Efficacy of Collagenase Clostridium Histolyticum for Dupuytren Disease: A Systematic Review

Eficacia de la colagenasa clostridium histolyticum para la enfermedad de dupuytren: revision sistematica

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Abstract

Introduction Collagenase Clostridium Histolyticum (CCH) has become a therapeutic alternative for Dupuytren disease. However, its efficacy in the medium to long term is unknown. The objective of our study is to carry out a systematic review of the studies conducted on the subject.

Material and Methods Systematic bibliographic search. Analysis depending on the time of progression, looking into 2 groups with the follow-up cut-off point of 1 year. Analysis of the number of patients who reached the primary endpoint, of the mean correction in degrees, and of the proportional correction of each joint.

Results The 50 selected clinical trials encompass a total of 4,622 patients (an average of 92.70). A total of 7,546 joints were treated with the mean being 148.15 joints per trial (3,925 metacarpophalangeal [MCP] and 2,350 proximal interphalangeal [PIP]). In less than one year of progression, the primary end point was reached in 48.9% of the joints (69.77% of the MCPs and 30.14% of the PIPs), the mean correction in degrees was 45.5 (standard deviation [SD]: 19.18) degrees; 40.8 degrees in the MCP (SD: 10.12) and 35.6 in the PIP (SD: 13.23), and the proportional correction of the joints was 72.9% (SD: 14.43) (83.9% for MCPs [SD: 12.58] and 64.2 for the PIPs [SD: 16.35]). In the follow-ups over 1 year, the primary end point was reached at a rate of 57.5% (68.9% of the MCPs and 43.3% of the PIPs), the mean correction in degrees was 37.6 degrees (SD: 10.93) (37.3 degrees in the MCPs [SD: 9.98] and 23.7 in the PIPs [SD: 16.33]) and the proportional correction of the joints was 87.3% (SD: 10.96) (90.3% for MCP [SD: 6.94] and 75% for PIP [SD: 13.54]).

Keywords
- collagenase
- clostridium histolyticum
- efficacy
- systematic review

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Conclusions The results indicate a satisfactory response to CCH treatment maintained in the short and medium term. The recurrence rate is uncertain given the available data.

Resumen

Introducción La Colagenasa Clostidium Histolyticum se ha convertido en una alternativa terapéutica para la enfermedad de Dupuytren. Sin embargo, se desconoce su eficacia a medio y largo plazo. El objetivo de nuestro trabajo consiste en la realización de una revisión sistemática de los trabajos realizados.

Material y Método Búsqueda bibliográfica sistemática. Análisis dependiendo del tiempo de evolución considerándose dos grupos con el punto de corte de seguimiento un año. Análisis del número de pacientes que alcanzaron el objetivo primario, la corrección media en grados y la alcanzada por cada articulación.

Resultados Los 50 estudios clínicos elegidos, engloban un total de 4622 pacientes (media de 92.70). Se ha tratado un total de 7546 articulaciones siendo la media 148.15 (3925 MCF y 2350 IFP). A menos de un año de evolución el *Primary End Point* se alcanzó en el 48,9% de las articulaciones (69,77% de las MCF y 30,14% de las IFP), la corrección media en grados fue de 45.5 (DE: 19.18) grados; 40.8 grados en las MCF (DE: 10.12) y 35.6 en las IFP (DE: 13.23) y la corrección proporcional de las articulaciones fue del 72,9% (DE: 14.43)(83,9% para las MCF (DE: 12.58) y 64.2 para las IFP (DE: 16.35). En seguimientos mayores a un año el *Primary End Point* se alcanzó en el 57,5% (68,9% de las MCF y 43,3% de las IFP), la corrección media en grados fue de 37.6 grados (DE: 10.93) (37.3 grados en las MCF (DE: 9.98) y 23.7 en las IFP (DE: 16.33) y la corrección proporcional de las articulaciones fue del 87,3% (DE: 10.96) (90,3% para las MCF (DE: 6.94) y un 75% de las IFP (DE: 13.54).

Conclusiones Los resultados indican una respuesta satisfactoria al tratamiento con CCH mantenida a corto y medio plazo. La tasa de recurrencias es un dato incierto con los datos disponibles.

Palabras Clave
- colagenasa
- clostridium histolyticum
- eficacia
- revision sistematica

Introduction

The collagenase clostridium histolyticum (CCH) used for Dupuytren Disease (DD) is a mixture of two enzymes that degrade collagen types I and III found in the abnormal tissue that constitutes this fibromatosis. The first attempt to inject substances inside the cord related to DD was made by Bassot,[1,2] in the 1960s. He coined the term "pharmacodynamical exeresis" and obtained relatively good results, published in 1969[3], looking for a proteolytic, anti-inflammatory and anesthetic effect. The term "enzymatic aponeurotomy" was adopted in 1971 by Hueston[3], who slightly modified the mixture for the injection. The treatment is identified as a valid alternative for patients who cannot be treated by the usual means. Using a similar technique, McCarthy obtained good results suggesting that the technique is an effective alternative as a substitute for fasciectomy.[2] Finally, the studies by Hurst and Badalamente[4,5] established the efficacy of the treatment with an enzyme, the CCH, that allowed to break the cord in a local and minimally invasive manner.

Since the publication of the first clinical trial with CCH[6] and its marketing in the USA and Europe, this drug has become more important over time[7,8] with regard to the treatment of DD. The development of the CORDLESS clinical trial,[9,10] which involved the follow-up of patients enrolled in four previous clinical trials, has improved the level of understanding of progression in the short and medium terms. Likewise, these studies have been the basis of other publications regarding the analysis of subgroups[11] and partial results.[12]

Numerous clinical series and comparative studies have been published since then, providing an independent point of view regarding the clinical results obtained with the treatment. The variability among them is the norm rather than the exception, and the comparability between studies is a complex matter.[13] Although CCH is nowadays an alternative adopted by numerous hand surgeons in the treatment of DD, the rate of recurrence is unknown; thus, its status in the therapeutic arsenal compared with surgery is not clear. The scientific evidence at this time is also limited since no systematic reviews have been performed so far, and comparative studies with other techniques have been limited. The objective of our study is to carry out a systematic review covering all these studies, which evaluate independent studies and demonstrates the result of the CCH treatment since its commercialization aimed at assessing the efficacy of the treatment.

Material and Methods

A structured bibliographic search was performed in the PubMed, Google Scholar, Ovid and Web of Science databases

with the following strategy: (Dupuytren disease [MeSH Terms]) AND (collagenase [MeSH Terms] AND clostridium histolyticum [MeSH Terms]). The search covered articles published from September 3, 2009 (date of publication of the CORD I study[6]) until June 15, 2017. A search of gray literature was performed in the databases of doctoral theses and at the US National institutes of Health Clinical Trials (www.clinicaltrials.gov), as well as through a manual review of the bibliography included in the articles.

We initially included all designs of cohort studies, clinical trials, case-control and case series published in English, Spanish, German, French and Italian; and those in which patient follow-up was specified for at least 30 days. Only studies that included patients diagnosed with Dupuytren contracture susceptible to surgical intervention with an initial contracture degree equal to or greater than 20°, and with at least one group of patients treated with CCH were considered. Reanalyzes of previous series, or those that did not provide data for the analysis, were excluded.

A structured form was used for the extraction and definitive collection of the data from the studies selected independently by two authors. The discrepancies that emerged upon comparing the results of both authors were resolved by a third author. To assess bias in the studies, we used the strategic orientation of business enterprises (STROBE) scale, with two researchers scoring each of the selected studies and using the mean of the two to assess their quality. Any disagreements were resolved through consensus with a third researcher.

The main variables collected from each study were the features and the design of the study, the interventions performed, the CCH doses utilized, the number of injections per patient, the extension time, and the criteria regarding severity and results, as well as the follow-up time. Finally, the funding from each study, if any, was collected. In clinical trials and comparative observational studies, only the clinical results of the group of patients treated with CCH were taken, and they were taken as a sample reference.

An analysis of the existing literature was conducted with regard to the results, taking into consideration two groups with a follow-up cut-off of 1 year. The clinical results were assessed based on three parameters: A) The number of patients who have reached the primary end point established in the CORD studies[6,14] (final extension after treatment between 0–5°) stating the result in total absolute percentage of joints that have reached the objective; B) The assessment of the mean correction of each joint in degrees was evaluated, defined as the result of the degree of initial contracture minus the degree of final contracture; and C) Data regarding the correction ratio of the treated joint was also collected. If an article stated the results of two different modes, both have been included. An assessment of the recurrences over time has been made in the studies intended for that purpose,[9,10] as well as in all those that cited them in their series. Finally, the concept of "non-effective" treatment in the series has been assessed. The missing data in the tables explain the lack of direct correlation between results (A + B≠C, as in one study overall results may have been given and not the results related to the metacarpophalangeal [MCP] and proximal interphalangeal [PIP] joints, for example).

The calculation of the results stated in the text has been performed as follows. The primary end point included in the CORD studies[6,14] was established as the primary reference for the results. The secondary end point is similarly indicated in the results of the CORD studies,[6,14] such as the patients who showed at least 50% of improvement since the initial contracture. In our analysis, the reflected number of these patients is that of those who have reached this point, while those included in the primary end point have been excluded, thus specifying the patients with improvement greater than 50%, but excluding those who have reached extensions between 0–5 degrees. The mean correction of the affected joints was obtained by acquiring direct data from the corresponding article, or the difference between the initial mean degrees of the middle and the endpoints. Finally, the proportion or percentage of the correction achieved was obtained in the same way, indicating the correction percentage for each of the treated joints.

The immediate measures to be implemented following treatment with CCH is a controversial issue. Therefore, in the articles analyzed, usage of orthosis and referrals to a physiotherapy protocol following CCH administration have been reviewed. In the final chapters, we analyzed both the recurrences and the treatment failures, commonly considered in the literature as "non-responders."

Results

Search Results

Total 598 articles were obtained, of which only 240 studies have met the inclusion criteria. After removing duplicates, the elimination followed the exclusion criteria following the reading of the review summary, clinical cases, letters to the director, editorials and meeting summaries. Total 61 articles were obtained for analysis. These studies were reviewed through a complete reading of the article. Eleven studies were eliminated for a variety of reasons: 6 due to insufficient data on clinical outcomes (including cost studies), 3 due to cross-references to previous studies (subgroup analysis), and 2 due to exclusive references to results related to thumbs (excluded from the analysis of the CORD study[6,14]). In the end, 50 publications were analyzed (►**Fig. 1**). The interobserver assessment performed using the STROBE scale of the included articles has shown great homogeneity among the researchers (kappa > 0.85).

Results of the Clinical Studies

The main features of the selected studies are shown in ►**Table 1**. The monitoring of progression corresponding to the 3-year CORDLESS study has been included in the series,[9] taking into account that the patients associated with the CORD I, CORD II, POINT I and POINT II studies have been excluded for the calculation of demographic data.[6,14,15] The POINT X study was also excluded[16] because it was conducted in a subgroup of patients associated with

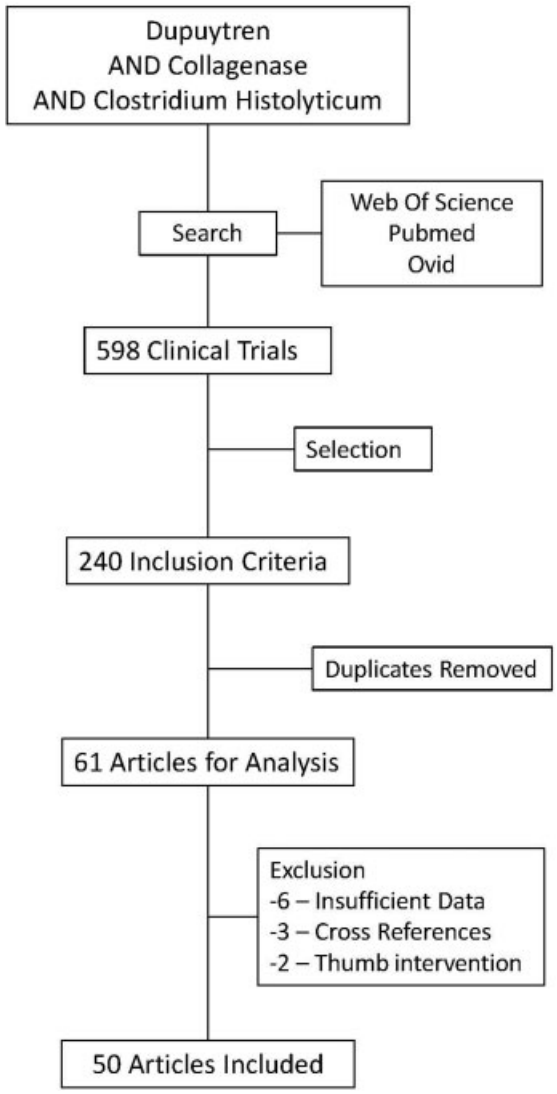

Fig. 1 Flowchart of the selection of articles analyzed.

the European POINT II study. The median follow-up of patients was 265 days (range 14–1,095; standard deviation [SD]: 233 days). The mean number of patients per study was 95 with a very variable range between 714[17] and 8, in the first independent series published in Germany[18] (►**Table 2**).

The mean age of the patients was 65.2 years (range 61.0–70.0). Male patients corresponded to 85% of the patients in the studies (mean 92.5, range 7–542). Thirty-three series were developed in a single center and 18 studies were multicenter projects. With regard to the temporal evolution, 36 studies were prospective and 15 were retrospective.

We have found a great heterogeneity of studies with many methodological variations. The two clinical trials corresponded to the CORD I[6] and CORD II[14] clinical trials performed in the USA and Australia, respectively, and which compared the effect of CCH over placebo. The nine case-control series compared the effect of CCH with that of surgery through fasciectomy[19–23] or with needle aponeurotomy.[24–27] Even though most of the studies were based on clinical series with a time-based follow-up, they ranged from cost studies,[28,29] implementation of treatment in selective population series,[30,31] physiotherapy protocols as a comparative group,[32] assistance with ultrasound treatment[33] or the selective reimplementation of treatment to patients who had undergone a previous treatment with CCH.[34] Two studies were limited to assessing the treatment of a single joint of the same finger comparing it with aponeurotomy: Stromberg,[25] on the MCP, and Skov,[27] on the PIP. Skirven[32] performed his study only with PIP results.

As for the study methodology, we have found different models of study design, such as case study series with different programs;[35,36] open label studies, such as JOINT[15] or ReDUCTo,[37] or studies such as CORD II,[14] that begin as double blind randomized and continue as open label, from which only the data from the first part was collected to include the results of the second part in the CORDLESS study.[9] Warwick[38] performed a series in which results regarding "unusual" cords (natatory, Y-shaped or crow-foot cords) were specified in the same way as Verheyden.[39] Several studies[40–42] assessed the impact with respect to the extension time following consistent administration of treatment.

The inclusion and exclusion criteria for the studies included were based on the drug's fact sheet. All patients included presented with a minimum initial contracture of 20° in the PIP or MCP joints. Studies that have strictly followed the CORD criteria have limited the maximum degree of flexion also included in the study. The follow-up criteria showed a great deal of heterogeneity. After reading the articles, 26 studies, directly or indirectly, followed the criteria of the CORD clinical trials to demonstrate their results. On the other hand, 5 followed the Tubiana classification,[18,28,43–45] and 1 followed its own criteria.[30] The remaining 19 have not specified their follow-up criteria. The measurement of results has mixed values at varying degrees of measuring: a priori 16 articles used the range of movement (ROM) to evaluate results in whole or in part, while the remaining 35 did not use this method, limiting themselves to assessing extension deficit results in degrees by separate joints, groups of joints (passive extension deficit [PED]), or one article even[44] includes the PIP (total passive extension deficit [TPED]).

The 50 selected clinical trials encompass a total of 4,622 patients (mean 92.70). A total of 7,546 joints were treated with an average of 148.15 joints treated per study (3,925 MCP [10.31 on average] and 2,350 PIP [58.03 on average]). The administered dose was standard in all studies, except for two studies that used double dose on the same hand at a time,[17,46] and four that used the standard dose plus the amount remaining in the vial in various formats.[39,47–49] Twenty-three studies followed an injection protocol in which they allowed one to three infiltrations per joint and patient, four[25,29,38,47] studies used one or two injections, even though they followed the CORD protocols, and presumably if it were needed, they would have used three, and the rest used a protocol of one injection for an infiltration of a joint. In the studies that specified how many vials were used per joint, the mean was 1.23 (range 0.8–1.6; SD: 0.36), with only one study having used less than one vial per joint,[50] and with

Table 1 Characteristics of included studies

Article	Date	Type	Progress	Center	Country of origin	Study design	Follow-up	Severity	Dose	TRT Cycle	Measure	Extension
Hurst[6]	2009	R	P	M	USA	double blind randomized 2:1	90	CORD	S	1–3 (1.44)	ROM	24
Gilpin[14]	2010	R	P	M	Australia	double blind randomized 2:1 + Open	90	CORD	S	1–3 (1.5)	ROM	24
Spanholtz[18]	2011	CS	P	U	Germany	Case series. Follow-up	14	Tubiana	S	(1–3)	Ext def	24–30
Coleman[57]	2012	S	P	U	Australia	1st step, 1 dose; 2nd step, 2 doses on the same hand	270	CORD	S	1	ROM	24
Peimer[9]	2013	CS	P	M	Europe - Australia - USA	Follow-up CORD I + CORD II + JOINT I + JOINT II	1,095	CORD	S	(1–3)	ROM	
Peimer[65]	2013	CS	R	M	USA	Retrospective on clinical histories	30	CORD	S	1.08 (1–3)	ROM	24
Vollbach[19]	2013	C	P	U	Germany	Comparison with fasciectomy	365		S		ROM	
Skirven[32]	2013	C	P	U	USA	Comparison between IFP with physiotherapy and without it	30	CORD	S	1	Ext def	24
Marmol[43]	2013	CS	P	U	Spain	Follow-up	30	Tubiana	S	1	Ext def	24
McMahon[35]	2013	CS	P	M	USA	Retrospective on clinical histories	450		S		Ext def	24
Alberton[44]	2013	CS	P	U	Italy	Limited to one joint	180	Tubiana	S	1	Ext def	24
Martin-Ferrero[45]	2013	CS	R	U	Spain	Limited to 1 joint	365	Tubiana	S	1	Ext def	24
Nydick[24]	2013	C	P	U	USA	Comparison with apo-neurotomy with needle	180		S	1–3	Ext def	24
Sanjuan[28]	2013	C	R	U	Spain	Cost study	180	Tubiana	S	1	Ext def	24
Witthaut[15]	2013	CS	P	M	USA - Australia - Europe	Open	270	CORD	S	1–3 (1.4)	ROM	24
Binter[51]	2014	CS	R	U	Austria	Retrospective review	365	CORD	S	1	ROM	24
Mickelson[40]	2014	R	P	U	USA	Differences between extension time	30		S	1	Ext def	1–7
Considine[52]	2014	CS	P	U	Ireland	Follow-up	45		S	1	Ext def	24
Garcia-Olea[64]	2014	CS	P	M	Spain	Follow-up	365		S		Ext def	
Muppavarapu[20]	2014	C	R	U	USA	Comparison with fasciectomy	426	CORD	S	1.08 (1–3)	ROM	24–48
Sood[30]	2014	CS	R	U	USA	Selection of "veteran" patients	369	Own criteria	S	1.6 (1–3)	Ext def	24

Table 1 (*Continued*)

Article	Date	Type	Progress	Center	Country of origin	Study design	Follow-up	Severity	Dose	TRT Cycle	Measure	Extension
Coleman[46]	2014	C	R	M	USA - Australia	Two doses on the same hand at the same time	60		S	1	ROM	24
Leclere[33]	2014	CS	R	U	Switzerland	Ultrasound-assisted injection	300		S	1.17 (1–3)	Ext def	24
Povlsen[21]	2014	C	P	U	UK	Comparison with fasciectomy			S	1	ROM	72
Manning[41]	2014	CS	R	U	UK	Comparison of the extension times after the injection	98		S	1	Ext def	48
Warwick[38]	2014	CS	P	M	Europe	Functional recovery and health resources	180		AV	1–2	Ext def	24–48 x
Verheyden[39]	2014	CS	R	U	USA	Revision and dose increase	60		AV	1	Ext def	24
Perez-Giner[53]	2015	CS	P	U	Spain	Follow-up	90	CORD	S	1.19 (1–3)	Ext def	24
Considine[52]	2015	CS	P	U	Ireland	Limited to one dose	45	CORD	S	1	Ext def	48
Zhou[22]	2015	C	R	M	Netherlands	Comparison with fasciectomy	84	CORD	S	(1–3)	Ext def	24–72
Kaplan[42]	2015	CS	P	M	USA	Randomized. Extension at different times	90	CORD	S	1	Ext def	24–96
Gaston[17]	2015	CS	P	M	USA - Australia - New Zealand - Europe	Two doses on the same hand	60	CORD	DB	1	ROM	24–48–72
Atroshi[47]	2015	CS	P	U	Sweden	Follow-up	21	CORD	AV	1–2	Ext def	24–48 x
Tay[23]	2015	C	R	U	Malaysia	Comparison with fasciectomy	730		S	1–3	Ext def	24
Waters[31]	2015	CS	R	M	USA	Patients with chronic immunosuppression	201	CORD	S	1	Ext def	24–48
Haerle[37]	2015	CS	P	M	Germany	Open, with no intervention	365		S	1–3	Ext def	24
Stromberg[25]	2016	C	P	U	Sweden	Comparison with apo-neurotomy (only MCP)	365	CORD	S	(1–2)	Ext def	24
Murphy[29]	2016	CS	P	U	UK	Cost analysis	690	CORD	S	1.1 (1–2)	Ext def	48
Odinsson[50]	2016	CS	P	U	Norway	Follow-up	365		S	0.8 (1–3)	Ext def	48

(*Continued*)

Table 1 (*Continued*)

Article	Date	Type	Progress	Center	Country of origin	Study design	Follow-up	Severity	Dose	TRT Cycle	Measure	Extension
Arora[58]	2016	CS	R	U	Austria	Follow-up	365	CORD	S	1–3	Ext def	24
Hirata[54]	2016	CS	P	M	Japan	Open	365	CORD	S	1.2 (1–3)	ROM	24
Verstreken[55]	2016	CS	P	M	Belgium	Multicenter	90	CORD	S	(1–3)	ROM	
Malafa[61]	2016	CS	R	U	USA	Follow-up	180	CORD	S	1 (1–3)	Ext def	24
Scherman[26]	2016	C	P	M	Sweden	Comparison with aponeurotomy	365		S	1	Ext def	24–72
Bear[34]	2017	CS	P	M	USA - Australia - Europe	Assessment of new treatments after recurrence	365	CORD	S	1.23 (1–3)	ROM	24
Lauritzon[48]	2017	CS	P	U	Sweden	Follow-up	730		AV	1	Ext def	24–48
Grandizio[49]	2017	CS	R	S	USA	One dose in one joint and the rest of the vial in another cord	30	CORD	AV	1	Ext def	24
Hansen[59]	2017	CS	P	S	Denmark	Comparison of the results between MCF and IFP	365	CORD	S	1.2 (1–3)	Ext def	24
Keller[60]	2017	CS	P	S	Austria	Follow-up	365		S	(1–3)	Ext def	24
Skov[27]	2017	C	P	S	Denmark	Comparison with aponeurotomy (only IFP)	730		S	1	Ext def	24

Abbreviations: Type: C: Cohorts; CS: Case series; R, Randomized. Centre: M, Multicenter; U, Single-center. Progress: P, Prospective, R, Retrospective. Dose: S, standard; AV, all vial, DB, double dose. TRT Cycle: number of doses stipulated in the protocol, in brackets the average number of injections per patient. Measurement: type of measurement for the treatment outcome. Ext Def: extension deficit; ROM: range of movement. Extension: Time elapsed from the CCH injection to extension in days (x indicates the implementation between 24–48 hours at the surgeon's discretion).

Table 2 Demographic features of the studies analyzed

Article	Date	Nº CCH	Mean age	Male (%)	Previous TRT	Fam His
Hurst[6]	2009	203	62.7	171	79	85
Gilpin[14]	2010	66	63.8	39	28	22
Spanholtz[18]	2011	8	62.5	6		
Coleman[57]	2012	12	63.7	11	5	6
Peimer[9]	2013	643	66	542		278
Peimer[65]	2013	463	65.5	342		
Vollbach[19]	2013	14				
Skirven[32]	2013	21	63	19	12	
Marmol[43]	2013	15	64			
McMahon[35]	2013	64	N/A	31		
Alberton[44]	2013	40	66	36		
Martin-Ferrero[45]	2013	35	68.1	35	3	
Nydick[24]	2013	29	67	25		
Sanjuan[28]	2013	91	65.1	38		
Witthaut[15]	2013	587	63.7	498	308	245
Binter[51]	2014	37	66	32	0	
Mickelson[40]	2014	43	64.5	35	10	19
Considine[52]	2014	10	66	10	2	
Garcia-Olea[64]	2014	148	64	140	24	44
Muppavarapu[20]	2014	73	64	61	24	
Sood[30]	2014	16	69.9	16		2
Coleman[46]	2014	60	64	51	26	25
Leclere[33]	2014	33	64.4	28		
Povlsen[21]	2014	10				
Manning[41]	2014	45	63	33	8	
Warwick[38]	2014	144	N/A	119		
Verheyden[39]	2014	40	66	38		
Perez-Giner[53]	2015	10	65.6	7		
Considine[52]	2015	104	61	83	27	56
Zhou[22]	2015	37	65.5	34		
Kaplan[42]	2015	714	64	616	376	337
Gaston[17]	2015	164	70	134	23	
Atroshi[47]	2015	29	65	13		
Tay[23]	2015	237	64			
Waters[31]	2015	8	66			
Haerle[37]	2015	86	65.1	69		28
Stromberg[25]	2016	69	66	56	0	34
Murphy[29]	2016	20	64.8	20		11
Odinsson[50]	2016	77	69	66		
Arora[58]	2016	120	62			
Hirata[54]	2016	77	68	70	35	
Verstreken[55]	2016	104	64.4	85	85	47
Malafa[61]	2016	36	65.1	33		

(*Continued*)

Table 2 (*Continued*)

Article	Date	Nº CCH	Mean age	Male (%)	Previous TRT	Fam His
Scherman[26]	2016	56		36		
Bear[34]	2017	52	66.5	50	52	
Lauritzon[48]	2017	48	68	38	6	
Grandizio[49]	2017	34	65	23		5
Hansen[59]	2017	212	66	195	0	
Keller[60]	2017	120	62	107		
Skov[27]	2017	29	62	45		

Abbreviations: Fam His, Number of patients in the series with a family history of DD; Nº CCH, Number of patients treated with CCH in the study; Previous TRT, Number of patients in the series who have received prior treatment for DD on the finger treated with CCH (any).

the studies by Gilpin[14] (1.5) and Sood[30] (1.6) being the ones that used more than one vial per joint. The extension time varied among the studies, ranging from 24 hours (predominantly) up to 7 days in a clinical trial by Mickelson.[40]

The systematic implementation of a physiotherapy protocol after CCH treatment is another controversial point regarding the outcomes. Thirteen articles indicate that patients were systematically referred to an established physiotherapy protocol or that monitoring was performed by specialist physiotherapists,[20,25,29,32,34,35,40,41,44,48,51–53] four specify that patients did not receive physical therapy,[6,22,49,54] two have indicated it only if necessary,[46,55] and the rest did not indicate whether or not a physiotherapy protocol was included in the treatment protocol.

Using night-time splints is recommended for a period of 3 months in the product fact sheet.[56] The bibliography is variable in this regard. Twenty-seven articles refer to the systematic use of this device,[6,14,15,17,20,22,25,26,30,33,35,36,38–41,44,46–49,51,54,57–60] and a multicenter study reports that only one of the centers used it without performing a statistical analysis of what this measurement could indicate.[61]

Clinical Findings

The studies analyzed indicate a timeline regarding the progression time. In spite of not having a formal indication as to the progression time, the studies mark a before and an after with a timeline of less or more than 1 year. Studies with a course of less than 1 year set out to assess the clinical effectiveness of the treatment or some of its modifications (if the treatment actually works by reducing contracture in DD), and the studies that took 1 year or longer try to assess the effectiveness of the treatment (if the achieved effect is maintained over time). To calculate the clinical outcomes (►**Appendix A**), data from studies that lasted less than 1 year (►**Table 3**) have been taken into account together with the figures from the intermediate results of the studies that took 1 year or longer (►**Table 4**).

Studies that Cover Less than 1 Year of Progress

The mean follow-up time was 104 (SD: 75) days. The analysis included a total of 4,666 joints (average of 194.41 joints per study), (2,467 MCPs (average of 129.84) and 1,516 PIPs (average of 75.80)). The primary end point objective has been achieved in 48.9% of the treated joints (69.77% of the MCPs and 30.14% of the PIPs). The mean correction for all joints treated was 45.5 (SD: 19.18) degrees; 40.8 degrees for MCPs (SD: 10.12) and 35.6 for PIPs (SD: 13.23). The proportional correction of the joints was at 72.9% (SD: 14.43) overall, (83.9% for the MCP [SD: 12.58] and 64.2 for the PIP [SD: 16.35]).

Studies that Cover More than 1 Year of Progress

The mean follow-up time was 467 days (SD: 196.36). The analysis included a total of 2,870 joints (average of 138.66 joints per study), (1,459 MCPs [average of 97.26] and 842 PIPs [average of 56.13]). The primary end point objective has been achieved in 57.5% of the treated joints (68.9% of the MCPs and 43.3% of the PIPs). The mean correction for all joints treated was 37.6 degrees (SD: 10.93), (37.3 degrees for the MCP [SD: 9.98] and 23.7 for the PIP [SD: 16.33]. The proportional correction of joints was at 87.3% (SD: 10.96) overall, (90.3% for the MCP [SD: 6.94] and 75% for the PIP [SD: 13.54]).

Recurrences

Apart from the CORDLESS studies,[9,10] few studies have collected the incidence of recurrences in their results.[19,30,34,35,37,48,58] The rate of recurrence during the follow-up period ranged from 1.7% in 1 year[37] to 59% in the series by Sood[30] within the same period, but with its own criteria of recurrence. Upon eliminating these two values, this rate ranged between 7–28%. All the articles that mentioned the rate of recurrence had a follow-up between 6 and 18 months. We should keep in mind that the series by Bear[34] had a 28% recurrence rate in patients previously treated with CCH after 1 year of follow-up.

The CORDLESS studies were designed as observational clinical studies for assessing the rate of recurrence over time. These follow-ups were published at 3[9] and 5 years.[10] The recurrence rate was calculated based on the secondary end point (at least 50% of correction since the initial contracture), demonstrating a recurrence rate of 38% (28% for the MCP and 58% for the PIP) at 3 years, and 48% (39% for the MCP and 65% for the PIP) at 5 years. Peimer indicates that 75% of the

Table 3 Studies with a follow-up period of less than one year

Article	Date	Follow-up	Total n°	N° MCF	N° IFP	PEP	PEP MCF	PEP IFP	SEC	SEC MCF	SEC IFP	Mean int corr	MCF	IFP	Corr mean	Corr MCF	Corr IFP	% Total	% MCF	% IFP
Hurst[6]	2009	90	203	133 (65)	70 (34)	130 (64)	102 (76)	28 (40)	73 (35)	31 (23)	42 (60)				36.7	41	29	79	87	64
Gilpin[14]	2010	90	45	20 (44)	25 (55)	20 (44)	13 (65)	7 (28)	25 (55)	7 (35)	18 (72)				25.4	42	32	70.5	79.5	57.6
Spanholtz[18]	2011	14	16												33	33	32			
Coleman[57]	2012	270	36	22 (61)	14 (38)										29.7	29	31	79.7	83.1	74.3
Peimer[65]	2013	30	629	398 (63)	231 (36)	284 (45)	222 (55)	62 (26)	125 (19)	62 (15)	63 (27)					38	34	75	81	66
Skirven[32]	2013	30	22		22 (100)												49			88
Marmol[43]	2013	30	31	24 (77)	7 (22)	31 (100)	24 (100)	7 (100)							44	47		98	100	94
Alberton[44]	2013	180	40	32 (80)	8 (20)	29 (72)						60	41	67	60	59	67			
Nydick[24]	2013	180	34	14 (41)	5 (14)											30	24			
Sanjuan[28]	2013	180	62	31 (50)	31 (50)											42	32	70	88	52
Witthaut[15]	2013	270	879	531 (60)	348 (39)	497 (56)	369 (69)	128 (36)	175 (19)	101 (19)	74 (21)					55	25	72.6	84	55.2
Mickelson[40]	2014	30	45	24 (53)	21 (46)	22 (48)	14 (58)	8 (38)	22 (48)	10 (41)	12 (57)					45	48	46.5	45	48
Considine[52]	2014	45	13													54	30			
Coleman[46]	2014	60	120	75 (62)	45 (37)	72 (60)	57 (76)	15 (33)							57	32	27		86	66
Manning[41]	2014	98	50	42 (84)	8 (16)		39 (92)						49	48		49	74	51	94	50
Warwick[38]	2014	180	521										49	45		43	33			
Verheyden[39]	2014	60		38 (N/A)	30 (N/A)		27 (71)	13 (43)					38	36		33	31		85	76
Perez-Giner[53]	2015	90	13													54	30			

(*Continued*)

Table 3 (*Continued*)

Article	Date	Follow-up	Total n°	N° MCF	N° IFP	PEP	PEP MCF	PEP IFP	SEC	SEC MCF	SEC IFP	Mean int corr	MCF	IFP	Corr mean	Corr MCF	Corr IFP	% Total	% MCF	% IFP
				12 (92)	5 (38)	13 (100)	12 (100)	5 (100)												
Considine[52]	2015	45		33 (50)	33 (50)				39 (59)	25 (75)	14 (42)					13	24			
Zhou[22]	2015	84	66				29 (N/A)									45				
Kaplan[42]	2015	90	1448	896 (61)	552 (38)	437 (30)	579 (64)	158 (28)	458 (31)	221 (24)	237 (42)	27			70			74	84	60
Gaston[17]	2015	60	159												55	39	28			
Atroshi[47]	2015	21	29	21 (72)	8 (27)											33	19		83	32
Waters[31]	2015	201	13	7 (53)	6 (46)										13	38	43			
Verstreken[55]	2016	90	111	74 (66)	40 (36)	72 (64)	58 (78)	14 (35)	28 (25)	23 (31)	5 (12)				45			86.1		
Malafa[61]	2016	180	47	40 (85)	7 (14)	36 (76)									40	41	38			
Grandizio[49]	2017	30	34			32 (94)	20 (N/A)	12 (N/A)							83	45	39		95	80

Abbreviations: % MCP: percentage of correction for the MCP joint at the end of the follow-up period; % PIP: percentage of correction for the PIP joint at the end of the follow-up period; % Total: percentage of correction for the treated finger at the end of the follow-up period; Mean int corr mean correction at intermediate cut-off point; Corr Mean, final mean correction; Follow-up, follow-up time; MCP, metacarpophalangeal joint; N°, number of cases; PEP,p end point; PIP, proximal interphalangeal joint; SEC, secondary end point.

Table 4 Studies with a follow-up period of more than one year

Article	Date	Follow-up	Total N°	N° MCF	N° IFP	PEP	PEP MCF	PEP IFP	SEP	SEP MCF	SEP IFP	Mean int corr	MCF	IFP	Corr mean	Corr MCF	Corr IFP	% Total	% MCF	% IFP
Peimer[9]	2013	1095	1080	648 (60)	432 (40)	623 (57)	451 (69)	172 (39)	301 (27)	152 (23)	149 (34)				21	28	15			
Vollbach[19]	2013	365	16									33			31					
McMahon[35]	2013	450	64	46 (71)	18 (28)							41	47	25	33	42	10			
Martin-Ferrero[45]	2013	365	35	30 (85)	5 (14)								56	63		60	58			
Binter[51]	2014	365	40	14 (35)	8 (20)	21 (52)														
Garcia-Olea[64]	2014	365	156	58 (37)	16 (10)								38	50		35	23			
Muppavarapu[20]	2014	426	100	56 (56)	44 (44)	29 (29)	26 (46)	3 (6)							28	21	37			
Sood[30]	2014	369	27	18 (66)	9 (33)				27 (100)	18 (100)	9 (100)					36	29		83.3	55.6
Leclere[33]	2014	300	52										33	31		28	21			
Tay[23]	2015	730	298	99 (33)	56 (18)	146 (48)	95 (95)	51 (91)	8 (2)	3 (3)	5 (8)					45	56	96	97	91
Haerle[37]	2015	365	86	63 (73)	23 (26)								28	20		31	8			
Stromberg[25]	2016	365	69	69 (100)		61 (88)	61 (88)					50	50		47	47				
Murphy[29]	2016	690											45	18		35	6			
Odinsson[50]	2016	365	109	70 (64)	71 (65)	84 (77)	56 (80)	28 (39)					32	23		28	16			
Arora[58]	2016	365	120			85 (70)			31 (25)							28	30			
Hirata[54]	2016	365	77	47 (61)	30 (38)	66 (85)	44 (93)	22 (73)	3 (3)	0 (0)	3 (10)				40	42	35	91	97	83
Scherman[26]	2016	365	56	40 (71)	16 (28)							48	55	3	45	50	-2	75		
Bear[34]	2017	365	51	31 (60)	20 (39)	18 (35)	11 (35)	7 (35)							32	33	31		83	69

(*Continued*)

Table 4 (*Continued*)

Article	Date	Follow-up	Total N°	N° MCF	N° IFP	PEP	PEP MCF	PEP IFP	SEP	SEP MCF	SEP IFP	Mean int corr	MCF	IFP	Corr mean	Corr MCF	Corr IFP	% Total	% MCF	% IFP
Lauritzon[48]	2017	730	50									66	49	17	59	45	14			
Hansen[59]	2017	365	235	170 (72)	65 (27)	104 (44)	76 (44)	28 (43)				47	47	47		47	39		91	76
Keller[60]	2017	365	120			85 (70)										28	18			
Skov[27]	2017	730	29		29 (100)						8 (27)				40		8			

Abbreviations: % MCP, percentage of correction for the MCP joint at the end of the follow-up period; % PIP, percentage of correction for the PIP joint at the end of the follow-up period; % Total, percentage of correction for the treated finger at the end of the follow-up period; Mean int corr, mean correction at intermediate cut-off point; Corr Mean, final mean correction; Follow-up, follow-up time; MCP, metacarpophalangeal joint; N°, Number of cases; PEP, primary end point; PIP, proximal interphalangeal joint; SEP, secondary end point.

recurrences occurred after the first 3 years of treatment[10] and are significantly minor regarding subsequent progression.

Treatment Failures

A concept not adequately clarified in the literature regarding CCH treatment is treatment failures, that is, the injection of CCH into a Dupuytren cord with no effect. Peimer,[10] at the 5-year follow-up of the CORDLESS study, indicates that the rate of patients treated ineffectively in the CORD and JOINT studies was 18% (9% of MCPs and 32% of PIPs), whereas among the patients who completed the follow-up for the CORDLESS study, the rate was 14% (7% of MCPs and 26% of PIPs). Only two more authors have covered this concept: Keller[60] indicates a 3% rate of treatment failures, and Peimer (ref), in another study that does not include patients from the CORD studies, reports a rate of 16% (8 patients).

Discussion

Collagenase clostridium histolyticum is currently a therapeutic alternative for DD both in Europe[8] and the USA.[7] However, the heterogeneity of publications has been more the norm rather than the exception in studies related to CCH. Even though virtually all studies have maintained a standard minimum contracture with which to begin the treatment (20 degrees), some have slightly increased this to 30 degrees. Other data, such as the loss of extension limit (initially set at 100 degrees for the finger), the variation in severity criteria with regard to adoption of own criteria rather than any other DD classification, show the heterogeneity in publications, as is common in publications related to Dupuytren surgery.[13]

The measurement of results is another example: the CCH treatment is performed at a joint level in an isolated manner; with the rupture of the cord, a compensatory correction of the adjacent joint of the same finger can be produced. Measuring both joints together after the treatment of only one of them constitutes an error that causes bias in clinical studies, as the correction of a joint can be masked by the affectation or the retraction of the adjacent finger.[62] Likewise, the inclusion of untreated joints in the results, when they present baseline contracture, worsens the final result if a joint finger assessment (MCP + PIP) is done. In fact, to mitigate these shortcomings, in CORD studies the results are presented in two modes: on the one hand in terms of the correction of the treated joint, and on the other in the form of "range of movement" (ROM).[6,14,54] Different forms of measurement (ROM, passive extension deficit [PED], isolated joints) are adopted in the studies, which complicate the comparability of results between the studies (►**Table 1**).

Clinical results indicate that full extension of the fingers has been achieved in ~ 50% of the cases maintained for a year, and the mean reduction in contracture for all patients is at around 75%, indicating a remarkable effectiveness of the treatment. The results of our study may seem contradictory with a higher reduction in digital contracture in studies lasting over 1 year than in studies covering less than

1 year of progress, but the heterogeneity of published papers and the lack of homogeneity between the protocols used[63] explain this variation, which does not invalidate the final result. The fact that a greater number of patients have reached the primary end point in studies lasting more than 1 year is due, in part, to the fact that many of these studies have been funded by or related to the company that markets the drug, which is why the patient selection criteria, the surgeon's experience or the protocol for patient maintenance, minimizing the losses of individuals with a positive result, may be regarded as biased.[9,34,35,37,48,54,60]

With regard to joint treatment, the demonstrated results concur with many of the series published. The outcome for the MCP joint is better than the outcome for the PIP, and the recurrences of the latter are also much more frequent. The data presented does not allow for a study of the severity of the affected joint as some authors do[9,14,46,57]; the analyzed data indicate that a more severe initial contracture signifies a worse outcome for the treatment, more specifically for the PIP. With respect to the issue of recurrence, the lack of studies in the medium and long term prevents an objective assessment; however, the CORDLESS studies show a clear tendency toward recurrence with an overall rate of 48% at 5 years.[10] Garcia-Olea[64] quantifies the deterioration of the patients in their series at 1.5 degrees per month.

Physiotherapy protocols have not been included in clinical trials; thus, the improvement or sustainability of treatment with them cannot be assessed. Although the use of night splints is indicated, many studies have avoided this adjunctive measure, possibly due to poor compliance of the patients,[41] and the discomfort it causes over an extended period of time. These two measures, without a doubt, are the most variable in the studies analyzed. One of the first comparative clinical studies[32] actually assessed the use of these measures for treatment with CCH and concluded that their apparent benefit is in the short term.

Among the main problems that are not taken into account in the analyzed series is the rate of poor and "non-effective" outcomes. The same analysis is not performed on these patients as it is performed on those with good outcomes. There is currently no explanation as to why some patients do not respond to the treatment.

Among the limitations of our study, the main one is the possibility of biases in terms of data collection. Injection on a joint and the measurement of the full result on the affected finger is in itself a bias that some of the cited papers comment on, and it has made it difficult to compare this technique with the surgical procedures (partial fasciectomy), where traditionally the whole radius is treated. The results are usually expressed as a difference in degrees between the initial and final results with a range in each value. While obtaining the difference between both results for the assessment of the correction achieved is very simple, it is practically impossible to evaluate the standard deviation of the sample. This prevents large-scale statistical studies from being conducted, and thus constitutes the main limitation of our study. Unfortunately, these limitations are insurmountable and evident in the analysis of bibliography.[13]

In conclusion, we can say that there is a lack of uniformity in the approach of the studies and in their outcomes with regard to the assessment of DD treatment with CCH. Despite this issue, the results indicate a satisfactory response to treatment in a large number of patients maintained in the short and medium term, with a recurrence rate of over 50%, occurring mainly within the first 3 years of follow-up. The exact recurrence rate is uncertain given the available data.

Conflicts of Interest

Authors declare that there were no conflict of interests for the writing of the present work.

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Appendix A Follow-up details of all studies analyzed

Article	Date	Follow-up	Total nº	N MCF	N IFP	PEP	PEP MCF	PEP IFP	SEC	SEC MCF	SEC IFP	Corr mean	Corr MCF	Corr IFP	% Total	% MCF	% IFP
Hurst	2009	90	203	133 (65)	70 (34)	130 (64)	102 (76)	28 (40)	73 (35)	31 (23)	42 (60)	36.7	41	29	79	87	64
Gilpin	2010	90	45	20 (44)	25 (55)	20 (44)	13 (65)	7 (28)	25 (55)	7 (35)	18 (72)	25.4	42	32	70.5	79.5	57.6
Spanholtz	2011	14	16									33	33	32			
Coleman	2012	270	36	22 (61)	14 (38)							29.7	29	31	79.7	83.1	74.3
Peimer	2013	30	629	398 (63)	231 (36)	284 (45)	222 (55)	62 (26)	125 (19)	62 (15)	63 (27)		38	34	75	81	66
Vollbach	2013	365	16									33					
Skriven	2013	30	22		22 (100)									49			88
Marmol	2013	30	31	24 (77)	7 (22)	31 (100)	24 (100)	7 (100)				44	47		98	100	94
McMahon	2013	450	64	46 (71)	18 (28)							41	47	25			
Alberton	2013	180	40	32 (80)	8 (20)	29 (72)						60	41	67			
Martin-Ferrero	2013	365	35	30 (85)	5 (14)								56	63			
Nydick	2013	180	34	14 (41)	5 (14)								30	24			
Sanjuan	2013	180	62	31 (50)	31 (50)								42	32	70	88	52
Witthaut	2013	270	879	531 (60)	348 (39)	497 (56)	369 (69)	128 (36)	175 (19)	101 (19)	74 (21)		55	25	72.6	84	55.2
Mickelson	2014	30	45	24 (53)	21 (46)	22 (48)	14 (58)	8 (38)	22 (48)	10 (41)	12 (57)		45	48	46.5	45	48
Considine	2014	45	13										54	30			
Garcia-Olea	2014	365	156	58 (37)	16 (10)								38	50			
Coleman	2014	60	120	75 (62)	45 (37)	72 (60)	57 (76)	15 (33)				57	32	27		86	66
Leclere	2014	300	52										28	21			

Appendix A (*Continued*)

Article	Date	Follow-up	Total n°	N MCF	N IFP	PEP	PEP MCF	PEP IFP	SEC	SEC MCF	SEC IFP	Corr mean	Corr MCF	Corr IFP	% Total	% MCF	% IFP
Povlsen	2014		10										20	17			
Manning	2014	98	50	42 (84)	8 (16)		39 (92)						49	74	51	94	50
Warwick	2014	180	521										43	33			
Verheyden	2014	60		38 (N/A*)	30 (N/A*)		27 (71)	13 (43)					33	31		85	76
Perez-Giner	2015	90	13	12 (92)	5 (38)	13 (100)	12 (100)	5 (100)					54	30			
Considine	2015	45		33 (50)	33 (50)				39 (59)	25 (75)	14 (42)		13	24			
Zhou	2015	84	66				29 (N/A)						45				
Kaplan	2015	90	1448	896 (61)	552 (38)	437 (30)	579 (64)	158 (28)	458 (31)	221 (24)	237 (42)	70			74	84	60
Gaston	2015	60	159									55	39	28			
Atroshi	2015	21	29	21 (72)	8 (27)								33	19		83	32
Waters	2015	201	13	7 (53)	6 (46)							13	38	43			
Haerle	2015	365	86	63 (73)	23 (26)								28	20			
Stromberg	2016	365	69	69 (100)		61 (88)	61 (88)					50	50				
Murphy	2016	690											45	18			
Odinsson	2016	365	109	70 (64)	71 (65)	84 (77)	56 (80)	28 (39)					32	23			
Hirata	2016	365	77	47 (61)	30 (38)	66 (85)	44 (93)	22 (73)	3 (3)	0 (0)	3 (10)	40	42	35	91	97	83
Verstreken	2016	90	111	74 (66)	40 (36)	72 (64)	58 (78)	14 (35)	28 (25)	23 (31)	5 (12)	45			86.1		
Malafa	2016	180	47	40 (85)	7 (14)	36 (76)						40	41	38			
Scherman	2016	365	56	40 (71)	16 (28)							45	55	3	75		

(*Continued*)

Appendix A (*Continued*)

Article	Date	Follow-up	Total n°	N MCF	N IFP	PEP	PEP MCF	PEP IFP	SEC	SEC MCF	SEC IFP	Corr mean	Corr MCF	Corr IFP	% Total	% MCF	% IFP
Lauritzon	2017	730	50									66	49	17			
Grandizio	2017	30	34			32 (94)	20 (N/A)	12 (N/A)				83	45	39		95	80
Hansen	2017	365	235	170 (72)	65 (27)	104 (44)	76 (44)	28 (43)				47	47	47		91	76

Abbreviations: % MCP, percentage of correction for the MCP joint at the end of the follow-up period; % PIP, percentage of correction for the PIP joint at the end of the follow-up period; % total, percentage of correction for the treated finger at the end of the follow-up period; Corr Mean, final mean correction; Follow-up, follow-up time; MCP, metacarpophalangeal joint; N°, number of cases; PEP, primary end point; PIP, proximal interphalangeal joint; SEC, secondary end point.