PROFESSOR ELI SPRECHER (Orcid ID : 0000-0002-4093-1032)

DR OFIR ARTZI (Orcid ID : 0000-0003-1391-5843)

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A treatment protocol for botulinum toxin injections in the treatment of pachyonychia congenita-associated keratoderma

A. Koren,[1] E. Sprecher,[1,2] E. Reider[3] and O. Artzi[1]

[1]Department of Dermatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [2]Department of Human Molecular Genetics & Biochemistry, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [3]Department of Anesthesiology and Intensive Care Medicine and Pain, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Corresponding Author: Dr. Amir Koren, Department of Dermatology, Tel Aviv Sourasky Medical Center, 6 Weizmann street, Tel Aviv 64239, Israel. Mobile phone: 972-54-6969625, e-mail: koren1am@gmail.com.

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Short title: Botulinum toxin for pachyonychia congenita-associated keratoderma

What's already known about this topic?

Plantar pain is considered by patients to be the most severe and debilitating manifestation of pachyonychia congenita (PC). Over the past few years, a number of reports have shown that plantar injections of botulinum toxin (Btx) reduce or even eliminate pain, blistering, and callosities in PC patients. However, the injection technique, doses of Btx, and methods of anesthesia varied between reports and patients.

What does this study add?

Here we report our four-year experience in providing 30 treatments to five patients following an optimized protocol. Btx was found to provide a quantifiable improvement in all patients treated.

Abstract

Background **S**everely debilitating plantar keratoderma pain is the most distressing clinical feature of pachyonychia congenita (PC). Several earlier publications reported therapeutic success with botulinum toxin (Btx) plantar injections.

Objectives: To describe our 4-year experience during which we administered a total of 30 plantar Btx injections to five PC patients following an optimized protocol.

Methods Five patients with PC (age 21-54 years) who were treated at our medical center from 4/2015 to 6/2018 were included in the study. After an ultrasound-guided nerve block performed by an anesthesiologist, the patients received plantar intradermal injections of Btx A. To ascertain the effect of the treatment, we used a dedicated quality-of-life questionnaire for PC patients (PCQoL) and asked the patients to evaluate the intensity of eight parameters

pertaining to their symptoms at baseline and before every treatment session. At study closure, patients were asked to evaluate the maximal improvement in the same eight parameters throughout the study period.

Results All patients demonstrated a decrease in PCQoL scores during the follow-up period. All patients showed a significant improvement in PCQoL after the first treatment session and at the last evaluation ($P = 0.043$). The best improvement scores concerned morning feet burning and long-distance walking (> 500 m). The scores were significantly lower if the intervals between Btx injections were <100 days.

Conclusions Btx treatment of PC-associated keratoderma following an optimized protocol leads to a major change in patients' quality of life.

Key words: pachyonychia congenita, botulinum toxin, pain, quality of life

Introduction

Severe pain, especially affecting weight-bearing areas, is the most distressing and incapacitating clinical feature in pachyonychia congenita (PC).[1-3] Although many options have been proposed for treating the various clinical manifestations of PC, the majority of conventional treatments are only marginally effective for managing the keratoderma and the pain.[4] The successful use of botulinum toxin (Btx) for treating plantar keratoderma in PC patients has been documented in 3 reports over the past decade.[5-7] Swartling and Vahlquist's pioneering study on three PC patients[5] was followed by two other reports on eight[6] and two[7] additional PC patients. All 13 patients were initially injected with Btx A, and three were

switched to Btx B due to treatment failure. The injection technique, doses of Btx, and methods of anesthesia varied between the reports and the patients.

Over the past years, we have adopted the same approach and have refined injection technique and anesthesia procedure, and have adjusted the toxin doses to ameliorate treatment outcomes. We now describe our four-year experience in providing 30 treatments to five patients following an optimized protocol.

Patients and methods

Ethics

The study was performed at the Tel Aviv Sourasky Medical Center and approved by the Institutional Review Board.

Patients

This study is a retrospective analysis of five patients with PC (age 21-54 years) who were treated at the Tel Aviv Medical Center between 4/2015 and 6/2018. The diagnosis of PC was established based on clinical criteria and candidate gene mutation analysis. All patients had a history of painful hyperkeratosis that negatively affected their activities of daily life (AOL). Their medical records were reviewed, and missing data were completed by a telephone interview. The following information was collected: demographic data (age, and gender), past medical history, medications, disease-related symptoms and signs, presence of hyperhidrosis, time of symptom onset, clinical exam findings, past treatment for PC, and specific details of the index Btx treatments.

Anaesthesia

An anesthesiologist performed an ultrasound-guided nerve block of the posterior tibial nerve, the deep branch of the peroneus nerve, the sural nerve, and the saphenous nerve by administering solution lidocaine 2% and bupivacaine 0.5%. Four cc of the solution was injected to the posterior tibial nerve, 2 cc to the deep branch of the peroneus nerve, 2 cc to the sural nerve, and another 2 cc to the saphenous nerve. The anesthesiologist used an ultrasound needle 50 mm in length and 22 gauge in diameter.

Botulinum toxin injection technique

All patients were asked to perform trimming of the palmoplantar keratoderma surface 1-2 days prior to plantar intradermal injections of Btx A (AbobotulinumtoxinA - Dysport, Ipsen, Slough, U.K or OnabotulinumtoxinA - BOTOX, Allergan, U.K.). Prior to treatment initiation, the patients were asked to indicate the location of painful areas on their feet (Fig. 1, points 'a'), after which the borders between the calluses and normal skin were marked (Fig. 1, lines 'b'). Their feet were immersed in lukewarm water for 15 minutes before commencing treatment.The starting total dose for both feet was 500 U for AbobotulinumtoxinA or 200 U for OnabotulinumtoxinA diluted in 5 cc sterile normal saline 0.9%. According to the reported treatment response, the dose was raised every session by 25%, reaching up to 1000 U for AbobotulinumtoxinA and 400U for OnabotulinumtoxinA. Between 0.5-1 ml of toxin (50-100 U of AbobotulinumtoxinA or 20-40U of Btx) was injected to points ‘a’ (perpendicularly, 2 mm depth of injection, Fig. 1). Successive injections of 0.2 ml/site (20 U of AbobotulinumtoxinA or 8U of Btx) were injected every 0.5 cm in a circular fashion along the border between the healthy skin and the calluses (i.e., along lines ‘b’). The needle was directed into the calluses at a 45 degree angle (Fig. 1). The rest of the toxin was injected between points ‘a’ and lines ‘b’.

Evaluation

Eight parameters were chosen to quantify the severity of PC disease: morning feet burning, pain while standing or walking, sweating, extent of hyperkeratosis or callosities, capability of long-distance walking (>500 m), difficulty in managing calluses with a pedicure, the amount and depth of fissures, and the general aesthetics of the feet. At baseline and before every treatment session, the patients were asked to score each parameter on a 0-4 scale where 0 = not noticeable, 1= minimal, 2 = moderate, 3 = severe, and 4 = maximal. In addition, before every treatment session, the patients were asked to answer the quality of life questionnaire for PC patients (PCQoL),[8] in which the results of all questions can be computed by summing the score of each question, resulting in a global value ranging from 0 to 36, with higher scores indicating lower quality of life. At the end of the study period, the patients were asked to evaluate the same eight parameters on a scale 0-5 where 0 = no improvement, 1 = minimal improvement, 2 = small improvement, 3 = moderate improvement, 4 = significant improvement, and 5 = highly significant improvement. Finally, following each treatment, the patients were asked to evaluate the degree of pain during the anesthesia and during the treatment on a scale of 1-10.

Statistical analyses

Results were evaluated per treatment session and per patient and summarized descriptively. The one-sample Wilcoxon signed rank test was applied for testing whether the change in PCQoL from baseline was significantly different than 0. In order to identify the optimal interval between treatment sessions, i.e., for controlling the patients' symptoms, we examined several interval cutoffs in the range of 80-120 days. The interval cutoff at which a satisfactory and comparable number of intervals were above and below it, and with representation for each subject for both interval lengths, was chosen as the reference cutoff (100 days). Fourteen

evaluations were made after intervals of 47-98 days, and 12 evaluations were made after intervals of 105-168 days. The evaluations made at intervals ≤100 days were compared with those made at intervals >100 days by the Mann Whitney test. Significance was defined as p = 0.05. All the analyses were carried out using SPSS 25.0.

Results

The patients' demographic, clinical, and treatment data are shown in Tables 1 and 2. The patients were treated with onabotulinumtoxinA or abobotulinumtoxinA with a starting dose of 200 U or 500 U, respectively, for both feet, with dose increments up to 400 U of onabotulinumtoxinA or 1000 U of AbobotulinumtoxinA . The changes in disease severity are demonstrated for patient 1 in Fig. 2: all scores decreased and remained low throughout the follow-up. Figure 2 demonstrates the changes in patients' PCQoL during the course of treatment. All patients demonstrated a decrease in PCQoL. The gradual decrease in the PCQOL score, with the last score being the lowest, was especially prominent for the patients who had more treatment sessions. All PCQol scores of all patients were lower after the first treatment compared to baseline. Table 3 shows the percent of change in the PCQoL score after the first treatment compared to baseline, and in the last evaluation score compared to baseline. The PCQoL score was lower at the last evaluation compared to the score after the first treatment session. The average scores of the five patients showed significant improvement in PCQoL after the first treatment session and at the last evaluation (P = 0.043 for both time points). The timing of the best PCQoL score is also shown in Table 3.

Figure 3 depicts the average maximal improvement scores during the follow-up period as evaluated by the patients at the end of the evaluation period. The best improvement scores were for "morning feet burning" and "long-distance walking >500 m", while the least improvement was seen for "sweating" and "extent of hyperkeratosis/callosities". Patients scores for all eight parameters and their PCQoL scores were significantly lower for intervals between Btx injections that were less than 100 days (Table 4, Fig. 4). The mean pain evaluation was 1.6 ± 0.55 (on a scale of 1-10) during the treatment, and 3.8 ± 0.84 during anesthesia.

Discussion

Plantar pain, especially on weight-bearing areas, is a major source of morbidity for individuals with PC. It interferes with almost all daily living activities, and it has the most profound impact on quality of life.[1-3] Physical pain in general can be of a nociceptive or a neuropathic origin. Neuropathic pain is caused by damage to the somatosensory nervous system, while nociceptive pain is caused by tissue damage. [9] Blister fotrmation between the dermis and the hyperkeratotic epidermis, as shown by ultrasound[10], may possibly underlie nociceptive pain in PC. Hyperhidrosis may contribute to the generation of subepidermal blisters and, therefore, may be an indirect cause of pain. Wallis et al.[9] reported neuropathic pain in 62% of 35 PC patients, and nociceptive pain in the remaining patients. Brill et al.[11] recently conducted a case-control study further supporting the role of neuropathic pain in PC-associated chronic pain.

Despite the importance of pain in PC, it is only recently[4] that novel therapeutic solutions have been tested in patients including small interfering RNAs,[12,13] rapamycin,[14] and simvastatin.[15] Unfortunately, these therapies have been found to be associated with major delivery, safety or efficacy flaws.

More recently, Btx has been shown to benefit patients with PC.[5-7] It has been hypothesized that the treatment's effect on pain results from the inhibition of sweating and therefore maceration of the fragile epidermis, consequently reducing blistering and pain. Alternatively, Btx may directly affect sensory nerves. Lucioni et al.[16] demonstrated that Btx significantly decreases neurotranmitters release from sensory nerve axons. Btx was also shown in previous studies to inhibit neurogenic flare. [17,18] In our current study, the patients were asked to evaluate the maximal improvement they felt during the study period. The average scores for improvement in the sweating category, as well as the improvement in the extent of hyperkeratosis/callosities were the lowest, while the scores for improvement in the various pain evaluations were the highest. These results lend further support to the possibility that Btx mechanism of action is mediated by direct modulation of sensory nerve function rather than sweat reduction.

Because of the nature and duration of the toxin's effect, the chronic nature of the disease, and the desire to maintain therapeutic benefit for as long as possible, we attempted at defining the optimal interval between treatment sessions. We found a significant difference in the patients' scores between treatment given at a ≤100-day interval compared to treatment given at a >100-day interval, with all scores being significantly superior for intervals ≤100 after the last treatment session. Moreover, successive treatments were associated with a progressive improvement in pre-treatment scores (Figs. 2 and 3), suggesting a long-term effect of Btx injections.

In all studies performed so far, Btx was injected every 15 mm over the sole and toes or only into the weight-bearing areas of the feet, while distributing the same total dose, especially below blisters and callosities.[5-7] In our experience, high-dose BTX to the most painful areas and to the border of the normal skin/callosities leads to the best treatment results and with a lower cumulative dose of the toxin.

Different methods of anesthesia have been described in previous reports.[5-7] In our study, ultrasound-guided nerve block of the posterior tibial, the deep branch of the peroneus nerve, the sural nerve, and the saphenous nerve, yielded very low pain scores (1.6 ± 0.55 on a scale of 1-10). The precise visualization of the target nerves utilizing ultrasound nearly eliminates inadvertent injection of unintended structures, accidental intra-neuronal injection. Furthermore, it provides an objective peri neuronal visualization of local anesthetic spread, permits using small volumes of local anesthetic solution thus, reducing the chance of compression neuropathy as well as the risk of reaching a toxic dose of the local anesthetic. All of these are even more important while performing repeating ankle blocks on a regular basis.

A major limitation of this study is its small sample size, calling for larger, multi-center, confirmatory placebo-controlled studies. In addition, as all patients enrolled in the present study carried mutations in *KRT16*, it is not clear whether our results are generalizable to PC patients with other genotypes.

In conclusion, the present report defined a structured approach to the management of PC patients with Btx which was associated with marked reduction in pain and improvement in quality of life.

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FIGURE LEGENDS

Figure 1. Injection technique. Points ‘a’ refer to painful areas as identified by the patient; line ‘b’ demarcates the borders between the calluses and normal skin. One ml of Btx was injected to point ‘a’ (perpendicularly, 2 mm depth of injection). Successive injections of 0.2 ml/site were injected every 0.5 cm in a circular fashion along line ‘b’, in which the needle was directed at an angle of 45 degrees into the calluses. The rest of the toxin was injected between the points ‘a’ and line ‘b’.

Figure 2. Patient 1 - the intensity of all parameters during the evaluation period. All scores decreased and remained low throughout follow-up.

Figure. 3. PCQoL assessement. Each color represents a different patient. The PCQoL scores of all patients decreased after the first treatment. PCQoL score decrease was more marked in patients who had more treatment sessions.

Figure 4. Maximal improvement scores. Shown are the average maximal improvement scores of the patients at the end of the evaluation period.

Figure 5. PCQoL by interval between treatment sessions. The PCQoL was significantly lower after shorter intervals between treatment sessions.

Table 1. Patient demographics and clinical data at baseline.

Pt.	Age, years/sex	Age at symptom onset	Family history	Mutant gene	Previous treatments	Symptoms other than keratoderma
1	25/F	15	Mother, grandmother	*KRT16*	Pedicure, urea/salicylic acid containing topical agents,	Hypertrophic nail dystrophy
2	39/M	14-15	Mother, brother, grandfather, great-grandmother	*KRT16*	Pedicure, topical salicylic acid ± 5-FU, insoles, CO_2 laser, surgical treatment	-
3	54/M	12-14	Father, daughter	*KRT16*	Urea/salicylic acid containing topical agents	Mild hypertrophic nail dystrophy, oral leukokeratosis
4	21/F	3	Mother	*KRT16*	Pedicure, urea/salicylic acid containing topical agents, moisturizers, topical tazarotene, Isotretinoin	-
5	22/M	10	Father, sister, grandmother, great-grandmother	*KRT16*	Pedicure, urea/salicylic acid containing topical agents	Hypertrophic nail dystrophy

Table 2. Patient treatment data

Pt.	Treatments, *n*	OnabotulinumtoxinA type and dose	Reported side effects*
1	13	OnabotulinumtoxinA 100-200U	Hematomas, swelling, pain
2	5	OnabotulinumtoxinA 200-400U AbobotulinumtoxinA 1000U	Hematomas, swelling, pain, Cold sensation 1-2 months after the first 1-2 tx
3	7	OnabotulinumtoxinA 200U	Swelling, pain
4	4	OnabotulinumtoxinA 200-400U	Hematomas, swelling, pain
5	1	AbobotulinumtoxinA 500U	Hematomas, pain

*Swelling and pain were reported to persist for up to 3 days. Hematomas were reported to persist for up to a 2-3 weeks. tx, treatments

Table 3. Change in quality of life questionnaire for PC patients (PCQoL)

Pt (visits)	Reduction in PCQoL score after first treatment	Reduction in PCQoL score at last evaluation	Timing of best PCQoL result	
			At visit *n*	Days (*n*) from the first treatment
1 (13)	41.2%	47.1%	12	1068
2 (5)	15.4%	30.8%	4	285
3 (6)	20.0%	72.0%	6	644
4 (4)	26.7%	20.0%	2	98
5 (2)	33.3%	33.3%	2	91
Average	27.3%	40.6%		
SD	10.3%	20.0%		
P value*	0.043	0.043		

*P value by one-sample Wilcoxon signed rank test for testing whether the change is significantly different than 0. The results show a significant improvement in PCQoL after the first treatment session and at the last evaluation. The percent of change in the PCQoL score of each patient was calculated for the score after the first treatment compared to baseline and the last evaluation score compared to baseline. The PCQoL of three patients was lower at the last evaluation compared to the score after the first treatment session. The timing of the best PCQoL score is shown in the two right-side columns.

Table 4. Mean evaluation scores by interval between treatment sessions. All the evaluation and PCQoL scores were significantly lower when reported after shorter intervals between the sessions

	<=100 days (***n*** =14)		>100 days (***n*** = 12)		***P***-value
	Mean	SD	Mean	SD	
Morning feet burning	1.5	0.7	2.67	0.98	0.004
Pain while standing/walking	1.6	0.6	2.92	0.90	0.001
Sweating	1.2	0.4	2.25	0.75	0.001
Extent of hyperkeratosis/callosities	1.9	0.5	2.67	0.78	0.013
Long-distance walking (>500 m)	1.6	0.6	2.83	0.83	0.001
Calluses difficult to manage with pedicure	1.5	0.5	2.58	1.08	0.011
Fissures	1.4	0.5	2.42	0.90	0.006
General aesthetics of feet	1.9	0.5	2.67	0.49	0.003
PCQoL	17.6	3.2	22.58	6.46	0.004

n = number of intervals <=100 or >100 days.

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