



## ORIGINAL ARTICLE

# Treatment of Dupuytren's disease using collagenase from *Clostridium histolyticum*<sup>☆</sup>

M.Á. Martín-Ferrero, C. Simón-Pérez\*, J.I. Rodríguez-Mateos, B. García-Medrano, R. Hernández-Ramajo, M. Brotat-García

Servicio de Cirugía ortopédica y Traumatología, Hospital Clínico Universitario de Valladolid, Valladolid, Spain

Received 10 June 2013; accepted 17 July 2013

### KEYWORDS

Collagenase;  
Clostridium;  
Histolyticum;  
Dupuytren

### PALABRAS CLAVE

Colagenasa;  
Clostridium;  
Histolyticum;  
Dupuytren

### Abstract

**Objective:** The collagenase from *Clostridium histolyticum* is a new therapeutic option, and the first pharmacological one, in the treatment of Dupuytren's disease.

**Material and methods:** A prospective study was conducted on 35 patients with Dupuytren's disease. The clinical and functional variables, as well as patient satisfaction and drug safety were evaluated.

**Results:** The functional and clinical results after its administration were good, with a rapid recovery, especially at the metacarpophalangeal (MCP) joint. The index finger contracture prior to MCP puncture was 64° and after puncture it was 4°. In the proximal interphalangeal (PIP) prior to puncture it was 83.3° and after puncture it was 15°; In the MCP/PIP prior to puncture it was 140°, and after puncture it was 25°.

**Conclusions:** Collagenase from *Clostridium histolyticum* an alternative of treatment of Dupuytren's disease, mainly in the elderly. More research is required in order to clarify the rate of recurrence of the disease, the possible adverse reactions, and to compare the efficiency and permanence with other treatment options.

© 2013 SECOT. Published by Elsevier España, S.L. All rights reserved.

### Tratamiento de la enfermedad de Dupuytren mediante la colagenasa del *Clostridium histolyticum*

### Resumen

**Objetivo:** La colagenasa del *Clostridium histolyticum* es una nueva opción terapéutica y el primer tratamiento farmacológico en el tratamiento de la enfermedad de Dupuytren.

<sup>☆</sup> Please cite this article as: Martín-Ferrero MÁ, Simón-Pérez C, Rodríguez-Mateos JI, García-Medrano B, Hernández-Ramajo R, Brotat-García M. Tratamiento de la enfermedad de Dupuytren mediante la colagenasa del *Clostridium histolyticum*. Rev Esp Cir Ortop Traumatol. 2013;57:398–402.

\* Corresponding author.

E-mail address: [simonclarisa@yahoo.es](mailto:simonclarisa@yahoo.es) (C. Simón-Pérez).

**Material y métodos:** Estudio prospectivo de 35 pacientes afectados de la enfermedad de Dupuytren. Se evaluó los resultados clínicos, funcionales, la satisfacción del paciente y la seguridad del fármaco.

**Resultados:** Los resultados funcionales y clínicos tras su administración son buenos sobre todo en la articulación metacarpofalángica, con una recuperación rápida. El índice de contractura del dedo MCF previo a la punción fue de 64° y tras la punción de 4°; en las IFP previo a la punción fue de 83,3 grados y tras la punción de 15°; en MCF/IFP previo a la punción fue de 140° y tras la punción de 25°.

**Conclusiones:** Es una alternativa de tratamiento de la enfermedad de Dupuytren, fundamentalmente en los ancianos. La investigación es necesaria para clarificar el índice de recurrencia de la enfermedad, las posibles reacciones adversas y comparar la eficacia y durabilidad con otras alternativas de tratamiento.

© 2013 SECOT. Publicado por Elsevier España, S.L. Todos los derechos reservados.

## Introduction

Dupuytren's disease is a progressive fibroproliferative disorder characterized by the development of collagen bands and nodules at the level of the superficial palmar aponeurosis, which causes progressive closure of the fingers.<sup>1</sup>

Recurrence of Dupuytren's disease is common after surgical treatment,<sup>2</sup> especially in young patients.<sup>1</sup> The recurrence rate after surgery is highly variable according to different publications, going from 0% to 85% depending on the characteristics of each patient, disease and type of surgery performed.<sup>1</sup>

In addition, surgical treatment of Dupuytren's disease entails significant morbidity, with a complication rate of about 17%, which includes skin problems, hematomas, nerve lesions and reflex sympathetic dystrophy.<sup>3</sup> Some published series report a 39% rate of complications, both during surgery and in the postoperative period.<sup>4</sup>

Collagenase from *Clostridium histolyticum* (CH collagenase) is the only approved pharmaceutical treatment for the treatment of Dupuytren's disease. This is a molecular compound formed by mixing fixed percentages of 2 purified collagenolytic enzymes (AUX-I and AUX-II) isolated from a culture of *Clostridium histolyticum*.<sup>5</sup>

The purpose of this study was to establish injection of collagenase as a safe and effective treatment modality to reduce the level of contracture in Dupuytren's disease and to assess the rate of recurrence of the disease within a short follow-up period.

## Material and Methods

We conducted a prospective study in the period from 2011 to the present, which included 35 patients suffering Dupuytren's disease. All were male, aged between 45 and 89 years with a mean age of 68.14 years, and treated at the University Hospital of Valladolid. A total of 15 patients participated in a phase IV, multicenter clinical trial.

All 35 patients included in the study were right-handed. In 15 patients we treated the left hand (42.8%) and in 20 patients we treated the right hand (57.1%).

We used the Tubiana classification to determine the severity of the disease, as reflected in Table 1.

A total of 22 patients (62.8%) were injected in a single and palpable band at the level of the metacarpophalangeal (MCP) joint (1 patient in the third radius, 15 patients in the fourth radius and 6 in the fifth radius), 6 patients (17.1%) in a Y-shaped band affecting 2 fingers, 5 patients (14.2%) were treated by injection in the band at the level of the proximal interphalangeal (PIP) joint and 2 patients (5.7%) underwent a double injection: at the levels of the MCP and PIP.

A total of 3 patients (8.7%) had undergone a previous intervention for Dupuytren's disease in the affected hand. Moreover, 22 patients (62.8%) presented concomitant diseases and risk factors for surgical treatment.

Inclusion criteria were adult patients with Dupuytren's disease, ensuring that the age was over 60 years except in cases in which the patient expressly requested this treatment option, with a palpable band in at least 1 finger, excluding the thumb, and contraction of at least 20–90° at the level of the MCP and 80° at the PIP.

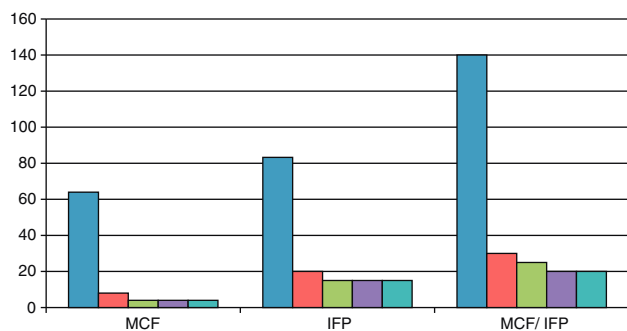
Exclusion criteria were patients with hemorrhagic disorders or recent stroke, with other neuromuscular hand disorders, patients who had received treatment including surgery for Dupuytren's contracture in the previous 90 days, allergy to collagenase or excipients, use of doxycycline in the previous 14 days and anticoagulant drugs in the previous 7 days.

All patients signed a specific consent document for the treatment prior to the injection of collagenase.

All patients were treated in an outpatient surgery regime, taking into account the specific doses necessary, both of collagenase and solvent, depending on the joints

**Table 1** Classification of the Patients in the Study According to the Tubiana Classification.

Grades	Angles	Patients	Percentage
0	0	0	0
I	1–45	1	2.9
II	46–90	18	51.4
III	91–135	9	25.7
IV	>135	7	20



**Figure 1** Levels of contracture prior to injection of CH collagenase and at 2 weeks, 2, 3 and 6 months after the injection.

to be treated according to the recommendations of the product.

Collagenase was administered by local injection directly into the palpable band, with EMLA (numbing cream) being topically administered in the injection area, half an hour earlier in an outpatient surgery room. After the injection, patients were applied compression bandage and recommended to avoid movement.

Extension of the finger and breakage of the band took place after 24 h in an outpatient operating room, with local anesthesia or sedation and subsequent compressive bandaging of the hand.

Follow-up consultations were conducted at 1 week, 2 weeks, 1 month, 3 months, 6 months and 1 year to assess local complications (hematoma, dehiscence of the skin, etc.), decrease of joint contracture and increase of range of motion as measured by a goniometer.

We evaluated patient satisfaction and drug safety by assessing possible complications and performing a blood test 1 month after the injection to seek possible abnormalities, mainly in hepato-renal function.

## Results

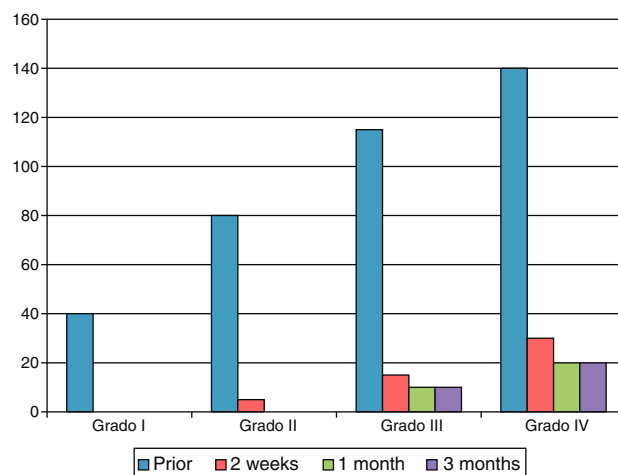
All patients treated with CH collagenase were administered a single injection in the palpable band. In 2 patients the dose was divided between the MCP and the PIP joints, using the maximum recommended dosage of the product, adding the corresponding solvent for the MCP joint and administering the result at 2 levels according to the indicated doses.

As shown in [Fig. 1](#), the finger contracture rate in the MCP group prior to injection was 64° and after injection it was 8° at 2 weeks and 4° in the reviews conducted after 2, 3 and 6 months. The finger contracture rate in the PIP group prior to injection was 83.3° and after injection it was 20° at 2 weeks and 15° in the reviews conducted at 2, 3 and 6 months. The finger contracture rate in the MCP/PIP group prior to injection was 140° and after injection it was 30° at 2 weeks, 25° in the review conducted after 2 months and 20° after 3 and 6 months.

In patients with dual MCP/PIP injection we observed a lower efficiency of the stretching at the level of the PIP.

As shown in [Fig. 2](#), the final result became worse as the degree of contracture was more severe.

Skin dehiscence appeared during finger stretching in 9 patients (25.7%). This was resolved by cures and without



**Figure 2** Levels of contracture prior and after administration of CH collagenase, according to the Tubiana classification.

complications ([Fig. 3](#)). A total of 13 patients (37%) presented hematoma and/or phlyctenas at the site of injection. There were no local, vascular, tendinous or neural complications or infections.



**Figure 3** Skin dehiscence after finger stretching, at 15 and 25 days (healing by secondary intention).



**Figure 4** Dupuytren's disease in fourth finger prior to the administration of CH collagenase and at 1 month after administration.

In 2 patients (5.7%) we detected axillary lymphadenopathy hours after injection, which disappeared within the first 48 h. One patient (2.85%) reported axillary pain with no palpable lymphadenopathy.

Two patients (5.7%) presented an increase in transaminases without clinical consequences in the analytical study conducted 1 month after the injection.

We observed no recurrences of the disease during the follow-up period.

Functional recovery was fast and painless. Only 3 patients (8.5%) required physiotherapy treatment.

## Discussion

Therapeutic options for the treatment of Dupuytren's disease are multiple depending on the characteristics of the patient and the disease itself. They include surgery: fasciectomy, dermofasciectomy, fasciotomy, etc., and pharmaceutical treatment: local injection of collagenase from *Clostridium histolyticum*.<sup>6</sup>

Collagenase from *Clostridium histolyticum* is a new therapeutic alternative and the first pharmaceutical option approved for the treatment of adult patients with Dupuytren's disease which avoids the complications associated with surgery.<sup>7</sup>

In order to obtain good results and minimize risks it is essential to follow the recommendations to ensure a proper use of the product, as explained in the technical data sheet.

The study revealed efficacy of CH collagenase in Dupuytren's disease with clinical and functional improvement in all patients who were administered the treatment and with rapid recovery, as in other published studies.<sup>1,3,5</sup>

The best results were obtained in patients in whom the injection was administered at the level of a palpable band in the MCP joint (Fig. 4) and in those patients with lower levels of contracture, as reported in other series.<sup>1,3-5</sup>

We established the safety of CH collagenase administration through the observation of a scarce number of low-severity, local and easily resolved complications. We did not observe severe local (tendinous, vascular, nerve lesions, etc.) or general complications,<sup>8</sup> although there are some reports documenting severe complications caused by intra-tendinous injection with ruptured tendons and major skin necrosis.<sup>9,10</sup> Comparing the overall complication rates after surgery, different series reached between 4% and 39%.<sup>4</sup>

The treatment was minimally invasive and with few complications, representing an alternative to the treatment of Dupuytren's disease, especially in elderly patients and those with multiple associated pathologies, with limitations in daily activities and in whom surgery represented an increase in the rate of local and general complications.<sup>11</sup>

This alternative pharmaceutical treatment for Dupuytren's disease has surgical indications comparable to those of percutaneous fasciotomy, a technique with a low economic cost, but with high recurrence rates, between 33% and 100%, according to different series.<sup>2</sup> It would be interesting to compare these during longer monitoring periods in order to determine whether or not the pharmaceutical treatment of Dupuytren's disease offers greater effectiveness.

Due to the follow-up period of our patients, we cannot report on long-term recurrence rates. Nevertheless, studies with longer follow-up periods have reported recurrences, especially in cases affecting the PIP group.<sup>1,3</sup>

Further research is required to clarify the recurrence rate of the disease, possible adverse reactions and to compare the efficacy and durability with those offered by other treatment alternatives.

## Level of Evidence

Level of evidence IV.

## Conflict of Interests

The authors have no conflict of interests to declare.

## References

1. Peimer CA, Blazar P, Coleman S, Kaplan TD, Smith T, Tursi J, et al. Dupuytren contracture recurrence following treatment with collagenase *Clostridium histolyticum* (CORDLESS Study): 3-year data. *J Hand Surg Am.* 2013;38:12–22.
2. Werker PM, Pess GM, van Rijssen AL, Denkler K. Correction of contracture and recurrence rates of Dupuytren contracture following invasive treatment: the importance of clear definitions. *J Hand Surg Am.* 2012;37:2095–105.
3. Watt AJ, Curtin CM, Hentz VR. Collagenase injection as non-surgical treatment of Dupuytren's disease: 8-year follow-up. *J Hand Surg Am.* 2010;35:534–9.
4. Witthaut J, Jones G, Skrepnik N, Kushner H, Houston A, Lindau TR. Efficacy and safety of collagenase *Clostridium histolyticum* injection for Dupuytren contracture: short-term results from 2 open-label studies. *J Hand Surg Am.* 2013;38:2–11.
5. Gilpin D, Coleman S, Hall S, Houstoun A, Karrasch J, Jones N. Injectable collagenase *Clostridium histolyticum*: a new non-surgical treatment for Dupuytren's disease. *J Hand Surg Am.* 2010;35:2027–38.
6. Desai SS, Hentz VR. The treatment of Dupuytren disease. *J Hand Surg Am.* 2011;36:936–42.
7. Bainbridge C, Gerber RA, Szczypa PP, Smith T, Kushner H, Cohen B, et al. Efficacy of collagenase in patients who did and did not have previous hand surgery for Dupuytren's contracture. *J Plast Surg Hand Surg.* 2012;46:177–83.
8. Swanson JW, Watt AJ, Vedder NB. Skin graft loss resulting from collagenase *Clostridium histolyticum* treatment of Dupuytren contracture: case report and review of the literature. *J Hand Surg Am.* 2013;38:548–51.
9. Zhang AY, Curtin CM, Hentz VR. Flexor tendon rupture after collagenase injection for Dupuytren contracture: case report. *J Hand Surg Am.* 2011;36:1323–5.
10. Hallock GG. Skin laceration as a serious adverse sequela of injectable collagenase for Dupuytren contracture. *Plast Reconstr Surg.* 2012;129:205e–6e.
11. Chen NC, Shauver MJ, Chung KC. Cost-effectiveness of open partial fasciectomy, needle aponeurotomy and collagenase injection for Dupuytren contracture. *J Hand Surg Am.* 2011;36:1826–34.