Botulinum Toxin Type A Induces Direct Analgesic Effects in Chronic Neuropathic Pain

Danièle Ranoux, MD,[1] Nadine Attal, MD, PhD,[2–4] Francoise Morain, Clinical Research Assistant,[2–4] and D. Bouhassira[2–4]

Objective: Botulinum toxin type A (BTX-A) has been reported to have analgesic effects independent of its action on muscle tone, possibly by acting on neurogenic inflammation. Such a mechanism may be involved in peripheral neuropathic pain.
Methods: A possible direct analgesic effect of BTX-A pain processing was investigated in 29 patients with focal painful neuropathies and mechanical allodynia using a randomized, double-blind, placebo-controlled design. Patients received a one-time intradermal administration of BTX-A (20–190 units) into the painful area. Outcome measures, evaluated at baseline, then at 4, 12, and 24 weeks, included average spontaneous pain intensity, quantified testing of thermal and mechanical perception and pain, allodynia to brushing (area, intensity), neuropathic symptoms, clinical global impression, and quality of life.
Results: BTX-A treatment, relative to placebo, was associated with persistent effects on spontaneous pain intensity from 2 weeks after the injection to 14 weeks. These effects correlated with the preservation of thermal sensation at baseline ($p < 0.05$). BTX also improved allodynia to brush and decreased pain thresholds to cold, without affecting perception thresholds. There were sustained improvements in the proportion of responders (number needed to treat for 50% pain relief: 3.03 at 12 weeks), neuropathic symptoms, and general activity. Most patients reported pain during the injections, but there were no further local or systemic side effects.
Interpretation: These results indicate for the first time that BTX-A may induce direct analgesic effects in patients with chronic neuropathic pain independent of its effects on muscle tone and suggest novel indications for BTX-A in analgesia.

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Botulinum toxin type A (BTX-A), a potent neurotoxin, is commonly used for the treatment of focal muscle hyperactivity, particularly dystonia and spasticity,[1,2] and the management of glandular hyperactivity, including hyperhidrosis.[3] The beneficial effect of BTX-A in these conditions is believed to result from the blockade of presynaptic nerve terminals releasing acetylcholine.[4–6] However, early in the use of BTX-A for dystonia, some authors noted that pain relief preceded muscle decontraction and exceeded what would have been expected solely as a consequence of muscle relaxation.[4] These findings suggest that BTX-A might have analgesic properties independent of its myorelaxant action. Further information came from in vitro experiments demonstrating that BTX-A could inhibit neurogenic inflammation, a process that results from the sensitization of C-fiber nociceptors[7]; the effects of BTX-A involved attenuation of the release of neurotransmitters including substance P,[8,9] calcitonin gene–related peptide,[10,11] and glutamate,[12] and inhibition of vanilloid receptor activity.[13] Consistent with these in vitro experiments, peripheral injections of BTX-A reduces nociceptive behaviors in animal models of inflammatory[12,14] and traumatic neuropathic pain.[15–17]

Neurogenic pain mechanisms may play a role in neuropathic pain because of peripheral nerve lesions,[18] particularly those associated with allodynia, such as postherpetic neuralgia and posttraumatic/postoperative nerve lesions.[18–21] These chronic pain conditions are significant causes of focal painful neuropathies[22,23] and are difficult to treat and often devastating.[24–26] In most cases, the area involved is limited; thus, local injections of BTX-A may be suitable. The efficacy of BTX-A in neuropathic pain has been suggested only in small anecdotal case reports.[27–30]

In this study, we investigated for the first time the

From the [1]Services de Neurologie, Neurochirurgie et Soins Palliatifs, Centre Hospitalier Universitaire de Limoges, Limoges, France; [2]Institut National de la Sante et de la Recherche Médicale U-792; [3]Centre Hospitalier Universitaire Ambroise Paré, Assistance Publique-Hôpitaux de Paris, Boulogne-Billancourt; and [4]Université Versailles-Saint-Quentin, Versailles, France.

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Address correspondence to Dr Attal, INSERM U-792, Centre de Traitement et d'Evaluation de la Douleur, CHU Ambroise Paré, 9, avenue Charles de Gaulle, 92100 Boulogne-Billancourt cedex, France. E-mail: nadine.attal@apr.aphp.fr

potential direct analgesic effects of one-time BTX-A in the painful area in patients with focal neuropathic pain (eg, posttraumatic/postoperative pain or postherpetic neuralgia) associated with allodynia using a double-blind, placebo-controlled parallel group design. The injections were performed intradermally to exclude effects on muscle tone.

Patients and Methods

This study was conducted at Ambroise Paré Hospital, Boulogne-Billancourt, and was approved by local ethics committee. Patients were recruited between June 2004 and October 2006 by means of physician referrals, and provided written informed consent before inclusion.

Patients

Consecutive patients with postherpetic neuralgia or posttraumatic/postoperative neuropathies confirmed by appropriate clinical and paraclinical examination when necessary (eg, electromyography) were recruited and gave written informed consent. Criteria for inclusion were daily pain for at least 6 months (numerical score of at least 3 of 10) clearly attributed to the nerve lesion, limited area of pain (not exceeding $60cm^2$, corresponding to the maximal doses of BTX-A as indicated later), and mechanical allodynia in the painful area. Exclusion criteria were contraindication for BTX-A (ie, diseases of the neuromuscular junction), hypersensitivity to the BTX-A formulation, coagulation disorders, any other painful condition, current major depression, a history of serious drug or alcohol abuse, compensation claim or litigation, and facial pain (caused by potential increased adverse effects of BTX-A in this area). Concomitant analgesic medication was authorized, provided the dose was stable for at least 1 month before enrollment and throughout the study. Treatments acting on neuromuscular junctions and topical medications or procedural therapies (eg, anesthetic blocks) were forbidden.

Protocol

A randomized, double-blind, placebo-controlled, parallel group design was used. A total of four visits was scheduled over 24 weeks (at baseline, and after 4, 12, and 24 weeks). During the 7-day baseline period, all patients underwent testing for allodynia and were asked to record their pain intensity in a diary; eligible patients were then randomly assigned to two groups: one given the active drug and the other the placebo. A pharmacist prepared a concealed allocation schedule randomly assigning the treatments in blocks of four, to a consecutive series of numbers. The treatment allocation code was kept in a sealed envelope until the completion of the study.

Treatment was administered by a neurologist not involved in the assessment. Aliquots of 100U/vial BTX-A (BOTOX, Allergan) were reconstituted with 4ml nonpreserved saline solution (0.9%) as recommended by the manufacturer (concentration of 5 units BTX-A/0.2ml), and placebo consisted of an equal volume of saline (9% NaCl). The injection of BTX-A or saline was performed according to a procedure adapted from that used for hyperhidrosis[31]: BTX-A or placebo was injected intradermally into the skin 1.5cm apart (0.2ml, and thus 5 units of BTX-A per site) (Fig 1). We first mapped with a pen the exact area of mechanical allodynia for all patients. We then determined the number of injections so as to cover the whole allodynic area, without exceeding the predetermined maximum number of sites, which was fixed at 40 (corresponding to a dose of 200 units).

The two solutions were limpid and indistinguishable. The injection syringes were prepared by the pharmacist in such a way that the physician performing the injection could not recognize the treatment. Patients and the investigator were blind to the treatments throughout the study.

All patients received a cream formulation of lidocaine and prilocaine (EMLA) applied to the painful area 60 minutes before the injections to minimize the pain caused by injections; a nurse also administered an equimolar mix of nitrous oxide and oxygen (N_2O/O_2) via a high-concentration mask for 5 minutes before the beginning and throughout the procedure.

Outcome Measures

The primary outcome measure was self-reported average pain intensity from each morning's record in a diary concerning the last 24 hours using the 11-point numerical scale (0 = no pain; 10 = maximal pain imaginable) of the Brief Pain Inventory.[32]

Sensory deficits and pain were measured and assessed by the same investigator at baseline, and after 4 and 12 weeks, as in prior therapeutic trials.[33,34] Brush-induced allodynia was evaluated by stroking the skin with a standardized brush (Senselab brush-0.5; Somedic AB, Horby, Sweden) and was considered as present if this evoked a clear sensation of pain. The intensity of allodynia (recorded on a 100mm visual analog scale) and its area (traced on a transparent paper, then digitized for measurement on Canvas 6.0 software) were measured. Mechanical sensations (detection thresholds to nonpainful stimuli) and pain thresholds were measured with calibrated von Frey hairs (0.06–300gm) (Somedic AB, Sweden). Thermal sensations and pain thresholds (in °C) were assessed with a Somedic thermotest (Somedic AB) by the method of limits, with baseline temperatures adjusted to the patient's skin temperature according to a procedure largely described elsewhere.[35] Measurements obtained in the area of maximal pain were compared with those of the homologous contralateral side.

Other secondary outcome measures (completed at baseline and follow-up visits) included a visual analog scale rating the average pain over the last 24 hours on a 100mm line; the neuropathic pain symptom inventory[36] rating the mean intensity of 10 neuropathic symptoms and their combination into 5 distinct dimensions during the last 24 hours on 11-point (0–10 points) numerical scales, the duration of spontaneous pain and number of pain paroxysms (assessed with the neuropathic pain symptom inventory on categorical scales), six of seven items for pain interference of the Brief Pain Inventory (with the exclusion of the item "ability to walk" judged irrelevant here) rated from 0 (does not interfere) to 10 (complete interference), the Hospital Anxiety and Depression Scale[37] including 14 items scored as anxiety and depression scores (each on 21), subjective pain relief because of the treatment over the past week (from 0% [no pain relief] to 100% [maximal pain relief]), the patients' overall im-

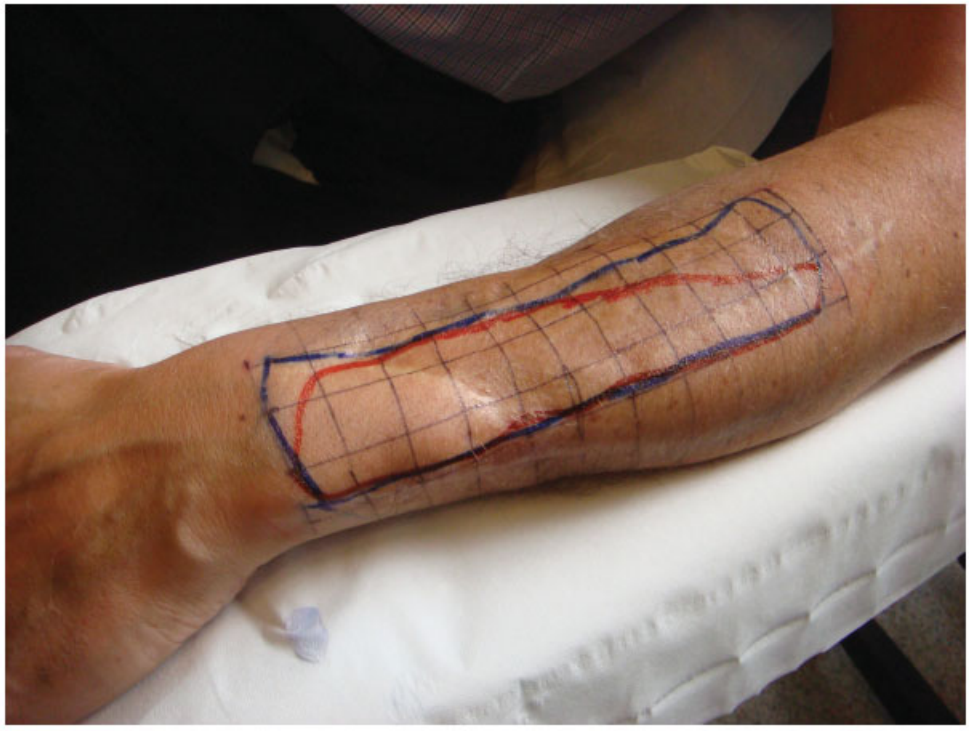

Fig 1. Photograph showing the botulinum toxin type A (BTX-A) intradermal injection technique for the painful area in one male patient with posttraumatic radial nerve lesion just before BTX-A injection. Intradermal injections were performed using equidistant grid lines 1.5cm apart (marked in black) aiming to cover the area of maximal spontaneous pain (in blue) and the whole area of allodynia (in red). The same procedure was used in patients with irregular areas of allodynia, except that the grid lines were sometimes incomplete in remote angles.

pression of change on a 7-point scale (from very much improved to very much worse), and the assessment of blindedness.

The safety of BTX-A, particularly for potential systemic adverse effects, was assessed throughout the study. Pain related to injections was rated as mild, moderate, or severe.

Statistical Analysis

Baseline clinical and demographic variables were compared by Fisher's exact test or an unpaired *t* test. The primary outcome measure was the change in the weekly averages of the daily ratings of pain on numerical scales from the baseline week through the 24th week of treatment. Changes in primary and secondary outcome measures (quantified measures of deficits and pains, pain scores, symptoms, quality of life, mood) expressed as differences between baseline and the values obtained at each time point were analyzed using a repeated-measures analysis of variance in which the factors were treatment group (BTX-A or placebo) and time at specified time points (ie, 4, 12, and 24 weeks, except for quantified measures that were not repeated at 24 weeks). Analyses of variance with the Bonferroni correction were used for post hoc comparisons. Spearman's rank correlation test was used to analyze the correlations between pairs of variables. The proportion of responders was defined as patients with 50% or more reduction in weekly mean pain scores, and numbers needed to treat were provided for 50% pain relief. Fisher's exact test was used to compare categorical variables. The intent-to-treat population analyzed for efficacy included all randomized patients who had a baseline evaluation and at least one postbaseline visit. Subjects who discontinued prematurely from the study were analyzed in two ways: (1) last observation carried forward (LOCF): the last observation before the time of discontinuation was carried forward to the end of the study period from which they discontinued; and (2) observed data: data were regarded as missing and no values were imputed. For the primary and secondary end points, analysis was performed in the intent-to-treat population with both the LOCF approach (primary analysis) and observed data (additional analysis). p values less than 0.05 were always considered significant. This study is registered with Clinicaltrials.gov (no. NCT0057202).

Results

We screened 61 consecutive patients (Fig 2), of whom 29 (19 women, 10 men) fulfilling the inclusion criteria were randomly assigned to BTX-A or placebo groups. Sociodemographic variables, pain characteristics, causative factors, and analgesic treatments did not differ between the two groups (Tables 1 and 2). Seven patients withdrew from the study before 24 weeks (see Fig 2).

Doses and Injections

The mean ($\pm$ standard deviation) number of injection sites was 20 $\pm$ 8.3 for BTX-A (with doses ranging

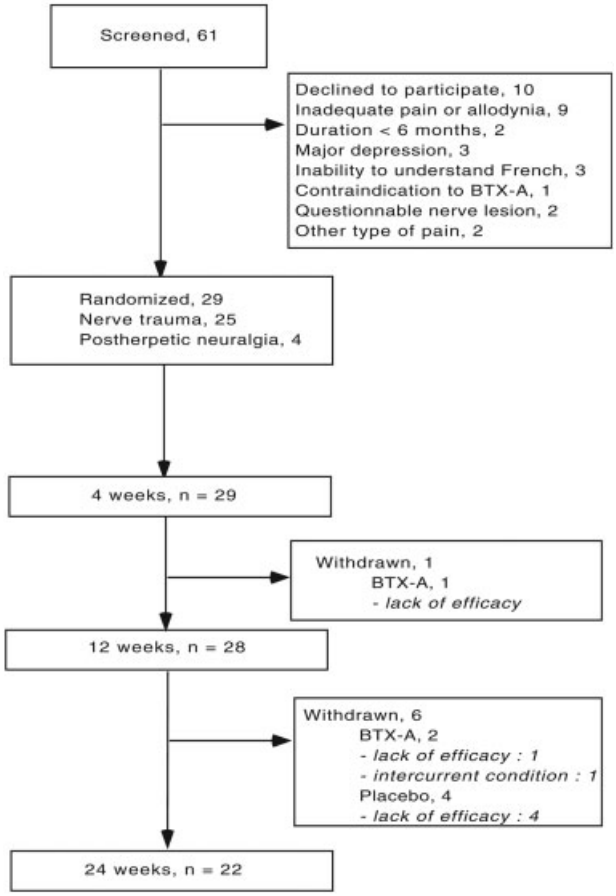

Fig 2. Study flow chart. BTX-A = botulinum toxin type A.

from 20–190 units) and 19.8 ± 5.2 for the placebo. The total volumes of injection were also similar for BTX-A (4.4 ± 1.6) and the placebo (3.9 ± 1.1).

Pain Intensity

As shown in Figure 3A, BTX-A improved weekly average pain intensity throughout the study in comparison with the placebo ($p = 0.038$, LOCF analysis). The improvement of pain was significant at several time points (post hoc analysis), starting from week 2 ($p = 0.025$). The effect increased thereafter for up to 4 weeks ($p = 0.036$), remained stable for up to 14 weeks (the mean pain scores decreased by 1.9 ± 1.9 with

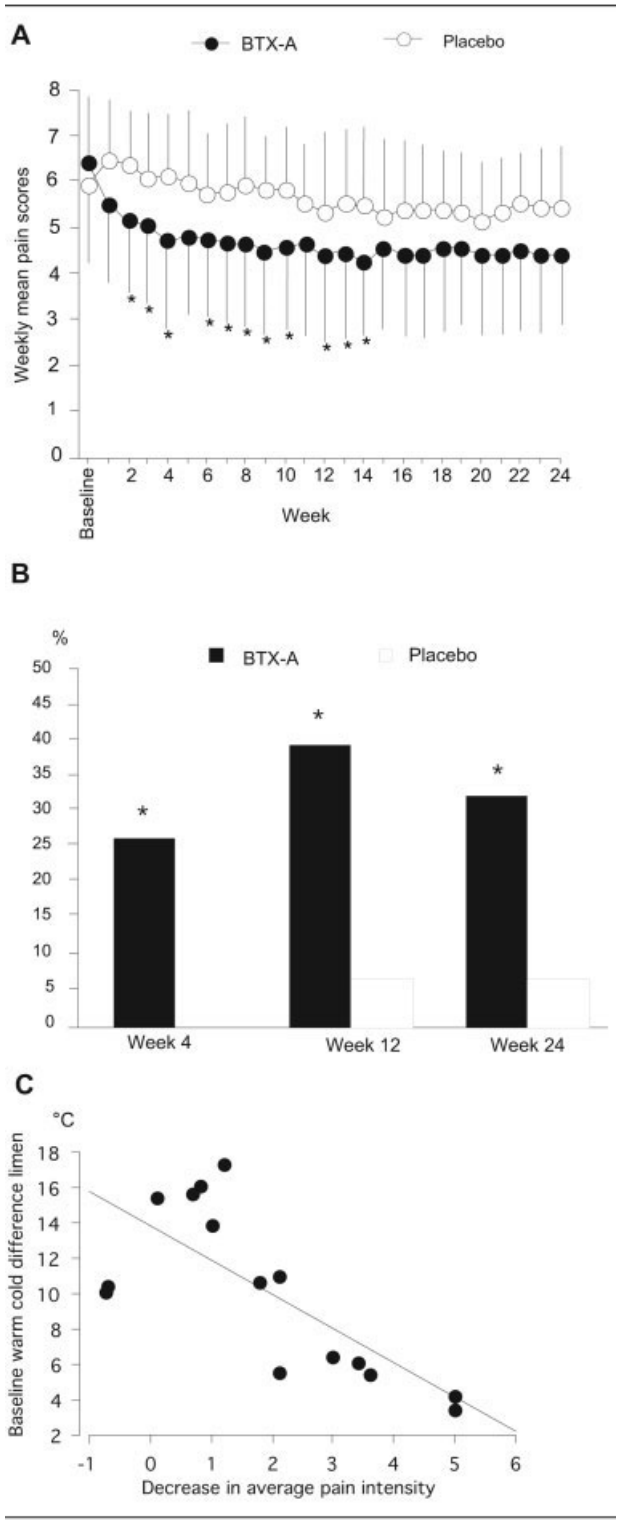

Fig 3. (A) Effects of botulinum toxin type A (BTX-A; black circles*) and the placebo* (white circles) *on weekly mean pain scores (intent-to-treat patients) from 1 to 24 weeks. *p < 0.05 versus placebo (post hoc analyses of variance). (B) Proportions of responders to BTX-A* (black bars) *and the placebo* (white bars; *≥50% pain relief from weekly mean pain scores) after 4, 12, and 24 weeks. There was no responder to the placebo at 4 weeks. *p < 0.05 versus placebo. (C) Correlation between the baseline severity of thermal deficits (expressed as the difference between warm and cold detection thresholds on the painful side) and the effects of BTX-A on weekly average pain intensity assessed from pain diaries at 12 weeks (expressed as the difference between pain intensity at baseline and 12 weeks). Rho = −0.69;* p *= 0.009. Similar correlations were found with pain intensity at 4 weeks (Rho = −0.63;* p *= 0.02) and at 24 weeks (Rho = −0.58;* p *= 0.03).*

Table 1. **Patient Characteristics and Baseline Values**

Characteristics	BTX-A (n = 15)	Placebo (n = 14)
Age ± SD (minimum-maximum)	53.8 ± 13.9 (31–78)	49.7 ± 15.9 (27–76)
Sex (F/M)	9/6	10/4
Pain duration in months ± SD (minimum-maximum)	49.2 ± 31.3 (6–108)	50.2 ± 66.1 (12–264)
Mean baseline weekly pain intensity ± SD	6.3± 1.8	5.9±2.0
Causes of pain, n		
Posttraumatic/postoperative	12	13
Postherpetic neuralgia	3	1
Site of maximal pain, n		
Hand	5	7
Foot	3	3
Trunk	4	1
Pelvis	2	2
Elbow	1	1
Concomitant treatment (some patients were taking more than one), n		
None	5	4
Weak analgesics/anti-inflammatories	2	3
Opioid analgesics	4	6
Tricyclic antidepressants	3	4
Antiepileptics	4	4
Benzodiazepines	4	5

BTX-A = botulinum toxin type A; SD = standard deviation.

BTX-A compared with 0.3 ± 1.8 with the placebo; $p = 0.03$), then was no longer significant (LOCF approach), but remained significant in analysis of observed cases ($p = 0.046$ at 24 weeks). Greater proportions of patients were responders to BTX-A than to placebo (see Table 2), and these proportions increased between 4 and 12 weeks (see Fig 3B). The number needed to treat for 50% pain relief with BTX-A was 3.70 (2.04–23.2) at 4 weeks and 3.03 (1.64–21.6) at 12 weeks. One patient treated with BTX-A became pain free after 12 weeks (no patient was pain free with the placebo) (see Table 2).

Effects on Quantified Measures of Perception and Pain

The area and intensity of allodynia to brush and cold pain thresholds on the painful side were reduced in the group treated with BTX-A (Fig 4). There was no effect on thresholds to nonpainful thermal and mechanical stimuli, or on heat and mechanical pain thresholds on either side (not shown).

Other Outcomes

BTX-A significantly improved average pain intensity assessed at each follow-up visit ($p = 0.0073$, repeated-measures analysis of variance) and provided global pain relief (Table 3). After 12 weeks, 40% of patients receiving BTX-A (and 14% with the placebo) rated themselves as much or very much improved, 53% were unchanged or worse (78% with the placebo), and 7% minimally improved (7% with the placebo). Three dimensions of the neuropathic pain symptom inventory (burning, paroxysmal pain, allodynia), corresponding to five neuropathic symptoms, improved in the BTX-A group, whereas other dimensions (deep pain, paresthesia/dysesthesia) were unaffected (see Table 3). The number of pain paroxysms was also reduced ($p = 0.05$ at 4 weeks; $p = 0.042$ at 12 weeks; $p = 0.039$ at 24 weeks), although pain duration was unaffected. BTX-A also improved some markers of quality of life including general activity and mood (see Table 3). The effect of BTX-A on general activity correlated with the improvement of average pain intensity (Rho = 0.71; $p = 0.008$ at 4 weeks; Rho = 0.43; $p = 0.02$ at 12 weeks). Anxiety scores of the Hospital Anxiety and Depression Scale slightly improved in the BTX-A group but tended to worsen in the placebo group, whereas the depression scores remained unchanged (see Table 3).

Table 2. **Individual Baseline Characteristics of the Patients Included in the Study (N = 29) and Responses to Treatment**

Patient No.	Age (yr)	Sex	Pain Duration (mo)	Cause of the Nerve Lesion	Treatment	% Reduction in Pain (week 12)[a]
1	53	F	12	Postsurgical (radial nerve)	Placebo	−11
2	67	M	48	Postsurgical (sural biopsy)	BTX-A	50
3	78	F	24	Postherpetic neuralgia[b]	BTX-A	16
4	45	F	72	Trauma (musculocutaneous nerve)	Placebo	46
5	51	F	36	Postherpetic neuralgia (thoracic)	BTX-A	72
6	27	F	24	Trauma (peroneal nerve)	Placebo	23
7	55	F	48	Postsurgical (postthoracotomy)	BTX-A	50
8	73	F	24	Postsurgical (herniorrhaphy)[c]	Placebo	36
9	76	M	84	Postherpetic neuralgia	Placebo	−21
10	45	M	72	Trauma (radial nerve)	Placebo	−50
11	31	M	96	Trauma (sural nerve)	BTX-A	38
12	39	M	12	Postsurgical (carpal tunnel syndrome)	BTX-A	4
13	44	M	84	Postsurgical (carpal tunnel syndrome)	BTX-A	59
14	51	F	36	Postsurgical (carpal tunnel syndrome)	BTX-A	15
15	40	F	24	Trauma (median nerve)	Placebo	58
16	57	F	36	Postsurgical (carpal tunnel syndrome)	Placebo	36
17	38	M	12	Trauma (ulnar nerve)	Placebo	−9
18	75	F	48	Postherpetic neuralgia	BTX-A	16
19	69	F	24	Trauma (peroneal nerve)	Placebo	8
20	75	F	60	Postsurgical (carpal tunnel syndrome)	BTX-A	−9
21	44	F	24	Postsurgical (carpal tunnel syndrome)	BTX-A	−8
22	54	M	18	Postsurgical (ulnar nerve transposition)	Placebo	−12
23	32	F	12	Postsurgical (herniorrhaphy)[d]	Placebo	−52
24	51	F	24	Postsurgical (carpal tunnel syndrome)	BTX-A	13
25	46	M	84	Trauma (radial nerve)	BTX-A	51
26	58	F	24	Postsurgical (carpal tunnel syndrome)	Placebo	1
27	29	F	264	Postsurgical (ulnar nerve transposition)	Placebo	−7
28	54	M	6	Postsurgical (herniorrhaphy)[a]	BTX-A	100
29	46	F	108	Postsurgical (hysterectomy)[b]	BTX-A	42

[a]The percentage reduction in pain at week 12 was calculated according to the following formula: 100 − (pain score at week 12/baseline score × 100). Negative values correspond to an increase in pain, and positive values correspond to a decrease in pain. In one patient (Patient 20) who stopped the study before week 12, the value obtained at the last follow-up visit (week 4) was taken into account. One patient (Patient 28) had a total pain relief (100% pain reduction).
[b]Postherpetic neuralgia always involved the trunk.
[c]Lesion of the ilioinguinal nerve.
[d]Lesion of the iliohypogastric nerve.
BTX-A = botulinum toxin type A.

Exploratory Analysis of the Predictive Factors for Botulinum Toxin Type A Analgesic Effects

The effects of BTX-A on average pain intensity did not differ between sexes and did not correlate with the age, duration, or intensity of pain or neuropathic symptoms. However, they were inversely correlated with the magnitude of thermal deficits on the painful side at baseline (see Fig 3C). Similar inverse correlations were observed regarding burning pain (Rho = −0.83 at 4 weeks, $p = 0.018$; Rho = −0.80 at 12 weeks, $p = 0.003$; and Rho = −0.79 at 24 weeks, $p = 0.008$) and brush-evoked pain (Rho = −0.66 at 12 weeks, $p =$

0.018; Rho = −0.59 at 24 weeks, $p = 0.048$). This suggested that the better the thermal sensation at baseline was preserved, the better the analgesic effects of BTX-A.

Study Safety and Assessment of Blindedness

Most patients reported that the injections were painful, with no difference between BTX-A (mild pain: 7; moderate pain: 4; severe pain: 2) and placebo (mild pain: 6; moderate pain: 4; severe pain: 2) groups. The severity of pain was related to the site of injection, being greater when at the hands or elbow. No other local or systemic side effects were reported during the injection or at any other time during the study. Seven patients experienced mild side effects associated with the anesthetic procedure (euphoria: three patients with placebo, three with BTX-A; anxiety: one patient with BTX-A).

No patient was able to recognize the active treatment from side effects, and seven patients (five with BTX-A) thought they had received BTX-A because of improvement. The other patients were unable to state which drug they had received.

Discussion

This study aimed to investigate the potential direct analgesic effects of BTX-A in patients with focal neuropathic pain using a randomized, double-blind, placebo-controlled design. Our main findings showed that one-time intradermal injections of BTX-A induce long-lasting analgesic effects counteracting focal chronic neuropathic pain. These effects involved self-assessment of pain and clinician-based quantified measures. In particular, we observed a reduction of the intensity and area of mechanical allodynia, and a decrease in cold pain thresholds on the painful side, whereas perception thresholds were not modified. These features indicate that BTX-A has selective effects on pathological pain processing. Moreover, several neuropathic symptoms and some measures of quality of life improved. Our data indicate new potential mechanisms of BTX-A in analgesia. They also suggest novel therapeutic indications for BTX-A.

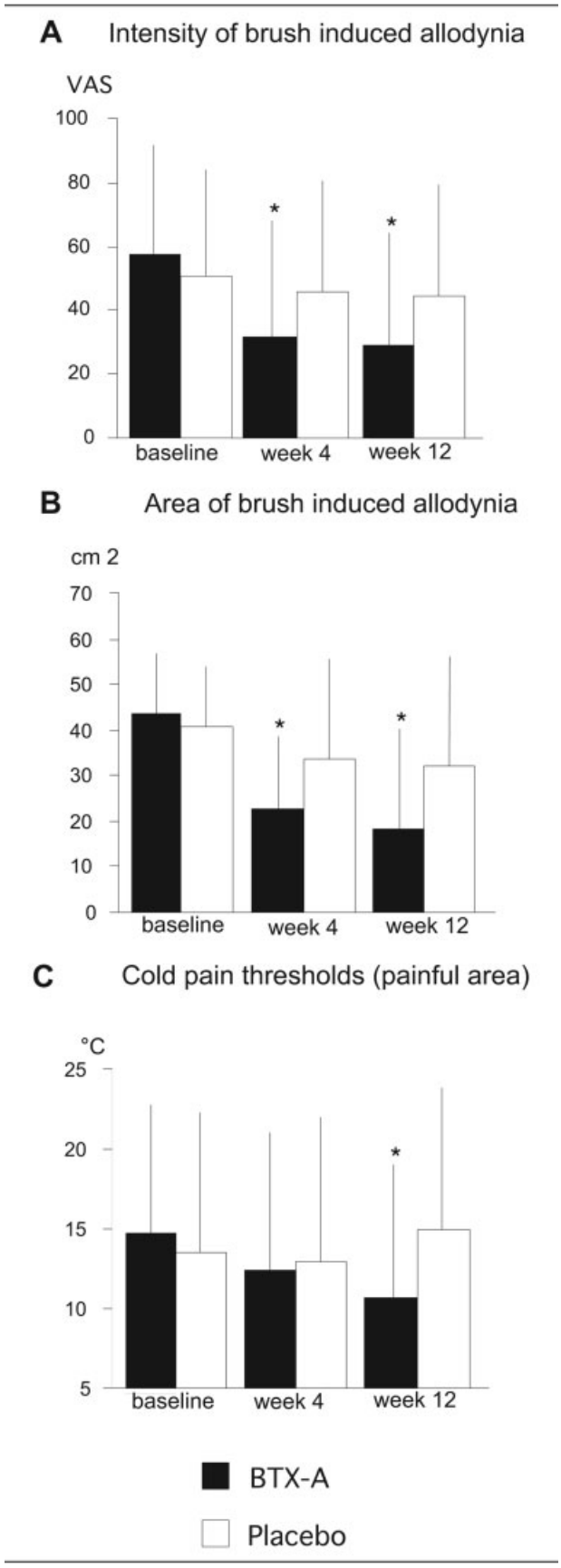

Fig 4. Effects of botulinum toxin type A (BTX-A; black bars*) and the placebo* (white bars) *after 4 and 12 weeks on (A) average intensity of allodynia to brush (rated on a 0–100mm visual analog scale [VAS]); (B) mean area of allodynia to brush (in cm^2); and (C) cold pain thresholds on the painful side. Compared with the placebo, BTX-A attenuated the intensity* ($p = 0.050$) *and area of allodynia to brush* ($p = 0.03$)*, and reduced cold pain thresholds on the painful side without affecting cold pain thresholds on the normal side, consistent with an effect on cold allodynia* ($p = 0.029$) *(repeated-measures analysis of variance at 4 and 12 weeks). *$p < 0.05$ compared with the placebo (post hoc analyses).*

Table 3. **Comparison of the Effects of Botulinum Toxin Type A or Placebo on Average Pain Intensity (Visual Analog Scale), Pain Relief, Neuropathic Symptoms of the Neuropathic Pain Symptom Inventory, Six Items of the Brief Pain Inventory Interference Scores, and Anxiety and Depression Scores of the Hospital Depression and Anxiety Scale**

Treatment	BTX-A				Placebo			
	Baseline	Week 4	Week 12	Week 24	Baseline	Week 4	Week 12	Week 24
Mean pain (VAS) (± SD)	68.6 ± 15.3	45.0 ± 30.0[a]	40.3 ± 27.3[a]	47.9 ± 28.8[a]	60.0 ± 18.9	54.0 ± 22.0	56.4 ± 26.4	58.5 ± 26.3
Pain relief (0–100%) (± SD)	—	28.6 ± 37.5	33.3 ± 40.9[a]	25.3 ± 36.0	—	10.0 ±16.7	7.7 ± 14.8	7.6 ± 15.8
NPSI symptoms (mean ± SD)								
Burning (0–10)	5.7 ± 3.3	3.7 ± 3.2[a]	3.4 ±3 .7[a]	3.9 ± 3.8	4.7 ± 3.3	4.6 ± 3.0	5.1 ± 3.3	4.6 ± 3.3
Squeezing (0–10)	3.7 ± 3.3	2.8 ± 3.1	3.1 ± 3.5	3.5 ± 3.7	4.2 ± 3.3	2.7 ± 3.4	1.7 ± 2.7	4.1 ± 2.7
Pressure (0–10)	4.5 ± 3.8	3.8 ± 3.1	4.1 ± 3.6	4.0 ± 3.5	4.0 ± 3.0	3.0 ± 3.0	2.4 ± 2.8	3.5 ± 2.9
Electric shocks (0–10)	6.5 ± 3.1	4.1 ± 3.4[a]	4.3 ± 3.7[a]	4.7 ± 3.7	5.9 ± 3.3	5.8 ± 3.3	5.7 ± 2.9	5.7 ± 3.0
Stabbing (0–10)	5.5 ± 3.7	2.9 ± 3.3[a]	4.0 ± 3.3	3.9 ± 4.0	5.0 ± 3.7	4.9 ± 3.5	5.1 ± 3.9	4.9 ± 3.4
Evoked pain to brush (0–10)	8.0 ± 1.6	5.4 ± 3.3[a]	5.0 ± 3.2[a]	6.0 ± 3.1	7.8 ± 2.0	6.8 ± 2.6	7.1 ± 2.9	7.0 ± 3.7
Evoked pain to pressure (0–10)	8.4 ± 1.6	5.7 ± 3.0	5.9 ± 2.9	6.3 ± 2.9	8.0 ± 2.0	6.5 ± 3.3	7.1 ± 2.8	7.1 ± 2.7
Evoked pain to cold (0–10)	5.3 ± 4.3	3.3 ± 3.6	2.5 ± 3.2[a]	3.3 ± 3.5	5.2 ± 3.4	4.1 ± 3.0	5.6 ± 3.7	5.5 ± 3.5
Tingling (0–10)	4.5 ± 4.4	4.2 ± 3.6	3.4 ± 3.7	3.9 ± 3.7	4.6 ± 3.4	3.9 ± 2.8	4.5 ± 3.2	4.2 ± 3.6
Pins and needles (0–10)	6.5 ± 4.6	4.2 ± 3.6	4.1 ± 3.5	4.7 ± 3.6	5.6 ± 3.4	4.9 ± 2.8	5.6 ± 3.5	5.5 ± 3.6
BPI–Interference (mean ± SD)								
General activity (0–10)	6.0 ± 2.6	4.2 ± 2.6[a]	3.6 ± 2.9[a]	4.3 ± 2.9	5.6 ± 2.6	5.4 ± 2.7	5.4 ± 2.6	5.3 ± 2.6
Sleep (0–10)	4.7 ± 3.5	2.9 ± 2.7	2.8 ± 3.3	3.2 ± 3.6	5.4 ± 2.4	4.7 ± 3.2	3.6 ± 3.3	4.8 ± 2.9
Mood (0–10)	3.9 ± 3.9	3.4 ± 2.8	2.2 ± 2.3[a]	3.2 ± 3.1	4.0 ± 2.7	4.4 ± 2.9	4.6 ± 3.2	4.8 ± 2.7
Normal work (0–10)	5.9 ± 3.0	4.7 ± 2.7	4.9 ± 2.5	5.3 ± 3.4	6.3 ± 2.7	5.6 ± 2.8	5.7 ± 2.7	5.2 ± 2.3
Social relations (0–10)	3.0 ± 3.2	2.3 ± 2.9	2.2 ± 2.6	2.7 ± 3.6	2.6 ± 2.0	2.9 ± 2.0	3.1 ± 2.4	2.3 ± 1.8
Enjoyment of life (0–10)	2.7 ± 2.7	2.3 ± 2.8	2.1 ± 2.8	2.4 ± 3.7	2.6 ± 2.4	3.1 ± 3.3	3.0 ± 3.3	2.3 ± 3.0
HAD score (mean ± SD)								
Anxiety score	9.7 ± 5.6	8.0 ± 4.6[a]	8.0 ± 3.9[a]	8.1 ± 5.6	9.2 ± 4.7	11.1 ± 4.6	10.2 ± 4.2	10.3 ± 4.8
Depression score	8.8 ± 3.8	7.5 ± 3.7	8.4 ± 4.3	8.1 ± 4.4	7.7 ± 3.2	7.2 ± 3.8	8.3 ± 3.7	8.2 ± 3.9

Data are presented for intention-to-treat patients (last observation carried forward analysis).
[a] $p < 0.05$ versus placebo. Effects on burning and electric shocks were significant at 24 weeks in analysis of observed data ($p < 0.05$).
BTX-A = botulinum toxin type A; VAS = visual analog scale; SD = standard deviation; NPSI = Neuropathic Pain Symptom Inventory; BPI = Brief Pain Inventory; HAD = Hospital Depression and Anxiety Scale.

In this study, we found that the preservation of thermal sensibility at baseline was correlated with the analgesic effects of BTX-A; for example, patients with less impaired sensory deficits were better responders. This observation is in keeping with recent preclinical data, showing that BTX-A blocks the protein kinase C potentiation of transient receptor potential vanilloid 1 (TRPV1), a capsaicin and heat-sensitive ion channel expressed in nociceptors, which participates in the transduction of thermal stimuli by sensory nerve endings.[13] It is thus possible that BTX-A acts on sensitized nociceptive fibers to produce its analgesic effects. This mechanism could also account for the early effect of BTX on pain observed here, as soon as week 2 after the injection. In keeping with our results, recent studies using models of experimental pain in healthy subjects showed that BTX-A reduces capsaicin-evoked pain and neurogenic vasodilatation in human skin.[38,39] However, several other studies using various experimental models of pain[40–44] yielded negative results. Several reasons may account for these discrepancies, including the use of different preparations of BTX, which are not bioequivalent,[45] and the application of different experimental stimuli. However, the main reason may be that the binding of BTX to its protein receptors,[46] the key step for its analgesic effects, is probably greater in chronic pathological pain than in acute experimental pain. It is thus difficult to translate data from experimental pain in healthy volunteers to sustained pathological pain.[5,6,47] In any case, a possible central target for the action for BTX-A cannot be ruled out,[4] particularly because several of our patients showed improved relief over time after one-time administration. Work in animals and humans is necessary to elucidate the mechanisms of the analgesic effects of BTX-A in neuropathic pain.

BTX is generally administered as intramuscular injection for focal spasticity or dystonia.[1,2] Because our patients presented with superficial pain and allodynia, and to exclude possible secondary effects of BTX on muscle tone, we used intradermal injections of BTX, matched to the extent of the painful area, according to a procedure recommended for hyperhidrosis.[3,31] This procedure was safe and relevant for our patients, although it may only be suitable for patients with focal neuropathies, where the extent of pain is limited. It remains to be established whether this mode of administration can also be used for patients with larger areas of pain, such as those with painful polyneuropathies.

Neuropathic pain is a common chronic pain condi-

tion affecting up to 7 to 8% of the general population[48,49] with a devastating impact on quality of life and substantial socioeconomic costs.[50,51] First-line treatments include antiepileptics or antidepressants.[24,25,52] However, these treatments have limited effectiveness: They reduce pain more than placebo in less than 30% of patients and are relatively frequently associated with negative side effects.[24,25] Topical analgesics such as lidocaine patches or capsaicin may be proposed, particularly for focal neuropathies, but their efficacy is modest.[24] BTX-A appears to have significant advantages over existing treatments, at least from this study, which included a highly selective group of patients with allodynia. One is the extended duration of its analgesic effects despite a one-time administration, with several patients still reporting improvement at 24 weeks. The efficacy of BTX-A also appears to compare favorably with that of other treatments, with a number needed to treat for 50% pain relief of 3 at 12 weeks. Finally, the drug was well tolerated: The only notable adverse effect was moderate-to-severe transient pain during injections in several patients especially when involving the fingers, despite a pretreatment with local anesthetics and administration of nitrous oxide. However, this problem could be overcome with other modes of analgesia, including peripheral nerve blocks, intravenous propofol, or lidocaine reconstructed BTX, as used for hyperhidrosis.[53] Large-scale studies are needed to confirm these results and to determine whether BTX-A may also be effective in other forms of neuropathic pain.

We conclude that intradermal injection of BTX-A has direct analgesic effects in patients with focal chronic neuropathic pain associated with allodynia. It is suggested that the observed analgesia may be caused by a local peripheral effect of BTX-A on nociceptive fibers, although subsequent central effects are possible. The treatment was particularly well tolerated. These data suggest that BTX-A should be considered as part of the therapeutic arsenal against focal neuropathic states.

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