MultiGuide aided by surgical navigation. Once MultiGuide needle tip reached the SPG, an aspiration for 5–10 seconds was performed to prevent intravascular injection. Estimated duration of the injection is 1–3 minutes, and for the whole procedure including patient preparation, injection area preparation, and injection of local anesthetic about 15–20 minutes. All patients who received repeated injections were injected with 25 or 50 IU BTA suspended in 0.5 mL isotonic saline.

Statistical Analysis and Outcomes.—Statistical analysis was carried out using SPSS (SPSS Inc., Chicago, IL, USA, version 21.0) and $P < .05$ was set as level of significance. The primary outcome (CH attack frequency per week in baseline versus month 18 and 24 counting from the first injection), as well as secondary outcomes (mean changes in intensity and duration of CH attacks, HIT-6, headache free days, and triptan doses) were assessed using Wilcoxon signed-rank test. The analysis was conducted without imputing missing data (no values were missing). The results are presented as mean and standard deviation (mean ± SD), which allows for comparison of the 18 and 24 months results to baseline data (expressed as mean ± SD) and data from the whole study period in the pilot study.[6] No corrections for 2 inferences were made. Wilcoxon test was used to find the median difference between baseline and month 18 and month 24. To calculate 95% confidence interval (CI), the Hodges–Lehman procedure was used. Some secondary outcome data were collected through questionnaires and were not eligible for statistical analysis. These data are presented in their entirety.

RESULTS

Seven (n = 7) per-protocol patients (3 female and 4 male with mean age 50 ± 13 years) from the pilot study[6] were included in the follow-up study. All participants completed the follow-up period and returned headache diaries and questionnaires.

Primary Outcome.—Baseline CH attack frequency per week 14.3 ± 8.9 was reduced to 3.1 ± 3.8 ($P = .018$) in month 18 counting from the first injection and to 6.1 ± 4.8 ($P = .018$) in month 24 (Table 1). The overall number of CH attacks of all intensity per month was decreased from 57.3 ± 35.6

in the baseline to 12.4 ± 15.2 (P = .018) at month 18 and to 24.6 ± 19.2 (P = .028) at month 24. Point estimates (median difference with 95% CI) between baseline and month 18 and month 24 for all significant results in Table 1 are provided in Table 2. The CH attack frequency per week was reduced ≥ 50% in 5 out of 7 patients during month 18 and in 4 patients during month 24 (Table 3).

Secondary Outcomes.—The number of CH attack-free days per month increased from 4.2 ± 5.9 at baseline to 19.1 ± 9.4 (P = .027) and 12.9 ± 8.8 (P = .018) in the months 18 and 24, respectively. Other, non-significant outcomes are shown in Tables 1 and 3.

Repeated Treatment (With a Percutaneous Infrazygomatic Approach).—During the first 24 months after first BTA injection, 5 of 7 patients received repeated treatment at different time points (as needed). One patient repeated treatment 1 time, 2 patients repeated 2 times, and 2 patients repeated treatment 6 times during the 24 months. The remaining 2 PP patients did not get repeated injections: one was headache-free after the initial injection and the other one was a non-responder after the first injection and did not repeat the treatment.

The mean pain/discomfort that participants experienced during the injection procedure, measured using VAS Pain (0–10), was 3.2 ± 1.9. All 5 patients reported that experiencing a CH attack is much more painful than receiving one injection using percutaneous infrazygomatic (lateral) approach under local anesthesia. Four out of 5 patients would prefer the lateral injection technique in local anesthesia over the transnasal technique with general anesthesia. One patient would prefer the transnasal approach, because the effect of the injection, in the patient's opinion, lasted longer. When asked how many aborted CH attacks would be needed to justify treatment with one injection, 2 patients answered one attack, 2 patients 2–5 attacks, and one patient 5–10 attacks.

Retrospective Headache Diary Data.—The headache diary data, collected for clinical purpose, is displayed graphically in Figure 3 (retrospective data). These data are not complete and therefore no calculations have been performed on them, but they may give an impression on the course of the headache pattern in all 7 patients. The timing of the injections have also been marked in the figures.

Adverse Events.—There were no ongoing AEs in the PP patients 6 months after the initial BTA injection.[6] Two (number of repeated injections for both patients = 6) of 5 patients reported occurrence of AEs after repeated treatment. One patient experienced transient accommodation problems 3 times after repeated injections (previously also experienced after the initial BTA injection) and jaw pain once. The second patient reported having difficulty with jaw opening after one of the repeated treatments, cheek swelling twice, and having headache and nose bleeding after one repeated treatment. All AEs were mild to moderate and transient.

Patient Satisfaction with the Treatment.—The overall patient satisfaction with the treatment (counting for both initial and repeated injections) was determined by the following scale: completely satisfied, satisfied, moderately satisfied, or little satisfied. Twenty-four months post injection 2 patients were completely satisfied with the received treatment, 2 patients satisfied, 2 moderately satisfied, and 1 little satisfied. All patients would like to repeat treatment when needed as well as recommend this type of treatment to a person equally afflicted with CH.

After the initial BTA injection none of the patients had started new preventive medication. One male patient, who had been suffering from CH continuously for 18 years, has not experienced any attacks since the first injection, discontinued using verapamil, and has returned to full-time work. Two patients (one of which reduced doses of verapamil and lithium) who had stopped working because of their CH attacks returned to half-time work 24 months after the first BTA injection.

DISCUSSION

The present report evaluates the long-term results of using stereotactically guided BTA injections toward the SPG in 7 subjects. Prospectively, but not placebo-controlled, we found a significant long-term reduction in number of CH attacks in CCH patients who received repeated injections. Of the 7 patients (5 of whom received repeated BTA injections) who supplied follow-up data at 18 and 24 months after the first BTA injection, a significant reduction was demonstrated in the number of CH attacks overall and in the number of attacks with severe and/

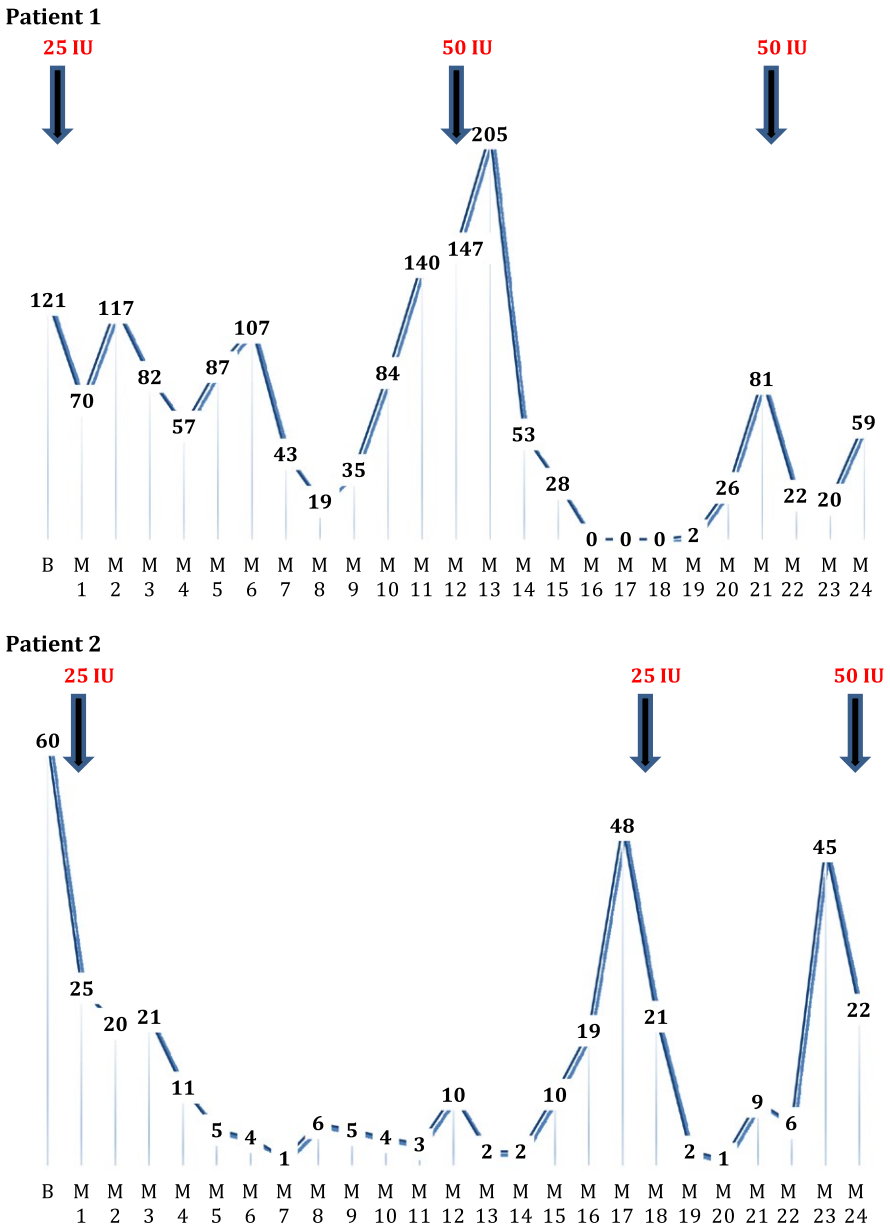

Fig. 3.—Retrospectively collected data on number of cluster headache attacks per month per per-protocol patient during a 24-month period. IU = units of onabotulinumtoxinA; B = baseline; M = month in follow-up after first injection of onabotulinumtoxinA. The first 6 months displayed are part of the pilot study. Months 18 and 24 are the months with prospectively collected data presented in this paper. The time of injection of onabotulinumtoxinA is marked with arrows. Patient 5 had a failed first injection as denoted in the pilot study.

or unbearable intensity. In addition, there was a significant increase in the number of headache-free days during month 18 and 24 compared to baseline. A significant long-term reduction (≥50%) in number of CH attacks was seen in 4 out of 5 patients who received repeated injections. A mean reduction of 5.2 in HIT-6 score may be a meaningful difference in quality of life, even though it was not statistically significant (Table 1).

A new technique using a lateral stereotactically guided percutaneous approach to inject BTA toward SPG was used to perform repeated injections in the 2 years after the pilot study. Compared to the initial BTA injection, which was performed with transnasal approach under general anesthesia,[6] the use of this new technique allowed us to perform injections using local anesthesia in an outpatient, office-based setting. The repeated injections performed in outpatient,

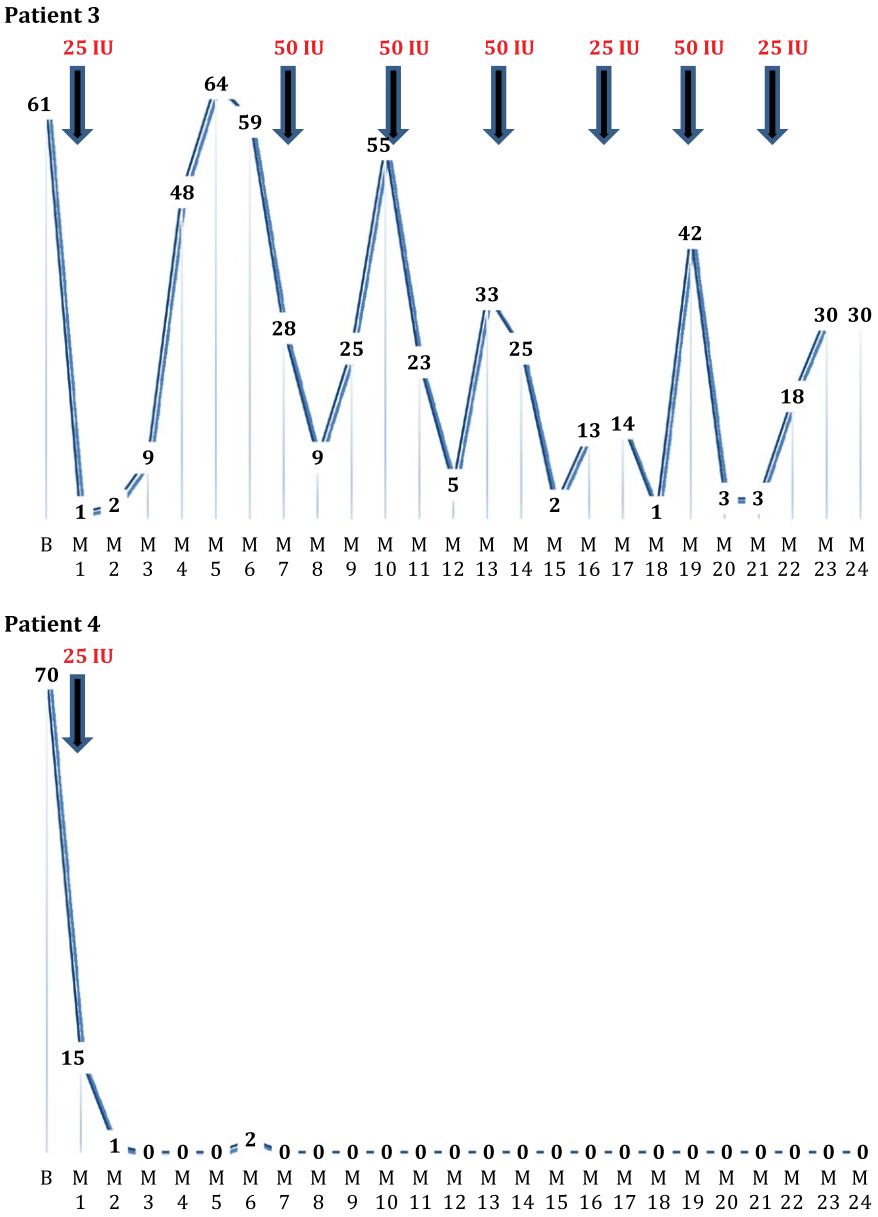

Fig. 3.—(Continued)

office-based setting were less time and resourse consuming: patients spent less time in the hospital, compared to initial injection performed in the operating room, and for the injections performed in office-based setting under local anesthesia, there was no need for anesthesia personnel.

Use of the infrazygomatic approach to reach the SPG has previously been performed using lateral fluoroscopy[7] or CT-guided injections.[8] The disadvantage of these methods, however, is that fluoroscopy requires continuous X-ray images and detailed anatomical knowledge of the area, while CT-guided injection is limited by the number of repeated injections that can be performed (radiation), in addition to being more resource demanding and cumbersome. The MultiGuide tool is basically an advanced needle, attached to a surgical navigation system, through which the drug can be deposited. The injection time is short (2–4 minutes), it can be performed in an ordinary office setting, and the procedure can be repeated as many times as necessary using just one CT image.

The lateral approach technique was well accepted by all patients who received repeated treatment (n = 5) and the AEs observed were transient and experienced as acceptable by the patients. Transient

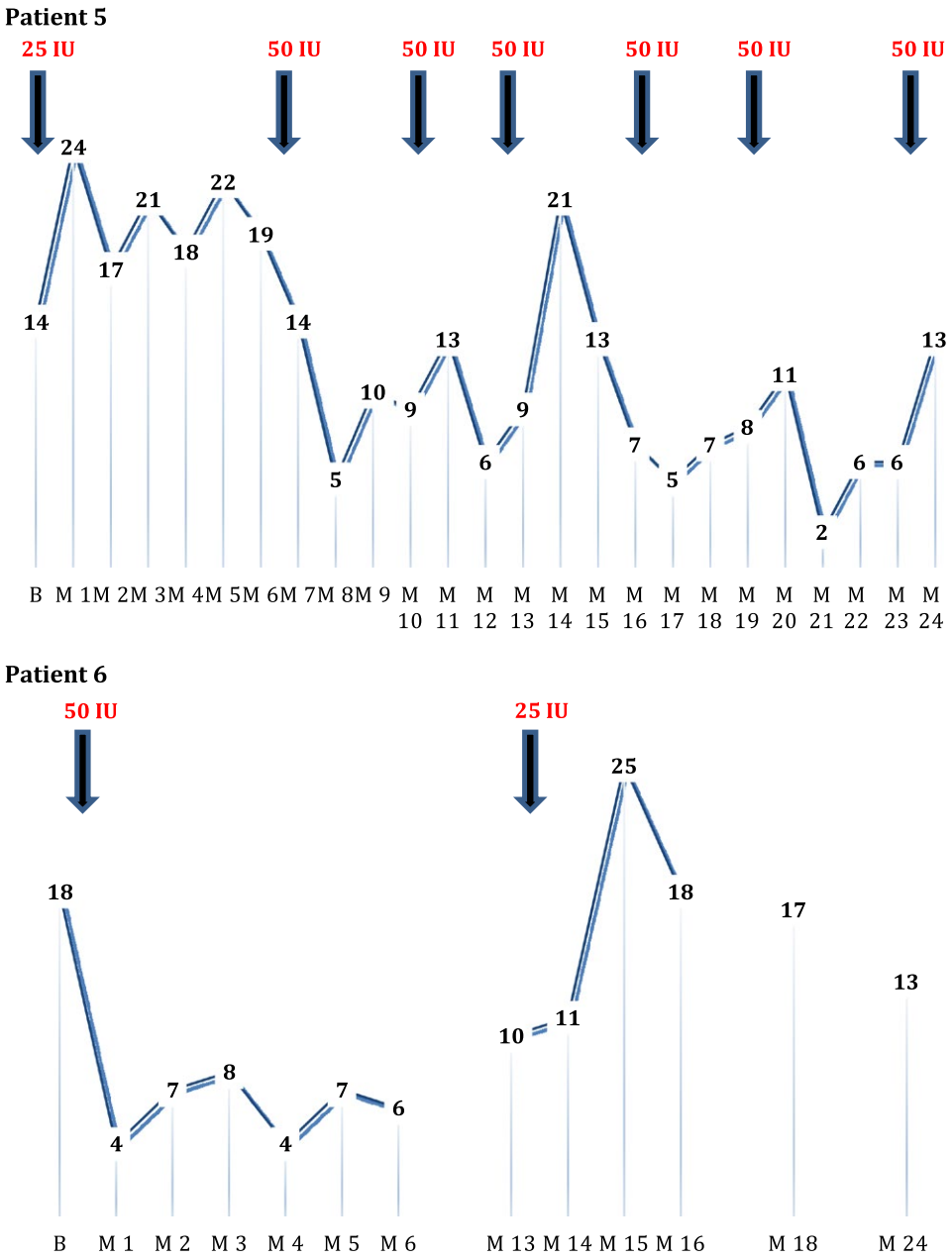

Fig. 3.—(Continued)

accommodation problems were present in one patient. This may be due to diffusion of botulinum toxin toward the rectus inferior muscle, but there was no diplopia or abnormal examination when examined by an ophthalmologist. There were no serious adverse events (SAE) registered. The same injection technique was also used in a small study with 10 patients with intractable chronic migraine (study performed by our research group) who received bilateral injections.[9] The procedure was well accepted also by these patients, and the AEs registered were classified as mild and resolved within 1–12 weeks. The lateral approach technique allows BTA block procedure to be performed on awake patients and thus excludes all risk associated with general anesthesia, as well as excludes the risk of nasal bleeding, which is associated with transnasal injection toward the SPG.

Different types of neurostimulation regimens have shown efficacy in treatment of CH.[10,11] These are more invasive and relatively expensive interventions, factors that may limit widespread clinical use. Compared to neurostimulation interventions, BTA injection toward the SPG using the lateral approach technique is less invasive, currently shown to have a low risk for SAE and

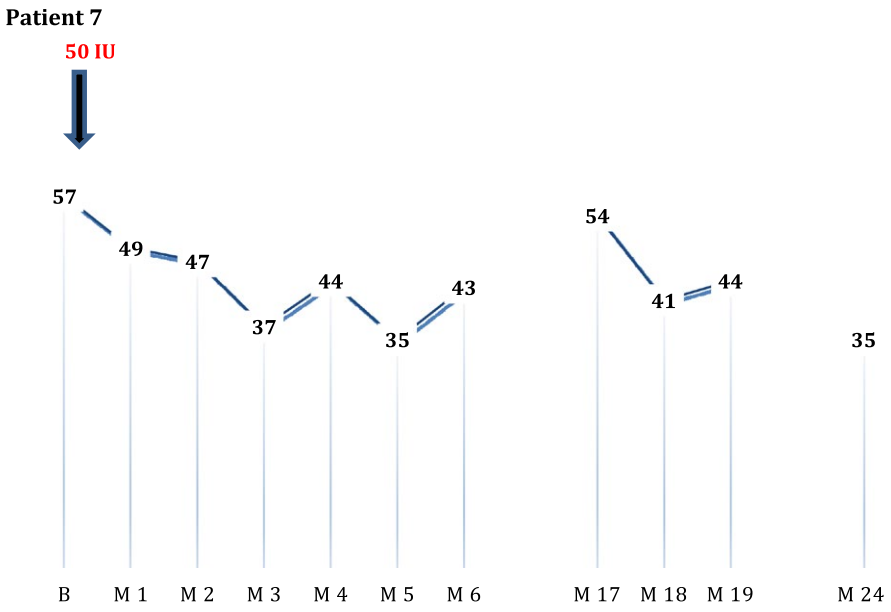

Fig. 3.—(Continued)

with emerging data showing promising results in CCH patients. However, a randomized, placebo-controlled trial is required to confirm the efficacy and safety of repeated injections of BTA toward the SPG.

Our findings after a 2-year follow-up suggest that injection with BTA toward the SPG has the potential to be an effective long-term treatment for CCH patients and thus this treatment modality should be investigated further.

LIMITATION

Due to the small sample size and uncontrolled design, the results of this follow-up study should be interpreted with extreme caution, and should be considered hypothesis-generating only. Three out of 10 patients receiving the initial injection were drop-outs. The fact that only 7 of the patients were available for follow-up could influence the actual effect size, considering the initial target population. However, it should also be taken into account that the overall results may be underestimated, since patients got repeated injections at different time points. The registration of headache diary data was performed at month 18 and 24 for all patients regardless of when their last injection was performed. For some patients this would mean that they were in a month where the therapeutic effect of the last injection was wearing off and they were experiencing an increased number of CH attacks while waiting for the next injection.

CONCLUSION

Randomized, placebo-controlled trials on a larger population, with regularly scheduled injections and long-term follow-up, are needed to confirm the effect of BTA injections toward the SPG in cluster headache.

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STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design

Irina Aschehoug, Daniel Fossum Bratbak, Erling Andreas Tronvik

(b) Acquisition of Data

Irina Aschehoug, Daniel Fossum Bratbak, Erling Andreas Tronvik

(c) Analysis and Interpretation of Data

Irina Aschehoug, Daniel Fossum Bratbak, Erling Andreas Tronvik

Category 2

(a) Drafting the Manuscript

Irina Aschehoug, Daniel Fossum Bratbak, Erling Andreas Tronvik

(b) Revising It for Intellectual Content

Irina Aschehoug, Daniel Fossum Bratbak, Erling Andreas Tronvik

Category 3

(a) Final Approval of the Completed Manuscript

Irina Aschehoug, Daniel Fossum Bratbak, Erling Andreas Tronvik

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