Overview of the pathogenesis, diagnosis and treatment of Dupuytren’s disease

Dupuytren’s disease (DD) is a fibroproliferative disorder affecting palmar and digital fascial structures of the hand that the rheumatologist is apt to encounter in the clinical setting and is well positioned to first identify. The etiology of DD is unknown and multiple genetic and environmental factors are thought to be involved. Histological and biochemical changes include increased fibroblasts and expression of extracellular matrix proteins, such as collagen, and the presence of contractile myofibroblasts. Development of fibrous cords is common and joint contractures can develop as the skin fuses with the underlying fascia and cords. Surgery is widely used treatment for contractures. A minimally invasive procedure, collagenase clostridium histolyticum injection, has been approved for adult patients with Dupuytren’s contracture with a palpable cord.

Keywords: collagenase clostridium histolyticum • collagen cords • Dupuytren’s contracture • surgical fasciectomy

Dupuytren’s disease (DD) is a fibroproliferative disorder affecting palmar and digital fascial structures of the hand [1]. Abnormal deposition of collagen causes nodular thickening of the palmar aponeurosis and contracture of joints; contracture most commonly affects the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, although distal interphalangeal joints can also be affected. Flexion contractures of affected joints limit hand function and quality of life. Treatment to date has been mainly surgical, which is associated with complications [2,3] extensive post-treatment care, and relatively high recurrence rates (e.g., up to 73% with fasciectomy and up to 100% with fasciomyectomy/needle aponeurotomy) [3–6].

This article reviews the pathogenesis, diagnosis and treatment of DD. We focus on a new novel noninvasive medical management with collagenase clostridium histolyticum (CCH; Xiaflex®, Auxilium Pharmaceuticals, PA, USA). CCH is currently approved in the US and Europe for the treatment of adult patients with Dupuytren’s contracture with a palpable cord.

Pathogenesis

The etiology of DD is unknown and multiple factors are thought to be involved (Figure 1) [7]. Genetic susceptibility, age and ethnicity are considered the main risk factors. Several environmental risk factors have been implicated, although some of these data are controversial.

Patients with a strong family history show onset at an earlier age and manifest a more severe form of the disease [7]. A maternally transmitted inheritance pattern has been shown among Caucasian DD patients; 90% showed a mutation within the mitochondrial 16s rRNA gene [8]. Specific human leukocyte alleles, in particular the class II HLA-DR loci, are associated with a predilection for or protection against DD [9]. A study in 960 patients with Dupuytren’s identified nine different loci involved in genetic susceptibility to the disease; six of these loci harbored genes encoding the Wnt signaling pathway [10],
which regulates the proliferation and differentiation of fibroblasts. Activation of the Wnt pathway by cytokines, notably TNF, leads to conversion of normal fibroblasts to myofibroblasts [11]. Thus, aberrations in the Wnt signaling pathway appear to be integral to the process of fibromatosis in DD.

Several additional factors are associated with DD. These include environmental factors such as trauma, alcohol consumption and smoking [1,7]. Comorbidities associated with DD include diabetes, epilepsy (and anticonvulsant treatment), HIV (and antiretroviral treatments) and cancer [1,7]. These factors are thought to lead to multiple processes that appear to be involved in the development of the disease, such as abnormal wound repair, altered immune responses and oxidative stress; these processes are consistent with observed molecular aberrations, as noted below [7].

Histological and biochemical changes seen in Dupuytren’s tissue – increased fibroblasts and expression of extracellular matrix proteins such as collagen, and the presence of contractile myofibroblasts – resemble changes that occur during wound healing [7]. The normal palmar fascia is composed mainly of collagen type I. In Dupuytren’s fascia, there is excessive production of collagen type III in early lesions that is gradually replaced by collagen type I, which is predominant in late lesions [12,13]. An imbalance in the expression of matrix metalloproteinases and tissue inhibitors of metalloproteinase is also noted [7,13].

A role for altered immune responses and oxidative stress in the development of DD is supported by reported alterations in levels of immune cells, growth factors and cytokines [7,13]. Oxidative stress may explain the association of DD with smoking, diabetes, alcohol consumption and aging. These factors can lead to microangiopathy and ischemia of the palmar fascia. Ischemia in the palmar fascia triggers production of xanthine oxidase, which catalyzes hypoxanthine to xanthine and uric acid, with subsequent release of free radicals. High concentrations of hypoxanthine in nodules and xanthine oxidase activity in palmar fascia have been observed in tissue affected by DD [14]. Free radicals lead to proliferation of fibroblasts and production of cytokines, particularly IL-1 [13]. Increased fibroblast density is associated with increased production of collagen type III [15], which, as noted above, is characteristic of early Dupuytren’s lesions. IL-1 stimulates responses that lead to fibroblast proliferation and production of growth factors, primarily TGF-β [13]. TGF-β has been shown to enhance myofibroblast proliferation, differentiation and contractility [16,17]. Additional effects of growth factors that ultimately contribute to the
development of joint contracture include increased production of extracellular matrix components, selective splicing of fibronectin and activation of platelets to produce lysophosphatidic acid [13].

Clinical manifestations & diagnosis
Patients may initially present with a small, pitted nodule or multiple nodules in the palm, which may slowly progress to contracture of the fingers [7,18]. Bilateral involvement is common; fingers predominantly affected are the fourth and fifth digits. Patients can experience difficulties in activities of daily living [18–20]. Disease progression may be characterized using a three-stage grading system based on histological changes, as described by Luck: proliferative, involu-
tional and residual [7,21]. Stage 1 (early proliferative) is defined by a thickened cellular fibroblastic nodule and a band in the palmar aponeurosis, which may progress to skin tethering, puckering or pitting. A large portion of the tissue at Stage 1 is comprised of myofibroblastic cells rather than collagen [7,18]. Stage 2 (active involu-
tional) is defined by presence of a peritendinous band and limited extension of the affected finger. Fibroblasts within the nodules align along the major lines of stress. In Stage 3 (advanced residual), the nodules disappear and tendon-like fibrous cords develop. The skin over-
lying the nodule fuses with the underlying fascia and cords, resulting in the characteristic flexion contracture of MCP and PIP joints [7,18]. Progression from one stage to the next varies and is more rapid in patients with risk factors [22]. Some, especially older patients, never progress beyond the nodule stage, while others progress to full contracture.

Dupuytren’s diathesis is a term originally used by Hueston that refers to an inherited tendency for the production of Dupuytren’s tissue in other areas out-
side the palmar region, including the knuckles (Gar-
rod’s pad), feet (Ledderhose’s disease) and penis (Pey-
ronie’s disease) [1,18,23]. The four main characteristics of Dupuytren’s diathesis are: bilateral disease, family history of DD, ectopic lesions and Northern European ethnicity [24]. Patients with Dupuytren’s diathesis are likely to develop disease at an earlier age, often experience a more severe form of the disease and tend to have post-surgical recurrences.

Upon presentation, the nodule site and any evidence of contractures, bands, skin pitting, tenderness or dimpling should be noted. The Hueston tabletop test can aid determining whether a contracture is significant and might benefit from treatment; the test is positive if the patient is unable to lay the palm flat on a table-
top [25]. Disease severity is determined more specifically by flexion deformity, which is measured using a goniometer. The modified Tubiana staging system can be used clinically to characterize disease severity based on flexion deformity; it also takes into consideration relevant risk factors that may affect prognosis in terms of disease progression and treatment outcomes [7,18,22,26].

Surgical treatment
Surgery is currently the most widely used treatment for DD. Surgery is generally recommended for functionally impaired MCP joint flexion contractures of ≥30°; some surgeons set a threshold of 40° flexion contracture, although many use 20° or 30°. Recommendations vary for PIP joints, however; because outcomes are clearly worse with more severe contractures, inter-
vention is often recommended earlier for PIP joints than for MCP joints.

Several reviews and studies have been published that elaborate on surgical approaches [4,27–29]. Common surgical procedures include open fasciectomy, percutaneous needle fasciotomy or needle aponeurotomy, and dermofasciectomy [7,22]. In mild-to-moderate disease, open fasciectomy removes the diseased palmar fascia with the cord and nodule using an open approach that is limited, segmental or radical. Percutaneous needle fasciotomy, used in early disease for MCP joints, divides the cord blindly to release contracture without removing the cord. Dermofasciectomy removes the diseased palmar fascia and overlying affected skin, followed by skin grafting.

Systematic review of surgical procedures does not support one technique above the other [30]. Surgery generally provides positive outcomes for the major-
ity of patients [2]. For example, a review of 48 studies reported that 61–97% of patients treated with fasci-
ectomy achieved 100% correction of contracture; the mean improvement in contracture angle with fasci-
ectomy ranged from 58 to 79% and with fasciotomy ranged from 46 to 88% [28]. Average recurrence rates at a median of 4 years of follow-up were 39% with fasci-
ectomy and 62% with fasciotomy [28]. Reported recur-
rence rates vary considerably depending on several fac-
tors, including the specific procedure performed, the definition of recurrence used, and the time period of follow-up, and generally tend to be higher with needle fasciotomy than with fasciectomy. It should be borne in mind that reports of surgical outcomes, including both short-term results and long-term recurrence rates, may be difficult to extrapolate or compare with reports of other interventions, due to considerable variation and lack of clarity in the way that outcomes are defined.

Potential risks associated with surgery include major complications such as digital nerve and artery inju-
ries, infection, hematoma and complex regional pain syndrome (CRPS); a review of 28 studies reported average rates of individual complications ranging from
approximately 2 to 5.5% [2]. Minor complications, such as flare reactions and wound healing complications, are more common (average rates of ~10 and 23%, respectively, in the aforementioned review) [2]. Some complications may be more common with surgery for recurrent disease than for primary disease [2]. Patients are subject to prolonged rehabilitation (occupational/hand) therapy after open surgery. Needle aponeurotomy historically reports complications such as skin breaks and nerve injury.

**Nonsurgical treatment**

Several nonsurgical therapies have been investigated but not found to be clinically effective [31]. These include hyperbaric oxygen, ultrasound, steroids, radiotherapy, vitamin E, and IFN-γ [34].

In contrast to these nonsurgical therapies, CCH is a novel treatment that hydrolyses collagen, and it has been shown to be clinically effective. CCH is a mixture of class I and II collagenases in a fixed-ratio that effectively digests multiple collagen types, including types I and III that characterize Dupuytren’s cords, while sparing type IV collagen that is a primary component of the basement membrane of neurovascular structures [12,32]. CCH was approved in the USA in 2010 for the treatment of adult patients with Dupuytren’s contracture with a palpable cord and approved in Europe in 2011 [35].

*In vitro* studies confirm that CCH decreases the tensile modulus and consequently weakens Dupuytren’s cord tissue [34]. Clinical studies show that CCH lyases collagen in injected Dupuytren’s cords. The treated cord is manipulated (finger extension procedure) the next day to rupture the cord (35,36). Treatment is office-based, minimally invasive, requires no extensive hand therapy [37] and local anesthesia is at the physician’s discretion. CCH has been investigated in a clinical trial program of over 1000 patients with DD (Table 1) [35–40]. A series of Phase II clinical trials demonstrated that CCH at a dose of 10,000 units (0.58 mg) was a safe and effective minimally invasive alternative to surgery for the treatment of DD [35,36].

**Phase III CCH studies**

In a double-blind, randomized, placebo-controlled trial (n = 35; 14 MCP; 9 PCP) [38], clinical success (contracture reduction to within 0°–5° of full extension within 30 days after last injection) occurred in 16/23 patients (70%) after one injection and 21/23 (91%) after up to three injections; no placebo patients (n = 12) achieved joint correction. Adverse events (AEs) were mild, transient in nature and resolved over several weeks. Most AEs were local reactions to injections and no major AEs were seen. Five patients had recurrences after 24 months.

In the Phase III CORD I study (n = 308; 133 MCP; 70 PIP) [37], up to three injections of 0.58 mg CCH per affected joint was administered. A treatment cycle included injection, manipulation, and 30-day follow-up. Patients had MCP and/or PIP joint contractures of ≥20° at baseline. The primary end point was reduction of joint contracture to ≤5°. More CCH patients than placebo patients met the primary end point (64 vs 6.8%; p < 0.001). By joint type, correction to ≤5° was achieved in 102/133 MCP joints (77%) and 28/70 PIP joints (40%). Joints with lower severity tended to respond better with CCH. Significant improvement in range of motion (ROM) versus baseline was noted with CCH in both MCP and PIP [37]. ROM in the CCH group was significantly greater than placebo (43.9–80.7° vs 45.3–49.5°; p < 0.001).

An analysis by joint type (MCP/PIP) of ROM in CORD I showed that CCH significantly improved ROM and patient satisfaction versus placebo [41]. The ROM improvements were considered clinically relevant. Significantly more patients given CCH versus placebo reported being ‘very/quite’ satisfied with treatment outcomes (87 vs 32%; p < 0.001).

Serious AEs in the CORD I study included one case of recurrent CRPS and two cases of tendon rupture. The most common AEs were localized swelling, pain, bruising, pruritus and transient regional lymph node enlargement and tenderness. Anticollagenase antibodies were seen in ≥85.8% patients after one injection and in 100% of patients after three injections. No systemic allergic responses were reported [41].

The Phase III CORD II study conducted in Australia (n = 66) had a similar design and primary end point as CORD I [39]. Significantly more cords injected with CCH (0.58 mg/injection) than placebo met the primary end point (44.4 vs 4.8%; p < 0.001). Primary end point was achieved in 13/20 MCP joints (65%) and 7/25 PIP joints (28%). ROM was greater with CCH than placebo (35.4° vs 7.6°; p < 0.001). Joints with lower severity responded better to CCH. Patient satisfaction and physician ratings of improvement correlated with ROM results. One serious AE was observed: small finger flexor pulley rupture. No recurrences were seen at 1-year follow-up.

Two open-label CCH studies, JOINT I (n = 201) and JOINT II (n = 386), were conducted in the USA and Europe/Australia (published together [40]). In the combined analysis, reduction in contracture to ≤5° was seen in 57% (497/879) of treated joints, with MCP joints showing better response (70%) than PIP joints (37%). Mean increase in ROM was 29.8° (MCP: 33.0°; PIP: 25.0°). No tendon ruptures or systemic immunological reactions were reported in either of these studies.
The findings of the Phase III studies confirm that CCH safely and effectively restores normal finger extension and improves range of finger motion in many patients; subgroup analysis showed no significant differences in clinical success rates by age, sex or presence of diabetes [42].

Safety & tolerability profile of CCH

AEs seen in the two placebo-controlled trials (Table 2) show that most AEs were related to the procedure (edema peripheral [swelling of the treated extremity], contusion and injection site pain) [33]. Serious AEs were two tendon ruptures and one CRPS. Both cases of tendon rupture required reconstructive surgery [43].

Postmarketing surveillance

Peimer et al. recently presented 3-year US postmarketing safety data for CCH [44]. A total of 1732 AEs in 846 patients were received voluntarily from patients or healthcare providers after approximately 49,000 injections. Most AEs were localized and were nonserious reactions. Palmar and digital skin tears were the most frequently reported (13.2%) and primarily included lacerations and skin lesions that healed without intervention. There were 19 skin grafts reported for 228 patients with skin tears postmanipulation. A total of 26 tendon ruptures, one A2 pulley injury and one ligament injury were reported. No additional clinical risks to those observed in the clinical trials of CCH were reported.

Risk evaluation & mitigation strategy for CCH

A voluntary risk evaluation and mitigation strategy training module has been put in place by the manufacturer of CCH (Auxilium) [51]. CCH is available only to physicians who have completed procedure training in its administration [45].

Avoiding tendon ruptures during CCH injections

Most AEs observed with CCH are self-limited. The manufacturer provides recommendations to avoid flexor tendon damage during the injection procedure when injecting a cord affecting a PIP joint of the fifth finger: the needle insertion should not be more than 2–3 mm in depth and avoid injecting more

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Table 1. Efficacy of collagenase clostridium histolyticum in Phase II and III clinical trials.

<table>
<thead>
<tr>
<th>NCT # (Acronym)</th>
<th>Study design</th>
<th>Phase</th>
<th>Number of subjects</th>
<th>MCP joint contracture correction, number of joints/total joints (%)</th>
<th>PIP joint contracture correction, number of joints/total joints (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>Open-label II</td>
<td>35</td>
<td>28/34 (82)</td>
<td>4/9 (44)</td>
<td>[35]</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>DB, placebo-controlled IIa</td>
<td>49</td>
<td>9/18 (50)</td>
<td>5/7 (71)</td>
<td>[36]</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>DB, placebo-controlled IIb</td>
<td>80</td>
<td>(90)</td>
<td>(70)</td>
<td>[36]</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>DB, placebo-controlled III</td>
<td>35</td>
<td>12/14 (86)</td>
<td>9/9 (100)</td>
<td>[38]</td>
<td></td>
</tr>
<tr>
<td>NCT00528606 (CORD I)</td>
<td>DB, multicenter, placebo-controlled</td>
<td>III</td>
<td>308</td>
<td>102/133 (77)</td>
<td>28/70 (40)</td>
<td>[37]</td>
</tr>
<tr>
<td>NCT00533273 (CORD II)</td>
<td>DB, multicenter, placebo-controlled</td>
<td>III</td>
<td>66</td>
<td>13/20 (65)</td>
<td>7/25 (28)</td>
<td>[39]</td>
</tr>
<tr>
<td>NCT005288840 (JOINT-I); ACTRN12607000217404 (JOINT II)</td>
<td>Open-label III</td>
<td>587</td>
<td>369/531 (70)</td>
<td>128/348 (37)</td>
<td>[40]</td>
<td></td>
</tr>
</tbody>
</table>

ACTRN: Australian New Zealand Clinical Trials Registry; DB: Double-blind; MCP: Metacarpophalangeal; NA: Not available (not registered at Clinicaltrials.gov); NCT: National (US) clinical trials; PIP: Proximal interphalangeal.
than 4 mm distal to the palmar digital crease [33]. Similarly, Zhang and colleagues suggest: injecting the cord more proximally between the PIP and MCP joint flexion creases; placing the needle parallel, not perpendicular, to the cord; and avoiding the needle hitting vital structures by using one hand to stabilize the syringe/needle and the other hand to push the plunger [43].

The small risk of tendon ruptures may be mitigated by using ultrasound to guide injections [46]. Ultrasound guidance may provide visualization of cord fibers and may aid in accurate needle placement during DD treatment [47]. In the Phase II study [36], ultrasound imaging of affected finger facilitated visualization of flexor tendon to avoid inadvertent tendon injection. DeMarco et al. reported that ultrasound guidance of CCH was safe and effective in delivering 17 injections in 11 patients; no tendon ruptures were seen in this small group of patients [46].

Use of local anesthesia
Use of local anesthesia during the finger extension procedure has resulted in lower number of injections per joint and a higher rate of successful cord release [48,49]. In a comparison of CCH use in the real-world setting versus published clinical trials, Skodny et al. reported a lower number of injections per joint (1.08 ± 0.32 vs 1.5 ± 0.7), which the authors attributed partly to the use of local anesthesia during manipulation [33,48]. Denkler et al. reported that full release rate after first injection was higher in clinical practice (63%) compared with the CORD I study (39%); the higher rate was attributed to use of local anesthesia during manipulation [49].

Limited long-term data exist on recurrence rates after CCH treatment. The ongoing, prospective, 5-year observational CORDLESS trial in 644 patients (1081 CCH-treated joints) has reported a 4-year recurrence rate of 42% in the 623 CCH-treated joints that had achieved full correction (contracture ≤ 5°) [50]. The recurrence rates were 35% in MCP joints and 62% in PIP joints. A lower rate of recurrence was seen in PIP joints with less severe (i.e., <40°) versus more severe (≥40°) baseline contracture. Using a modified definition of recurrence based on an increase in contracture of ≥30° (the typical threshold for surgery), the recurrence rate was 28% in all treated joints (22% of MCP; 43% PIP). A total of 87% of successfully treated joints did not require further medical or surgical intervention at 4 years.

Conclusion
DD is a disease of the hand associated with specific demographics and risk factors, and rheumatologists are well suited to identify patients with DD and educate them with regard to disease course and treatment.

<table>
<thead>
<tr>
<th>AE</th>
<th>CCH (n = 249), % AEs</th>
<th>Placebo (n = 125), % AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>98</td>
<td>51</td>
</tr>
<tr>
<td>Edema peripheral†</td>
<td>73</td>
<td>5</td>
</tr>
<tr>
<td>Contusion‡</td>
<td>70</td>
<td>3</td>
</tr>
<tr>
<td>Injection site hemorrhage</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>35</td>
<td>6</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>35</td>
<td>4</td>
</tr>
<tr>
<td>Tenderness</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>Pruritus</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Skin laceration</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Lymph node pain</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Erythema</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Axillary pain</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

† Most of these events were swelling of the injected hand.
‡ Includes the terms: contusion (any body system) and ecchymosis.

AE: Adverse event; CCH: Collagenase clostridium histolyticum.

Data taken from [33].

Tendon rupture seen at 0.3% and complex regional pain syndrome at 0.1% with CCH.

Table 2. Adverse events (>5%) in collagenase clostridium histolyticum-treated patients in placebo-controlled trials.
Future perspective
While minimally invasive techniques may allow patients to be treated earlier in the course of DD in an office setting, the issue of early intervention needs to be carefully studied to determine whether earlier intervention with CCH or surgery achieves enduring clinical success with less progression and recurrence than later intervention. However, major inconsistencies in reporting recurrence and lack of a consistent definition make it difficult to compare the durability of treatment. Standardization of successful outcomes, including patient-reported outcomes and recurrence would allow for treatments to be compared and allow the patients and physicians to make more informed choices about treatment options. Additionally, patient-reported outcomes and satisfaction need to be incorporated as a study end point, as limited data suggest the affected joint, digit and degree of contracture correction have an important bearing on decisions regarding further treatment. At present, only limited data exist concerning the safety of treating multiple joints concurrently with CCH. Additional studies on a larger scale are needed to establish if concurrent multiple injections of CCH can be effectively and safely administered.

During the next several years there will likely be more education in medical and rheumatology training programs about DD and its potential to cause significant impairment. Additional basic research will take place on the role of cytokine dysregulation, which leads to an imbalance collagen synthesis and other signaling pathways (e.g., Wnt) involved in DD. A greater understanding of these processes may lead to the development of novel treatments that target these pathways (e.g., inhibitors of TNF); such treatments may help to address the problem of recurrence that exists with current treatment options. The use of CCH will continue to offer a safe alternative to surgery.

Author contribution
Both authors contributed equally to the drafting and revision of this manuscript, and both meet the requirements for authorship. Both reviewed the final manuscript and gave approval for submission.

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Executive summary
Pathogenesis
• Etiology of Dupuytren’s contracture is unknown and genetic susceptibility, age and ethnicity are considered to be the main factors.
• Dupuytren’s disease is also associated with chronic metabolic and inflammatory diseases.

Clinical manifestations & diagnosis
• In the advanced residual stage of Dupuytren’s disease, nodules disappear and tendon-like fibrous cords develop.

Surgical treatment
• Surgery has generally been recommended for functionally impaired metacarpophalangeal joint flexion contractures of ≥30°, although surgeons may set a threshold from 20–40° flexion.
• Recommendations vary for proximal interphalangeal joints, but the threshold for surgical intervention is lower.

Nonsurgical treatment
• Collagenase clostridium histolyticum (CCH) is a safe, effective noninvasive procedure for treatment of Dupuytren’s contracture.
• Postmarketing surveillance of CCH has revealed no clinical risks not previously reported in clinical trials.
• Small risk of tendon rupture may be mitigated by using proper injection technique; ultrasound-guided injections of CCH have been used in some practice settings.
• Limited long-term data on recurrence rates for CCH show a lower degree of recurrence in patients achieving full correction in clinical trials.

Conclusion
• Rheumatologists are often the first point of contact for patients with joint deformities and are, therefore, well suited to identify patients with Dupuytren’s disease, and this review is a resource to help them educate these patients with regard to disease course and treatment.
and VQ Orthocare. PJ DeMarco—consulting fees: Auxilium; speakers bureau: Abbott, Sonosite and Takeda; research PI/Sub: Abbott, Amgen, Ardea, Celgene, Centocor, Genentech, Nuon, Pfizer, Roche, Sanofi, Savient, Takeda and UCB. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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References
Papers of special note have been highlighted as:
• of interest; •• of considerable interest


• Long-term randomized study that provides a recommendation regarding patients most suitable for intervention with percutaneous needle fasciotomy.


• Comprehensive peer review of important considerations in the clinical management of Dupuytren’s contracture.


•• Updated analysis of diathesis factors that extends on original research of this important topic and identifies patients who may be at higher risk for the progression of Dupuytren’s contracture.

Overview of Dupuytren’s disease

Review


33 Xiaflex® (collagenase Clostridium histolyticum), prescribing information. Auxilium Pharmaceuticals, Inc., PA, USA (2013).


**Publication of the results of the CORD I clinical trial.


**Publication of the results of the CORD II clinical trial.


**Presentation of a safe and effective ultrasound guided method for rheumatologists to consider in treating patients with collagenase clostridium histolyticum.


**Analysis of 4-year recurrence in patients who were originally treated with collagenase clostridium histolyticum in clinical trials.