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ORIGINAL STUDY

Effectiveness and safety of collagenase *Clostridium histolyticum* in Dupuytren's disease : an observational study in Belgium

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Dupuytren's disease is a connective tissue disorder leading to contractures. It can be treated surgically or through injections of collagenase *Clostridium histolyticum* (CCH). Patients with Dupuytren's contracture (> 20°) and a palpable cord were included in this observational study, aiming to characterise the Belgian patient population and to assess the effectiveness and safety of CCH. Overall, 108 patients (114 joints) received at least one injection of CCH, and 104 patients completed the study. The percentages of joints achieving a degree of contracture of 5° or less, or a relative contracture reduction of at least 50% after the extension procedure were 64.9% and 90.1%, respectively. The mean number of injections per cord was 1.0. The Unité Rhumatologique des Affections de la Main score decreased from 29.4 ± 11.0 to 12.9 ± 6.3 (mean ± SD ; p < 0.0001). CCH was demonstrated to be effective, safe and able to increase quality of life.

Keywords : Dupuytren ; collagenase.

INTRODUCTION

Dupuytren's disease is a benign connective tissue disorder caused by a fibro-proliferative process affecting the palmar fascia and leading to slowly progressive contractures. Although the exact aetiology is still not fully understood, studies have shown that the process involves abnormal myofibroblast-mediated collagen deposition in the palm leading to the formation of pathologic cords (*5,6*). The disease displays a high variability in clinical presentation and behaviour, with a spectrum ranging from benign and limited to widespread and progressing disease, recurring fast and severely after surgery (*8*).

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Dupuytren's disease is highly prevalent in male Caucasians over 50 years of age (*9,27*). It affects around 1% of the US population (*13*) and 2 to 42% of the European population with a much higher incidence in Scandinavian countries (*5,6*). A recent study in Flanders, in 500 patients over 50 years-old, has revealed a high prevalence of 32% (24% Stage I and 8% Stage II) (*7*).

In the past years, treatment options were limited to surgical interventions : the sectioning of the cord without excision (needle fasciotomy), the excision of the fibrous tissue (fasciectomy) or the removal of the affected palmar fascia and the overlying skin (dermofasciectomy). Currently, partial fasciectomy is the most commonly used technique in those patients who are candidates for surgery (*5,6,11,12,20*).

The use of collagenase *Clostridium histolyticum* (CCH) (Xiapex®, Swedish Orphan Biovitrum AB, Stockholm, Sweden) as a potential minimally-invasive, non-surgical option to treat Dupuytren's contractures has been approved by the Food and Drug Administration in 2010, and by the European Medicines Agency in 2011. When injected into the Dupuytren's cord, the collagenase leads to collagen lysis at the application site. The patient returns the following day for an extension manipulation of the involved joints in an attempt to rupture the cord. The injection and extension procedure cycle can be repeated, if needed, after 30 days. Three injections per cord are permitted, with an interval of 4 weeks between injections (*10*). The results from two randomised controlled trials (RCTs) confirmed that CCH use was safe and efficacious when used within the appropriate guidelines. In the CORD I study, CCH injection reduced contractures to 0°-5° in 64% of all joints that were injected, compared to 6.8% in the placebo group (*15*). In the CORD II study, 44% of all the joints that were injected with CCH reduced contractures to 0°-5° compared to 4.8% in the placebo group (*14*).

Information concerning the epidemiology and the treatment of the disease in Belgium is relatively sparse, and as far as we know, no real-life observational study has been conducted with CCH in Belgian patients. The goals of this observational study were therefore to characterise the population of patients with Dupuytren's disease and treated with CCH in Belgium, and to assess the effectiveness and safety of this new treatment with a particular focus on the patient's quality of life.

PATIENTS AND METHODS

Patients aged 18 years and over, presenting with Dupuytren's contracture (> 20°) with a palpable cord and having been treated or going to be treated with CCH were included in this non-interventional (observational), multicentre, prospective, pharmaco-epidemiological study. It was approved by the local Ethics Committees and was conducted in nine Belgian clinical centres, in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients gave their written informed consent and were followed up as per usual clinical practice. The only exclusion criteria were the hypersensitivity to the active substance or to any of the excipients of the product, the participation in another clinical study within 3 months before the current study began and/or during study participation, and the presence of a severe acute or chronic medical, psychiatric condition, or laboratory abnormality that could increase the risk associated with study participation, or could interfere with the interpretation of study results.

The demographics, medical history related to Dupuytren's contracture, current diagnosis, symptoms and severity of the disease were collected at the baseline visit. After the drug injection and the cord extension procedure, the effectiveness of the treatment was assessed using goniometry (degree of contracture, passive extension deficit and range of motion) at the 30-day post-injection follow-up visit. The percentage of joints achieving a degree of contracture of 5° or less, and the percentage of joints achieving a relative contracture reduction of at least 50% after the extension procedure were determined. The pre- and post-treatment patient's quality of life was assessed using the Unité Rhumatologique des Affections de la Main (URAM) score (*4*). The patient's global assessment and the physician's global assessment were collected at the end of study visit using a discrete scale. The safety of the treatment was assessed during the whole study by collecting the adverse events (AEs) and the serious AEs. All data were collected using an electronic case report form.

There was no pre-defined statistical hypothesis to be tested in this study. The sample size had therefore not been calculated on this basis. It was planned to enrol around 100 patients to get a representative sample of the Belgian population. Descriptive statistics were used to characterise all types of variables. The changes versus

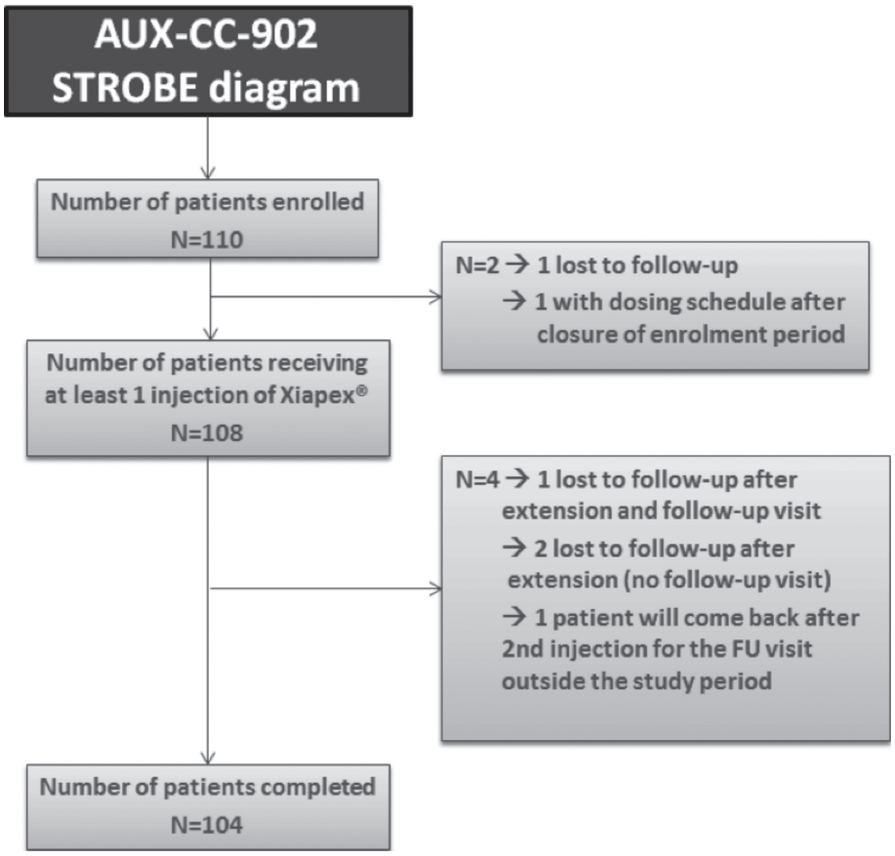

Fig. 1. — Patient flow

baseline in the effectiveness parameters were analysed using paired Student's t tests. The software IBM-SPSS Statistics (Version 21.0) was used throughout the analyses. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA 17.0).

RESULTS

Overall, 110 patients were included in the study between 18 December 2013 and 23 July 2014 by 9 Belgian centres, 108 patients received at least one injection of CCH. The number of patients completing the study was 104. No study discontinuations were related to AE. One patient was lost to follow-up after the extension procedure and follow-up visit, 2 patients were lost to follow-up after the extension procedure but before the follow-up visit, and 1 patient came back after a 2nd injection for the follow-up visit but outside the study period. The patient flow can be found in Figure 1.

Patients (all Caucasians) had a mean age ± SD of 64.4 ± 10.9 years. There were three times more men than women (Table I). A total of 116 joints were affected at baseline in the 110 patients. The majority of patients (n = 104) had only one (94.5%) affected joint. Two joints were affected in 6 (5.5%) patients. No patients had more than 2 affected joints. Functional complaint was reported by 102 (92.7%) patients, positive table top test by 102 (92.7%) patients, appearance complaint by 24 (21.8%) patients, and pain by 14 (12.7%) patients. Two patients (with one affected joint each) did not receive any injections.

A total of 114 injections were done in the fibrous cord of 114 joints (108 patients) : 74 (64.9%) at the metacarpophalangeal (MCP) joints and 40 (35.1%)

Table I. — Demographics and baseline characteristics of the patients

Parameter		N	Mean	SD	Median	Min	Max
Age (year)		110	64.4	10.9	65.0	20.0	87.0
Disease duration (year)		110	8.2	8.1	6.0	0.0	41.0
		N		n		%	
Gender		110					
	Male			85		77.3	
	Female			25		22.7	
Working		110		39		35.5	
Retired		110		63		57.3	
Bilateral disease		110		19		17.3	
Number of prior treatment procedures		110					
	0			64		58.2	
	1			26		23.6	
	2			10		9.1	
	> 2			10		9.1	
Type of prior procedure		85					
	Fasciotomy			16		18.8	
	Dermofasciectomy			5		5.9	
	Fasciectomy			46		54.1	
	Collagenase injection			18		21.2	
Recurrence* after successful surgical treatment		74		48		64.9	
Family history		110		47		42.7	
Medical history		110					
	Diabetes			12		10.9	
	Knuckle pads			15		13.6	
	Peyronie's disease			2		1.8	
	Alcoholism			5		4.5	
	Hand trauma			13		11.8	
	Epilepsy			2		1.8	
	Hypercholesterolemia			33		30.0	
	Ledderhose's disease			7		6.4	
	Smoking			21		19.1	

SD = Standard deviation ; Min = Minimum ; Max = Maximum.

* It should be noted that no precise definition of recurrence was provided. It was left to the interpretation of the investigator.

at the proximal interphalangeal (PIP) joints. No fibrous cord was injected twice or more. Overall, 102 patients had an injection in one fibrous cord (1 single joint) and 6 patients in two fibrous cords (2 different joints).

The effectiveness of injections was assessed in 111 joints (73 MCP and 38 PIP) (Table II). The number of joints achieving a degree of contracture of 5° or less after the extension procedure was 72 out of 111 (64.9%). The number and percentage of MCP and PIP joints achieving a degree of contracture of 5° or less after the extension procedure were equal to 58 out of 73 (79.5%) and 14 out of 38 (36.8%), respectively. The number of joints achieving a relative contracture reduction of at least 50% after the extension procedure was 100 out of 111

Table II. — Effectiveness of collagenase *Clostridium histolyticum* injection

Parameter		N	Mean	SD	Median	Min	Max
Absolute reduction of contracture (°)		111	-45.1	18.9	45.0	10.0	110.0
Relative reduction of contracture (%)		111	-86.1	21.5	100.0	16.7	100.0
URAM score at baseline		104	29.4	11.0	29.0	9.0	52.0
URAM score at the follow-up visit		104	12.9	6.3	9.0	9.0	40.0
		N		n		%	
Joints achieving ≤ 5° of contracture		111		72		64.9	
MCP joints achieving ≤ 5° of contracture		73		58		79.5	
PIP joints achieving ≤ 5° of contracture		38		14		36.8	
Joints with a relative reduction ≥ 50% of contracture		111		100		90.1	
Number of working days lost in working patients		39					
	0			13		33.3	
	1			2		5.1	
	2			4		10.3	
	3			3		7.7	
	> 3			17		43.6	
Satisfaction level of the patient		104					
	Very satisfied			70		67.3	
	Quite satisfied			26		25.0	
	Neither			1		1.0	
	Quite dissatisfied			6		5.8	
	Very dissatisfied			1		1.0	
Satisfaction level of the physician		105					
	Very satisfied			76		72.4	
	Quite satisfied			24		22.9	
	Neither			1		1.0	
	Quite dissatisfied			3		2.9	
	Very dissatisfied			1		1.0	

SD = Standard deviation ; Min = Minimum ; Max = Maximum ; URAM = Unité Rhumatologique des Affections de la Main ; MCP = metacarpalphalangeal ; PIP = proximal interphalangeal.

(90.1%). There was a statistically significant decrease in the absolute and relative contracture between baseline and the follow-up visit ($p < 0.0001$). Overall, 104 joints (93.7%) were considered successfully treated by the investigator at the follow-up visit : 73 MCP joints (70.2%) and 31 PIP joints (29.8%). Among the 39 patients who were working, the treatment procedure did not lead to any loss of working days in 13 patients (33.3%). The number of working days lost remained modest and was ≤ 10 days for 48.7% and > 10 days for 17.9% of the patients. The URAM score decreased from 29.4 ± 11.0 to 12.9 ± 6.3 (mean ± SD ; $p < 0.0001$). Overall 96 (92.3%) out of the 104 completed patients were very satisfied or quite satisfied with their treatment. Physicians were very satisfied or quite satisfied with the treatment for 100 out of 105 patients (95.3%).

After the treatment with CCH, 89.2% of patients were treated with night splinting and 0.9% with

physiotherapy. For 12 joints (10.8%) no further treatment was given following manipulation. Fasciectomy was planned for one joint.

Overall, 184 AEs were reported in 84 patients (77.8%), and 175 AEs considered related to the treatment or to the procedure were reported in 82 patients (75.9%). The majority of AEs (84.2%) were mild, 14.7% were moderate and 1.1% was severe. The most frequent AEs were local swelling (42 ; 22.8%), pain in the extremity (19 ; 10.3%), ecchymosis (16 ; 8.7%), injection site haemorrhage (16 ; 8.7%), laceration (15 ; 8.2%) and injection site swelling (13 ; 7.1%). No serious AEs were reported (Table III).

Table III. — Adverse events classified by preferred terms (alphabetical order) according to the Medical Dictionary for Regulatory Activities (MedDRA 17.0) (Total N = 184)

Adverse event (Preferred Term)	n	%
Blood blister	5	2.7
Burning sensation	1	0.5
Contusion	4	2.2
Ecchymosis	16	8.7
Grip strength decreased	2	1.1
Haematoma	10	5.4
Hyperkeratosis	1	0.5
Injection site haematoma	6	3.3
Injection site haemorrhage	16	8.7
Injection site hyperaesthesia	1	0.5
Injection site laceration	8	4.3
Injection site pain	4	2.2
Injection site paraesthesia	1	0.5
Injection site swelling	13	7.1
Joint ankylosis	4	2.2
Joint hyperextension	1	0.5
Laceration	15	8.2
Local swelling	42	22.8
Muscle spasms	1	0.5
Oedema peripheral	1	0.5
Pain in extremity	19	10.3
Paraesthesia	2	1.1
Post procedural haemorrhage	1	0.5
Pruritus	1	0.5
Skin wound	8	4.3
Sleep disorder	1	0.5

DISCUSSION

The two goals of the study, i.e., to characterise the population of patients with Dupuytren's disease and treated with CCH in Belgium, and to assess the effectiveness and safety of this new treatment with a particular focus on the patient's quality of life were achieved.

In this Belgian population with Dupuytren's contracture in a real world setting, 64.9% of joints were treated successfully, resulting in a degree of contracture of 5° or less after the extension procedure. Overall, treatment outcome efficacy and safety results, the number of injections used, and the characteristics of the population studied are all in accordance with the majority of epidemiological studies and RCTs on Dupuytren's contracture, including larger controlled and open studies of CCH in the treatment of the disease (*1,14,15,19*).

Observational studies in quite large populations are useful to complement the findings from RCTs by assessing treatment effectiveness and safety in patients encountered in daily clinical practice (*17,21-23*). However, the limitations of this observational study are also inherent to its design : no control group, no comparative data, no long-term follow-up and no possibility to evaluate the recurrence rate. On the other hand, the percentage of patients completing the study was high (104 out of 110 patients ; 94.5%), which is quite unusual for observational studies (*21-23*).

The rate of patients with a contracture recurrence after a previous successful surgical treatment was 64.9% in our study, which is also in agreement with previous studies. The effectiveness of CCH injection did not seem to be influenced by the fact that the contracture was recurrent or not (data not shown). This is in agreement with Bainbridge *et al* (*3*) showing that previous surgery for Dupuytren's contracture does not affect the efficacy or safety of CCH, suggesting it is an option in patients with recurring contractures.

The mean number of injections per cord was 1.0. This is in agreement with the numbers of injections/joint (1.08 and 1.2) measured in real world observational US (*17*) and European/Australia (*26*) studies, respectively, but lower than the numbers of injections/joint (1.4 to 1.7) recorded in early RCTs (*2,5,15*). The low number of injections used in the real world setting of this study may reflect an experience of this treatment developed among treating physicians in comparison to earlier data.

The percentage of joints achieving a degree of contracture of 5° or less after the extension procedure was equal to 64.9%. This result is in agreement with the 64% success rate measured in the CORD I study (*15*) but higher than the success rate (44%) measured in the CORD II study (*14*). In the CORD I study, as it is the case in the majority of studies, MCP joint contractures appeared more likely to correct, and corrected to a more significant degree when compared with PIP joint contractures. In our study, the percentages of MCP and PIP joints achieving a degree of contracture of 5° or less after the extension procedure were 79.5% and 36.8%, respectively. Again this is in agreement with the CORD I results (76.7% and 40.0%, respectively) (*15*). Overall, it could be concluded that the efficacy measured in this observational study was similar to the one measured in RCTs but with a lower number of injections per joint.

As far as hand functionality and quality of life are concerned, the mean URAM score decreased of 16.5 points between the baseline and the end of study visit. This decrease was clinically and statistically significant ($p < 0.0001$). A decrease of about 2.9 points on the URAM has been considered clinically relevant by Beaudreuil *et al* (*4*). In a recent open study, a decrease of 9.5 points on the URAM scale has been measured in 254 European patients after a single cycle of CCH injection and cord extension (*24*).

It is also important to note that the treatment of 33.3% of the patients was not accompanied by a loss of working days. The number of working days lost remained modest and was ≤ 10 days for 48.7% and > 10 days for 17.9% of the patients. In the study of Warwick *et al* (*24*), no patient had to miss work, less than 1% had to reduce their work hours and only 3% had to modify their usual job duties. In the study of Naam (*16*), the patients returned to work 1.9 days after CCH and 37.4 days following surgery.

Overall, physicians and patients were very satisfied or quite satisfied of the treatment in 95.3% and 92.3% of cases. This level of satisfaction corroborates the one found in two recent studies (*25,26*). In the first of these two studies (*25*), 87% of the patients reported to be very satisfied or quite satisfied with the CCH treatment and 86% of the patients were rated by the physicians as very much improved or much improved. In the second study, 92% of the patients were very or quite satisfied with the CCH treatment and 82% of the physicians rated the change from baseline as very much improved or much improved (*26*).

The most frequent related AEs were local swelling, pain in the extremity, ecchymosis, injection site haemorrhage, laceration and injection site swelling. No tendon rupture or any other serious AEs were reported. This safety profile is in agreement with the recent meta-analysis of Peimer *et al* (*18*). The AE profile, in terms of nature, severity, frequency/rate, as well as resolution, was also in general agreement with the current label of CCH and previous RCTs data.

In conclusion, this observational study provided a characterization of the Belgian population with Dupuytren's contracture, in which CCH was demonstrated to be effective, safe, and able to increase quality of life. However, CCH is a symptomatic treatment and therefore further studies are needed to find a permanent cure for Dupuytren's disease.

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