Treatment of Dupuytren’s contracture with collagenase clostridium histolyticum under clinical practice conditions: ReDUCTo study

Abstract

Background: To date, real-life data on non-surgical correction of Dupuytren’s contracture with collagenase clostridium histolyticum injection (CCH, Xiapex®) are limited.

Methods and results: In an open-label non-interventional study in 87 patients in Germany (mean age 65.1±9.8 years, 79.3% males), patients were followed up until 1 year after injection. 63 (73.3%) received the injection at the MCP joint, and 23 (26.7%) at the PIP. The mean grade of contracture in the presently treated finger at baseline was for the MCP joint 32.4°±25.1, for the PIP° 29.2±31.5, and for the DIP° 0.5±2.0. At days 30/360 compared to baseline, the degree of contracture of the MCP joint was reduced by 28.2°±24.6/30.8°±25.0, of the PIP by 20.0°±24.7/8.5°±29.6, and of the DIP by 0.01°±1.9/0.7±2.3. Improvement of hand function at day 30/360 was rated by physicians as very good in 69.5/60.9%, as good in 23.2/28.3%, and as poor in 7.3/8.7%, and none in 0.0/2.2%. No serious adverse drug reactions (SADR) occurred. Adverse drug reactions (ADR) were noted within 24 hours injection in 64 patients (74.4%), mostly contusion/swelling, pain, blood blister or other bleeding at the injection site, or ecchymosis. In an overall assessment, at day 30/360, 73.5%/95.7% of the physicians rated tolerability of CCH in their patients as very good, 22.9%/2.2% as good, and 3.6%/2.2% as moderate. On the EQ-5D Visual Analog Scale the mean score improved from 79.5±17.9 to 83.8±15.8 at day 30, and to 85.4±14.1 at day 360. On the Michigan Hand Questionnaire, the total score was 67.5 points at baseline, 75.7 points at day 30 and 75.2 points at day 360.

Conclusions: Overall, treatment with CCH under clinical practice conditions was effective and well tolerated. Quality of life and hand function improved substantially. No unknown safety issues were identified during the study.

Keywords: Dupuytren’s contracture, microbial collagenase, injection, range of motion, patient satisfaction, EQ-5D, safety, treatment outcome
Zusammenfassung

**Hintergrund:** Daten zur medikamentösen Behandlung des Morbus Dupuytren mit mikrobieller Kollagenase aus Clostridium histolyticum (Xiapex®) fehlen bisher weitgehend in der klinischen Praxis.

**Methoden und Ergebnisse:** In einer offenen nicht-interventionellen Studie an 87 Patienten in Deutschland wurden die Patienten (mittleres Alter 65,1±9,8 Jahre, 79,3% Männer) bis zu einem Jahr nach der Behandlung mit mikrobieller Kollagenase dokumentiert. 63 (73,3%) Patienten erhielten die Injektion am Metacarpophalangealgelenk (MCP) und 23 (26,7%) am proximalen Interphalangealgelenk (PIP). Zu Studienbeginn war der Kontrakturgrad am behandelten Finger am MCP-Gelenk 32,4°±25,1, am PIP-Gelenk 29,2°±31,5 und am distalen Interphalangealgelenk (DIP) 0,5°±2,0. Im Vergleich zum Ausgangswert wurde bis zu den Tagen 30 bzw. 360 der Kontrakturgrad reduziert: am MCP-Gelenk um 28,2°±24,6 bzw. 30,8°±25,0, am PIP um 20,0°±24,7 bzw. 8,5°±29,6, und am DIP um 0,01°±1,9 bzw. 0,7±2,3. Die Verbesserung der Handfunktion an den Tagen 30 bzw. 360 wurde von Ärzten als sehr gut in 69,5% bzw. 60,9%, als gut in 23,2% bzw. 28,3%, und als schlecht in 7,3% bzw. 8,7%, und als nicht zutreffend in 0,0% bzw. 2,2% bewertet. Es traten keine schwerwiegenden unerwünschten Arzneimittelwirkungen auf. Unerwünschte Arzneimittelwirkungen wurden innerhalb von 24 Stunden nach Injektion bei 64 Patienten (74,4%) dokumentiert, vor allem Schwellungen, Schmerzen, Blutblasen oder andere Blutungen an der Injektionsstelle oder der umgebenden Haut. An den Tagen 30 bzw. 360 stuften 73,5% bzw. 95,7% der Ärzte die Verträglichkeit der mikrobiellen Kollagenase als sehr gut ein, 22,9% bzw. 2,2% als gut, und 3,6% bzw. 2,2% als moderat. Auf der visuellen Analogskala (EuoQol-5D) zeigte sich die Lebensqualität im Vergleich zum Ausgangswert (79,5±17,9) verbessert am Tag 30 (83,8±15,8) bzw. am Tag 360 (85,4±14,1). Die Gesamtpunktzahl des Michigan Hand Questionnaire (MHQ) betrug 67,5 Punkte vor Behandlungsbeginn, 75,7 Punkte am Tag 30 und 75,2 Punkte am Tag 360.

**Schlussfolgerungen:** Insgesamt war die mikrobielle Kollagenase unter Bedingungen der klinischen Praxis wirksam und gut verträglich. Die Lebensqualität und Handfunktion wurden deutlich verbessert. Während der Studie ergaben sich keine Hinweise auf bisher unbekannte Unverträglichkeiten.

**Schlüsselwörter:** Dupuytren-Kontraktur, mikrobielle Kollagenase, Injektion, Bewegungsbereich, Patientenzufriedenheit, EQ-5D, Sicherheit, Behandlungsergebnis
Introduction

Dupuytren’s disease is a slowly progressive debilitating connective tissue disorder that affects the tissue in the palm of the hand and the fingers [1]. An increase in collagen deposits triggers the formation of nodules early in the disease, and later, pathological cords, which cause debilitating joint contractures and fixed-flexion deformities (where the finger is permanently bent inwards into the palm of the hand), known as Dupuytren’s contracture [1]. The etiopathogenesis is multifactorial with a strong genetic predisposition [2]. Several factors are statistically correlated to Dupuytren included smoking, alcohol intake, trauma, diabetes, epilepsy and use of anticonvulsant drugs, and exposure to vibration without evidence of any etiopathogenic agent [3]. Compared to other populations, the disease seems more prevalent in people of white northern European descent [4]. Most cases of Dupuytren’s disease occur in patients older than 50 years, and the condition is more common in men who also tend to be more severely affected by Dupuytren’s disease than female patients [4]. In Germany about 1.9 million people are chronically ill because of Dupuytren’s disease [5]. The mainstay of treatment is surgical release or excision of the affected palmodigital tissue, but symptoms often recur [6]. Nonsurgical correction of Dupuytren’s disease contractures can be achieved by collagenase clostridium histolyticum (CCH) injection. Collagenases are proteinases that hydrolyze collagen under physiological conditions. Injection of CCH into a Dupuytren’s cord, which is comprised mostly of interstitial collagen types I and III, results in enzymatic disruption of the cord. In controlled clinical studies, the benefits with CCH were shown in its ability to demonstrate a reduction in the contracture of all joints treated (metacarpophalangeal and/or proximal interphalangeal) to 5° or less, approximately 4 weeks after the last injection [7], [8]. CCH also demonstrated a decrease in the degree of contracture and increasing both the range of motion from baseline for all joints treated (metacarpophalangeal) to 5° or less, approximately 4 weeks after the last injection [7], [8]. CCH also demonstrated a decrease in the degree of contracture and increasing both the range of motion from baseline for all joints treated and the subject global assessment of treatment satisfaction [7].

Data on the effectiveness and tolerability of CCH under daily practice conditions are limited. Further, there is a lack of data on quality of life of patients in the long term after CCH administration.

Against this background, the observational ReDUCtO study initiated to document various aspects of CCH treatment and outcomes in patients with Dupuytren’s contracture. The present study aimed to collect data on the drug utilization of CCH in the hand of physicians, with focus on feasibility, treatment patterns, and effectiveness in clinical practice (setting, patient characteristics, concomitant treatment, follow-up therapy), effectiveness (with focus on functionality), tolerability, and patient-related outcomes (patient satisfaction, health-related quality of life, physician satisfaction with therapy).

Methods

This was a prospective, open, observational, non-randomized study based on the EU Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 and the Declaration of Helsinki. The study was approved by the Ethics Committee of the Medical Faculty, Technical University Dresden. It was performed in 18 hospitals or other medical facilities in Germany. The ClinicalTrials.gov identifier is NCT01567397.

Patients were eligible for documentation, if they met the following inclusion criteria:

1. Palpable cord due to Dupuytren’s disease (pretreated or untreated);
2. satisfactory knowledge of German to be able to fill out questionnaires;
3. written informed consent.

The exclusion criterion was contraindication to microbial collagenase.

Microbial collagenase (CCH, Xiapex®) was used in its marketed form only, according to the prescribing information. Xiapex® had to be applied on the basis of the prescribing information. The application was determined solely by medical and therapeutic needs. The physician had to observe that in the presence of contractures in several palpable cords in one session only one cord could be treated with CCH (i.e., 1 injection every 3 weeks was possible). No control drug or treatment was used.

The main criteria for evaluation were, for efficacy degree of contracture of MCP joint, PIP joint and DIP joint, range of motion, nail-table distance, fingertip-palm distance, and for safety incidence, severity and outcomes of adverse drug reactions (ADR).

Patient relevant outcomes, in particular related to functionality of the hand and quality of life, are a central component of this study. All following questionnaires were to be filled in by the patient:

- Michigan Hand Questionnaire (MHQ): Questionnaire with 25 unilateral and 12 bilateral questions, validated among others also in German. The resulting score of ranges from 0 (very bad) to 100 (no restriction) quantifies the limitation, if any, of hand function, also over time. Both hands are assessed separately. The MHQ allows assessing the subjective limitations due to Dupuytren’s disease experienced by the patient. Details on the German version are have been described [9], [10].
- EQ-5D (approx. 3 min): Health questionnaire of the EuroQol group, which expresses the quality of life of a patient in a one-dimensional measure. The EQ-5D is a standardized measure of health status, applicable to a wide range of health conditions and treatments. It provides a simple, generic measure of health for clinical and economic appraisal. The EQ-5D provides a simple descriptive profile and a single index value for health status that can be used in the clinical and eco-
nomic evaluation of health care as well as in population health surveys [11].

- WHO-Five Well-being Index (WHO-5) (1 min): A short 5 questions but also concise test, to test the current well-being or to make statements about depression. The 5 items of the questionnaire cover the areas of mood, vitality, and general health [12], [13], [14].

Data were collected on standard paper/pencil case report forms and were entered into the database in the data center in Dresden.

In the statistical analysis, continuous variables were summarized with descriptive statistics (absolute numbers n, means, standard deviation (SD), standard error of mean, and boxplot-figures minimum, 25th percentile, median, 75th percentile and maximum). Categorical data were described by the number (n) and percentage (%) of subjects in each category. No subgroups were analyzed. Percentages were calculated based on patients with valid data for each respective parameter (i.e., no percentages for missing values are provided).

IBM SPSS Statistics version 19 was used for analysis.

Results

The study was performed from December 2011 until April 2013. Of the 87 patients included at baseline, 83 (94.3%) were documented at day 30 and 47 (53.4%) at day 360.

Efficacy

Baseline characteristics are presented in Table 1. More men than women were included (79.3% vs. 20.7%). Mean age of patients was 65.1±9.8 years, with a range from 38–88 years. Mean age of onset of Dupuytren’s Disease was 59.6±13.3 years (range 16–79 years). In terms of employment status, 48 patients were retired (62.3%), and 25 were working (32.5%). As concomitant diseases or conditions, most frequently arterial hypertension (38 patients, 43.7%), osteoarthritis/arthrosis (26 patients, 29.9%), smoking (18 patients, 20.7%), and diabetes mellitus (14, 16.1%) were reported.

The familial form of Dupuytren’s disease was reported in 28 patients (33.7%). Only 1 patient (1.4%) reported inability to work due to Dupuytren’s disease. The majority of patients were right-handed (78 patients, 89.7%).

As examinations to ascertain Dupuytren’s disease diagnosis, assessment of hand function, tabletop test, and sensitivity test were performed in all but up to 3 patients, for each test, respectively. X-ray examinations for confirmation of diagnosis were done in 4 patients only (4.7%), magnetic resonance tomography in 3 patients (3.5%).

Treated hands were documented at the same frequency for left and right (right in 45 patients, 51.7%, left in 42 patients, 48.3%). As affected fingers, most frequently the little finger (48 patients, 55.8%) was named, followed by the ring finger (44 patients, 51.2%), middle finger (11 patients, 12.8%), the thumb (7 patients, 8.1%) and the index finger (2 patients, 2.3%).

Median time between diagnosis and CCH injection was 22.0 months (interquartile range 0 to 82.5 months). CCH pretreatment was reported in 5 patients (5.7%) at another cord, and in 1 patient (1.1%) in the currently treated cord. The treated cords at baseline, and the injection sites, by finger, are shown in Figure 1. Patients received the injection in the little finger (40 patients, 51.3%), the ring finger (35 patients, 40.7%), and infrequently the middle finger (2 patients, 2.6%) and the index finger (2 patients, 2.3%). Of the 86 treated patients, 63 (73.3%) received the injection at the MCP joint, and 23 (26.7%) at the PIP. Problems during injection were reported in 1 patient only (1.7%) as “suspected extravasation or misapplication”, while no problems were reported in 59 patients (98.3%). The majority of patients underwent the extension procedure 24±2 hours after the CCH injection as recommended (77 patients, 89.5%), while 5 patients (5.8%) received it less than 22 hours, and 4 patients (4.7%) more than 26 hours after the injection. After the procedure, the treated hand was immobilized with a dressing in 60 patients (75.9%), and in further 19 patients (24.1%) with another methods such as splint (15 patients) or a cast (2 patients). Local anesthesia was used in 71 patients (87.7%). One extension attempt was performed in 52 patients (65.8%), 2 in 15 patients (19.0%), 3 in 9 patients (11.4%), and five or more in 3 patients (3.8%).

The mean degree of contracture in the presently treated finger at baseline was for the MCP joint 32.4°±25.1, for the PIP 29.2°±31.5, and for the DIP 0.5°±2.0 (Table 2).

At day 30 compared to baseline, the degree of contracture of the MCP joint was reduced by 28.2°±24.6, the PIP by 20.0°±24.7, and the DIP by 0.01°±1.85. At day 360 compared to baseline, the degree of contracture of the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65.1 ± 9.8</td>
</tr>
<tr>
<td>Gender, male</td>
<td>69 (79.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>18 (20.7%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.3 ± 3.3</td>
</tr>
<tr>
<td>Statutory</td>
<td>68 (82.9%)</td>
</tr>
<tr>
<td>Private</td>
<td>14 (17.1%)</td>
</tr>
<tr>
<td>Right</td>
<td>45 (51.7%)</td>
</tr>
<tr>
<td>Left</td>
<td>42 (48.3%)</td>
</tr>
<tr>
<td>Patients by treated finger</td>
<td></td>
</tr>
<tr>
<td>Little</td>
<td>43 (50.0%)</td>
</tr>
<tr>
<td>Ring</td>
<td>35 (40.7%)</td>
</tr>
<tr>
<td>Middle</td>
<td>5 (5.8%)</td>
</tr>
<tr>
<td>Index</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Thumb</td>
<td>2 (2.3%)</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± standard deviation. For affected joints and cords, see Figure 1.
Figure 1: Treated cords at baseline, by finger

The figure displays the location of the Dupuytren cords that were chosen for treatment with Xiapex in this study, and the injection sites. The frequency of the mentioned points was transferred to brush thicknesses. For example, if a given joint was reported 50 times, this location was assigned a diameter of 50 pixels. This results in dots of the different sized in the figures below. The lines were produced in an analogue manner: it was counted how often a connection between two points was mentioned and accordingly assigned to a specific line thickness. Transparency of lines in the graphics program was set to 50% so that overlaps were visible.
Table 2: Degree of contracture in the presently treated finger

<table>
<thead>
<tr>
<th>Degree of contracture</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>21</td>
<td>26.6</td>
</tr>
<tr>
<td>&gt;5–20</td>
<td>10</td>
<td>12.7</td>
</tr>
<tr>
<td>&gt;20</td>
<td>48</td>
<td>60.8</td>
</tr>
<tr>
<td>Total</td>
<td>79</td>
<td>100.0</td>
</tr>
<tr>
<td>PIP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>30</td>
<td>42.3</td>
</tr>
<tr>
<td>&gt;5–20</td>
<td>9</td>
<td>12.7</td>
</tr>
<tr>
<td>&gt;20</td>
<td>32</td>
<td>45.1</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>100.0</td>
</tr>
<tr>
<td>DIP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>53</td>
<td>96.4</td>
</tr>
<tr>
<td>&gt;5–20</td>
<td>2</td>
<td>3.6</td>
</tr>
<tr>
<td>&gt;20</td>
<td>0</td>
<td>.0</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>100.0</td>
</tr>
</tbody>
</table>

MCP joint was reduced by 30.8°±25.0, the PIP joint by 8.5°±29.6, and the DIP joint by 0.7°±2.3. Improvement of hand function at day 30 was rated by physicians as very good in 69.5%, as good in 23.2%, and as poor in 7.3%. At day 360, physicians rated improvement as very good in 60.9%, as good in 28.3%, as poor in 8.7%, and as none in 2.2% (Figure 2).
Table 3: Adverse drug reaction reported on Day 1 (top) and Day 30 (bottom)

<table>
<thead>
<tr>
<th>ADR</th>
<th>Day 1</th>
<th>Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>22 (25.9%)</td>
<td>50 (60.2%)</td>
</tr>
<tr>
<td>blood blister at the site of flexion tendon</td>
<td>51 (60.0%)</td>
<td>7 (8.4%)</td>
</tr>
<tr>
<td>blood blister at the site of the extension tendon</td>
<td>5 (5.9%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Lymphadenopathy/Lymph node pain</td>
<td>20 (23.5%)</td>
<td>5 (6.0%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8 (9.4%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>13 (15.3%)</td>
<td>5 (6.0%)</td>
</tr>
<tr>
<td>Pain (injection site or limbs)</td>
<td>55 (64.7%)</td>
<td>24 (28.9%)</td>
</tr>
<tr>
<td>Contusion/Swelling</td>
<td>66 (77.6%)</td>
<td>22 (26.5%)</td>
</tr>
<tr>
<td>Bleeding (at injection site)</td>
<td>31 (36.5%)</td>
<td>7 (8.4%)</td>
</tr>
<tr>
<td>Sensibility disorder</td>
<td>4 (4.7%)</td>
<td>5 (6.0%)</td>
</tr>
<tr>
<td>Other**</td>
<td>10 (11.8%)</td>
<td>13 (15.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>85 (100.0%)</td>
<td>83 (100.0%)</td>
</tr>
</tbody>
</table>

* multiple entries possible  ** 4 hematoma, 3 skin rupture; 1 headache; 1 nausea; 1 pain

Safety

With regards to tolerability, during the course of the study no serious adverse drug reactions (SADR) occurred. Adverse drug reactions (ADR, Table 3) occurred within 24 hours after CCH injection in 64 patients (74.4%), mostly contusion/swelling, pain, blood blister/other bleeding at the injection site, or ecchymosis. Skin rupture with bleeding occurred in 19 cases (23.5%). Nine ADR were rated as severe (2 blood blister or bleeding at injection site; 4 pain; 3 contusion/swelling). Between day 1 (after extension) and day 30, a total of 33 patients experienced ADR, mostly pain or contusion/swelling. In the overall assessment by the physicians, at day 30, 73.5% rated tolerability as very good, 22.9% as good, and 3.6% as moderate. At 360 days, physicians rated tolerability in 95.7% of cases as very good, in 2.2% as good, in 2.2% as moderate.

Patient-reported outcomes

Questionnaires on hand function or quality of life were filled out by 85 patients (97.7%) at baseline, by 82 patients (98.8%) at day 30 and by 46 patients (97.9%) at day 360. On the EQ-5D Visual Analog Scale (0 = worst imaginable health state, 100 = best imaginable health state) the mean raw value improved from 79.5±17.9 to 83.8±15.8 at day 30, and to 85.4±14.1 at day 360. In categorical terms, 59.7% improved at day 30 compared to baseline, 16.9% were unchanged, and 23.4% worsened. By day 360 compared to baseline, 64.4% improved, 15.6% were unchanged and 20.0% worsened. On the WHO-5 questionnaire on depressive disorders, in all 5 questions about 70–80% of the patients improved or were unchanged.
On the Michigan Hand Questionnaire, the total score was 67.5 points at baseline, 75.7 points at day 30 and 75.2 at day 360. The score improved on average by 8.6 between baseline and day 30 and by 8.9 between baseline and day 360.

Discussion

According to the present study performed under clinical practice conditions, CCH was effective and well tolerated in patients with Dupuytren contracture. Our results are in line with a number of previous open-label extensions of randomized studies on CCH as well as with the POINT-X study, the only non-interventional study published to date on Xiapex®. As the studies were performed on various settings and applied various endpoints and definitions for success of treatment [15], they can only be compared with caution.

In a retrospective chart review, Peimer et al. reported outcomes form 10 U.S. community and academic practice sites with major experience using CCH in 463 patients who predominantly (93%) received on 1 injection. Mean contracture was reduced by 75% from 49° ± 21 at baseline to 12° ± 17 degrees, similar to the 71% to 79% reduction in clinical trials. Mean range of motion was improved by 37° from 44° ± 20 at baseline to 81° ± 14, similar to the increase of 35° and 37° in the 2 clinical trials; and 67% of first injections resulted in full correction to 0° –5°, compared with the clinical trial rate of 39%. Thus, the study found a lower injection rate, but a similar correction of joint contracture and range of motion compared to the findings from clinical trials [16].

According to Witthaut et al., in the JOINT I (USA) and JOINT II (Europe and Australia) studies 587 patients followed-up to 9 months achieved similar favorable outcomes, with clinical success (reduction in contracture to within 0° to 5° of full extension 30 days after the last injection) in 57% of treated joints and clinical improvement (at least 50% reduction from baseline contracture) in 69% [17].

The CORDLESS study reported 3-year follow-up data from patients in 5 previous randomized controlled studies (including the JOINT trials). The recurrent rate in previously successfully treated joints was 35%; and no new long-term or serious adverse events were noted [18].

With 8 years, in 8 of the 23 patients from the original Phase II study is the longest follow-up reported to date. Six patients had disease recurrence, 2 patients had not, and 7 patients stated that they would pursue further injection for the treatment for their recurrent or progressive Dupuytren’s disease [19].

In POINT X, a non-interventional European study, 254 patients received open-label collagenase for Dupuytren’s contracture. The most severely affected joint was treated first in 74% of patients. In total, 52%, 41%, 7%, and 1% of patients selected the little, ring, middle, and index finger, respectively; 79% had one or two joints treated. Only 9% of patients (n = 24) received 4 or 5 injections. The mean improvement in total passive extension deficit (TPED) was 34 degrees on day 1, improving further by day 7 to 42 degrees. This secondary improvement was maintained by day 90 and month 6. The mean number of injections/joint was 1.2 for the MCP joint and 1.25 for the proximal interphalangeal joint. Median time to recovery was 4 days; the mean improvement in hand function was clinically relevant as measured by the Unité Rhumatologique des Affections de la Main (URAM) score. In total, 87% and 86% of patients and physicians, respectively, were very satisfied or satisfied with treatment at month 6. Collagenase was well tolerated, with 10 (3.9%) patients experiencing severe adverse events [20].

The patient-related outcomes in our study are of interest, as the measured contracture does not necessarily correlate well with the subjective assessment of the patient [21]. The MHQ has been used in a number of studies on surgical aponeurectomy/fasciectomy in patients with Dupuytren contracture, where Johnston et al. reported in 19 patients an improvement from 58±16 points to 87±12 at 14 months [22], Herweijer et al. in 46 patients from 75±13 to 84±15 points [23], or Knobloch et al. a value 76±12 points 27 months post surgery [10]. Thus, the improvement of 9 points on the MHQ between baseline and day 30 (and also day 360) and the value of 75 achieved after treatment is for CCH in our study is in the same order as for the described surgical interventions. The improvement on the EQ-5D scale supports the positive findings of CCH treatment on patient’s quality of life. Notably, the study was performed at a time when CCH was newly introduced, and there might have been a learning curve in centers over time. It is noticeable that the postoperative treatment was not homogeneous across centers: all patients received one or more extension procedures as planned but the time of the extension procedure varied; some patients were immobilized while some were not (the immobilization was not standardized but very different performed by dressing, casts or splints). A number of further limitations need to be addressed when the current results are interpreted. Given that this was an observational non-randomized study, different biases can obscure any true causal association [24].

Clinical decisions of the treating physicians may assign selected patients to drug treatment as compared to conventional surgical treatment disease severity, disease duration, presence of comorbidities, and other factors. This can potentially introduce allocation or channeling bias and confound the association between treatment and outcomes.

Due to the premature discontinuation of the study owing to administrative reasons a high proportion of patients have no follow-up after one year. Thus the long-term outcomes must be interpreted with caution.

Conclusions

In the present study, CCH (Xiapex®) used by surgeons who had been trained on the appropriate use of the agent
according to the specifications of the prescribing information was effective and well tolerated. No safety issues were identified during the study. Quality of life and hand function improved after CCH administration and remained in those patients who could be followed up at 1 year. Overall, the ReDuCTO study outcomes are in line with the results of the previous randomized controlled trials and as well as open-label long-term studies.

Notes

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Competing interests

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