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Determining Clinically Important Changes in Range of Motion in Patients with Dupuytren's Contracture

Secondary Analysis of the Randomized, Double-Blind, Placebo-Controlled CORD I Study

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Abstract

Background and Objective: Injectable collagenase Clostridium histolyticum is efficacious in correcting Dupuytren's contracture as assessed by changes in the angle of contracture and range of motion (ROM). However, clinically important changes in ROM have not been evaluated in depth. The objective of this secondary analysis of the CORD I trial was to identify severity levels using baseline ROM, estimate a clinically important difference (CID) for ROM, and link the results to collagenase treatment and patient satisfaction.

Methods: In the CORD I trial, patients with Dupuytren's disease and joint contractures ≥20° were randomized to receive a maximum of three collagenase 0.58 mg or placebo injections into the cord of the affected hand at 30-day intervals. The primary endpoint was reduction in contracture to ≤5° 30 days after the last injection (day 30). The secondary endpoints, which are reported in this analysis, were ROM, physician- and patient-rated severity ('normal', 'mild', 'moderate', 'severe') and improvement, and treatment satisfaction. Linear regression was used to model data for severity classification and CID estimation for ROM based on physician and patient ratings.

Results: At baseline, mean ROM was 43.9° in the collagenase-treated joints (n = 197) and 45.3° in the placebo-treated joints (n = 102). On day 30, mean ROM was 80.7° in the collagenase-treated joints and 49.5° in the placebo-treated joints. The mean increase in ROM was 36.7° in the collagenase-treated joints ($p < 0.001$) and 4.0° in the placebo-treated joints (not significant). The estimated CID for ROM was 13.5° (95% CI 11.9, 15.1), reflecting a one-category change in severity. The mean increase in ROM exceeded the CID in the collagenase-treated joints but not in the placebo-treated joints; the difference between collagenase treatment and placebo in the mean increase in ROM also exceeded the CID, implying that the improvement with collagenase was clinically relevant. The severity classification for ROM was: ≥67.0°

('normal'), ≥54.3 and <67.0° ('mild'), ≥41.6 and <54.3° ('moderate'), and <41.6° ('severe'). More collagenase- than placebo-treated patients achieved 'normal' (81% vs 25%; $p < 0.0001$) status, and more collagenase- than placebo-treated patients reported being 'very/quite satisfied' (87% vs 32%; $p < 0.001$).
Conclusion: Injectable collagenase significantly improves ROM and treatment satisfaction versus placebo. ROM improvements are clinically relevant as well as statistically significant. These data support the potential need to include ROM and physician- and patient-rated severity and satisfaction as standard assessments for Dupuytren's contracture treatment outcomes.

Trial Registration: ClinicalTrials.gov Identifier: NCT00528606; other study identification number: AUX-CC-857 (Auxilium Pharmaceuticals, Inc.).

Introduction

Dupuytren's disease, a progressive, proliferative disorder of the palmar fascia, is estimated to affect 3–6% of the general population.[1] Owing to the contracture of one or multiple fingers, affected individuals have difficulty performing activities of daily living and work-related tasks. Many are also embarrassed by the visible deformity.[2] Such disabilities may have a substantial negative impact on patients' health-related quality of life.

Corrective surgery to excise or divide the diseased fascia is the current standard treatment, and studies evaluating the effectiveness of this and other therapeutic interventions typically use changes in range of motion (ROM), the active full flexion and extension of a finger, as a functional outcome measure.[3] Efficacy can also be assessed globally, for example, as patients' and/or physicians' perception of improvement.

The efficacy of injectable collagenase Clostridium histolyticum in correcting Dupuytren's contracture has been demonstrated in clinical trials[4-6] and was recently approved in the US as the first, non-surgical, office-based pharmacotherapy for the disease. The phase III clinical trial programme used changes in objective measures of joint contracture and ROM to assess efficacy. However, it is not only important to evaluate the effects of treatment on ROM and physical appearance, but also to assess whether these changes impact patients in meaningful ways.

To date, the clinical relevance of treatment-related changes on ROM from the patients' perspectives has not been evaluated in depth. Nevertheless, some patient-reported outcome (PRO) measures were used in the CORD (Collagenase Option for Reduction of Dupuytren's) I study.[6] Patients and physicians were asked about the perceived level of disease severity, treatment-related improvements and treatment satisfaction.

Linking objective changes in ROM with subjective changes in patient and physician ratings increases the clinical relevance of ROM values. The clinically important difference (CID), a statistically determined value that is associated with observed changes in PROs, can help in the interpretation of the magnitude and relevance of changes in ROM in relation to treatment differences.[7,8] The CID is widely used to evaluate treatment response in a broad spectrum of therapeutic areas, including fibromyalgia,[9,10] chronic pain,[11] erectile dysfunction[12] and overactive bladder.[13] In addition to the CID, interpretation of ROM can be enhanced by reference to disease severity levels. Gauging the impact that disease severity can have on ROM can enrich our understanding of patients' condition at baseline and follow-up, and how this situation has changed with treatment.

In this secondary analysis, we used data from the CORD I study[6] to identify Dupuytren's disease severity levels based on baseline ROM, to estimate the CID for ROM, and to link these findings with collagenase treatment response and patient satisfaction.

Methods

Study Design and Patient Population

Data from the CORD I study (study 857), a 90-day, randomized, double-blind, placebo-controlled trial in patients aged ≥18 years with Dupuytren's disease, were included in the analysis (ClinicalTrials.gov Identifier: NCT00528606; other study identification number: AUX-CC-857 [Auxilium Pharmaceuticals, Inc.]).[6] Full details regarding the design and patient population of the CORD I study have been published.[6] Briefly, patients with Dupuytren's disease and fixed-flexion contractures of ≥20° and ≤100° in the metacarpophalangeal joint or ≤80° in the proximal interphalangeal joint were enrolled. Key exclusion criteria were: bleeding disorder; recent stroke; previous treatment of the primary joint within 90 days of study start; treatment with collagenase or any other investigational drug within 30 days of study start; and chronic muscular, neurological or neuromuscular disorder affecting the hand.

Eligible patients were randomized (2 : 1) to receive injectable collagenase Clostridium histolyticum 0.58 mg or placebo into the cord of the affected hand; the primary joint could undergo a maximum of three treatment cycles, which consisted of injection, manipulation (if needed) and 30-day follow-up. The primary endpoint was a reduction in primary-joint contracture to ≤5° of full extension 30 days after the last injection (day 30). All patients provided written informed consent. The study was conducted in accordance with the principles of Good Clinical Practice, the International Conference on Harmonisation guidelines and the US Code of Federal Regulations title 21; the study protocol was approved by institutional review boards or independent ethics committees.

Assessments Included in the Analysis

Finger goniometry, used to measure the fixed-flexion contracture angle of the joint when passively extended toward the neutral position of 0°, was performed at screening, before each injection and at each of the follow-up visits (1, 7 and 30 days post-injection). The mean change in ROM was defined as the difference between the full flexion (i.e. ability to make a fist) and full extension angles (i.e. the ability to straighten the fingers).

At baseline, patients rated the severity of their contractures on a 4-point scale: 1 = 'normal', 2 = 'mild', 3 = 'moderate' and 4 = 'severe'. At baseline and day 90, physicians rated the severity of patients' contractures using the same 4-point scale. In addition, patients rated their percentage improvement in contracture from baseline on a scale from 0% to 100% (in 10% increments) and rated their satisfaction with treatment on a 5-point scale: 1 = 'very satisfied', 2 = 'quite satisfied', 3 = 'neither satisfied nor dissatisfied', 4 = 'quite dissatisfied' and 5 = 'very dissatisfied'. At day 90, physicians rated the degree of improvement in the severity of the patients' contractures on a 7-point Likert scale: 1 = 'very much improved', 2 = 'much

Table I. Baseline demographic and clinical characteristics of patients in the CORD I study[6]

Variable	Collagenase Clostridium histolyticum (n = 204)	Placebo (n = 104)
Age (y) [mean ± SD]	62 ± 10	63 ± 9
Male [n (%)]	171 (84)	74 (71)
Total contracture index[a]		
mean ± SD	149.1 ± 127.6	149.3 ± 111.4
median	105.0	119.0
range	20–860	20–489
Total affected joints per patient (n)		
mean ± SD	3.0 ± 2.2	3.0 ± 2.1
range	1–13	1–10
Family history of Dupuytren's disease [n (%)]	85 (42)	53 (51)
Age at diagnosis (y)		
mean ± SD	53 ± 13	53 ± 12
median	54	53
range	12–78	19–75
Previous treatment for Dupuytren's disease [n (%)]		
none	125 (61)	54 (52)
surgery[b]	73 (36)	44 (42)
hand therapy	28 (14)	16 (15)
injection	5 (3)	3 (3)
other	8 (4)	4 (4)

a Sum of fixed-flexion contractures (≥20°) in all 16 joints measured at screening.

b Fasciotomy, fasciectomy or unspecified.

Table II. Results of the objective efficacy measures in the CORD I study[6]

Efficacy measure	Collagenase Clostridium histolyticum (n = 197)	Placebo (n = 102)
Reduction in contracture to ≤5° (%)	64.0	6.8
time to ≤5° (d) [median]	56	NC
Clinical improvement [≥50% decrease in contracture] (%)	84.7	11.7
Change in contracture		
baseline (°) [mean]	50.2	49.1
day 30 (°) [mean]	12.2	45.7
decrease from baseline to day 30 (%) [mean]	79.3	8.6
Change in ROM		
baseline (°) [mean]	43.9	45.3
day 30 (°) [mean]	80.7	49.5
increase from baseline to day 30 (%) [mean]	36.7	4.0

NC = not calculated; **ROM** = range of motion.

improved', 3 = 'minimally improved', 4 = 'no change', 5 = 'minimally worse', 6 = 'much worse' and 7 = 'very much worse'.

Data Analysis

For the statistical modelling used to determine the CID, CORD I study data were combined across treatment groups; for the subsequent interpretation of treatment effects in the context of the CID, data from the collagenase and placebo groups were compared. Because there was little difference in results for the metacarpophalangeal and proximal interphalangeal joints when evaluated separately, the findings are reported as the average across joints by type. The values do not represent sums for all joints or rays.

An anchor-based approach was used to determine the CID for ROM.[7,8] In general, an anchor-based method relies on patient (or physician) ratings that are external to the target measure of interest (e.g. ROM). Ratings from the anchor measure can serve to quantify the extent of change perceived during treatment. A suitable anchor is one that is interpretable and bears an appreciable correlation with the target measure. Meaningful changes on an anchor measure are then mapped onto the changes noted for the target measure of interest.

To derive an estimate of the CID for ROM, each patient's change from baseline in ROM (the outcome) was assessed against the patient's rating of improvement (0–100%), which served as an anchor, in a regression model. Patient ratings of improvement were analysed as a continuous variable to gauge the relationship between it (the predictor) and changes in ROM (the outcome). Four distinct categories of patient improvement were created: 0% = 'no change', 33.3% = 'minimally improved', 66.7% = 'much improved' and 100% = 'very much improved'. Here, the CID is the extent of change in ROM that the patients perceive as clinically meaningful. Thus, in the context of this analysis, the CID links objective data (i.e. ROM) to subjective data (i.e. patient's perceived improvement in hand function), which then conveys a meaningful difference. In this case, the change in ROM is functionally clinically significant. In a sensitivity analysis of CID, each patient's change from baseline in ROM was assessed against physician ratings of change (instead of patient rating of improvement).

In another regression model, each patient's change from baseline in ROM (outcome) was modelled as a function of a level of satisfaction (as defined above in the 'Assessments Included in the Analysis' section), which served as an anchor. To determine appropriate severity categories for ROM, we regressed each patient's baseline ROM

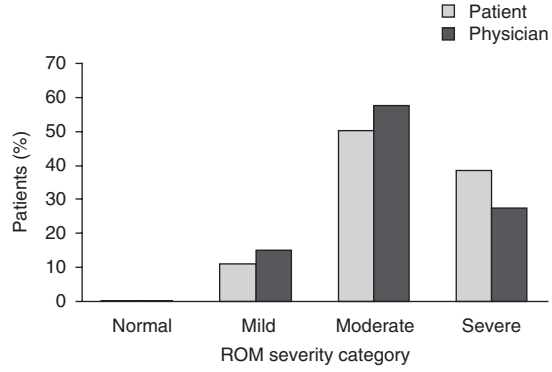

Fig. 1. Distribution of patient and physician ratings of disease severity at baseline. **ROM** = range of motion.

Table III. Range of motion (ROM) categories[a]

Severity rating	ROM (°)
Normal	≥67.0
Mild	≥54.3 and <67.0
Moderate	≥41.6 and <54.3
Severe	<41.6

a Based on modelling of the relationship between ROM and patient-rated disease severity at baseline.

measurement (the outcome) against baseline patient severity rating (the predictor), which served as an anchor in a regression model. Patient severity rating (1 = 'normal', 2 = 'mild', 3 = 'moderate', 4 = 'severe') was used as a continuous variable to determine the relationship between the predictor and the outcome. Boundaries for ROM severity categories were established using mid-point values (i.e. 1.5, 2.5, 3.5) from the severity scale.

Results

In the CORD I study, 308 patients were enrolled; 204 joints received collagenase and 104 joints received placebo.[6] Efficacy was assessed for 306 joints: 203 injected with collagenase and 103 injected with placebo.[6] For this analysis, 299 primary joints were evaluable: 197 in the collagenase group and 102 in the placebo group. Baseline demographics and key efficacy endpoints from the primary analysis[6] are summarized in table I. In the CORD I study, a significantly larger proportion of joints that received collagenase versus placebo injections met the primary endpoint of a reduction in contracture to ≤5° (64.0% vs 6.8%; $p < 0.001$) [table II], as well as all secondary endpoints ($p \leq 0.002$).[6] Overall, compared with baseline, mean ROM was significantly improved after treatment with collagenase (from 43.9° to 80.7°; $p < 0.001$) but not with placebo (from 45.3° to 49.5°; p = not significant [NS]) [table II].[6]

At baseline, 50% of patients (155/308) rated their disease severity as 'moderate'; nearly 40% (119/308) selected a rating of 'severe' (figure 1). A small percentage (11%; 34/308) of patients rated their severity as 'mild'; none rated their severity as 'normal'. When severity rating was evaluated as a continuous variable, the linear relationship between severity rating and ROM was assumed. Because none of the patients rated themselves as 'normal' at baseline, the range for this level was extrapolated from the data. Based on these modelling results, the suggested ROM categories are shown in table III. Investigator ratings of severity and ROM closely paralleled those reported for patient-based ratings (figure 1).

After treatment with collagenase (day 30), the mean ± SD improvement in contracture as rated by the patients was 77% ± 27% in the collagenase group and 5% ± 19% in the placebo group. Likewise, 51% of collagenase-treated patients were rated by the physicians as 'very much improved', 35% as 'much improved' and 10% as 'minimally improved'. The overall improvement rating (i.e. 'very much improved', 'much improved' or 'minimally improved') was 95% as rated by physicians. In the placebo group, the vast majority of patients (93%) were rated by the physicians as showing 'no change'. Patient- and physician-rated measures of improvement in contracture demonstrated close functional relationships with improvements in ROM (figure 2). Based on these results, we suggest that the value corresponding to a 33.3% improvement in patient-rated contracture be used as the estimated CID for ROM; this value was

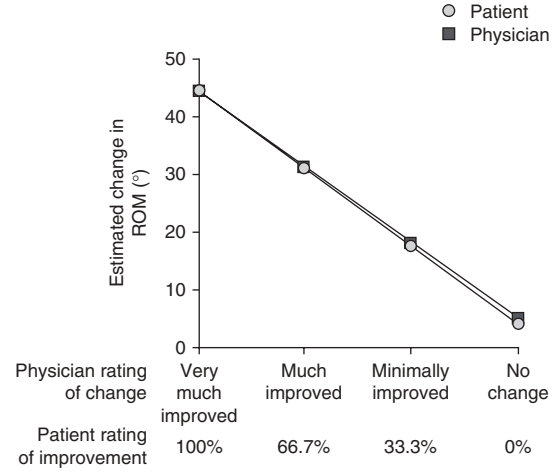

Fig. 2. Relationship between patient and physician ratings of improvement in contracture and mean changes in range of motion (ROM) after collagenase Clostridium histolyticum treatment (day 30).

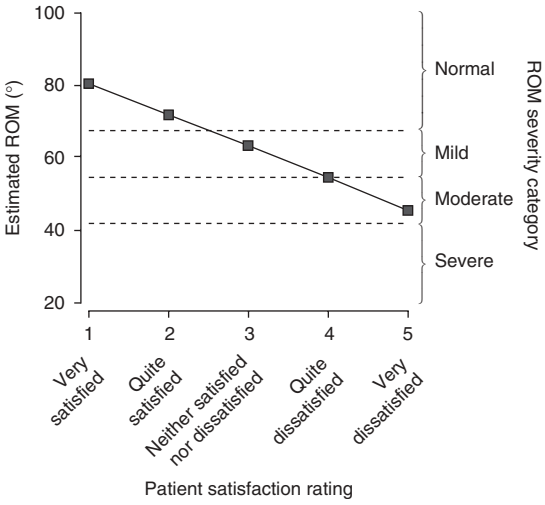

Fig. 3. Mean range of motion (ROM) expressed as a function of patient satisfaction ratings superimposed on ROM severity categories after collagenase Clostridium histolyticum treatment (day 30).

13.5° (95% confidence interval [CI] 11.9, 15.1). In other words, 13.5° is the magnitude of the increase in the change in ROM associated with 0% (4.1°) to 33.3% (17.6°) improvement in contracture as rated by the patient. This value also closely corresponds to a one-category change in physician-rated improvement (e.g. from 'no change' to 'minimally improved').

After collagenase treatment (day 30), patients who rated themselves as 'very satisfied' or 'quite satisfied' were in the 'normal' category of severity for ROM (80.8° and 71.9°, respectively); patients who were 'neither satisfied nor dissatisfied' were in the 'mild' category (63.0°); and patients who were 'quite dissatisfied' or 'very dissatisfied' were in the 'moderate' category (54.2° or 45.3°, respectively) [figure 3]. In the collagenase group, 87% of patients reported being 'very satisfied' or 'quite satisfied' with treatment; in the placebo group, the corresponding value was 32% ($p < 0.001$). Greater treatment satisfaction was correlated with improved ROM ($r = 0.51$; $p < 0.001$).

Using the ROM severity categories, most patients were classified as 'severe' based on their ROM at baseline, which was a mean of 43.9° in the collagenase group and a mean of 45.3° in the placebo group (figure 4). After collagenase treatment (day 30), mean ROM in the collagenase group was 80.7°, consistent with a classification of 'normal'. Mean ROM in the placebo group was 49.5°, remaining consistent with a classification of 'moderate' severity (figure 4).

The mean increase in ROM exceeded the CID in the collagenase group (36.7°; $p < 0.001$) but not in the placebo group (4.0°; NS), and the difference between collagenase treatment and placebo exceeded the CID, suggesting that the improvement with collagenase was clinically relevant (figure 5).

In addition, there was a significant difference in the proportion of patients who reached the 'normal' classification in the collagenase versus placebo groups (81% vs 25%; $p < 0.0001$) [figure 6].

Discussion

In this *post hoc* analysis of data from the CORD I study, we identified Dupuytren's disease severity levels using baseline ROM and estimated the CID for ROM based on the relationships between these categories and subjective assessments of treatment-related improvements and patient satisfaction. Using the modelling results, we derived ROM severity categories to assess the level of ROM consistent with 'normal' (i.e. ≥67.0°).

After treatment with collagenase, mean ROM (80.7°) was consistent with 'normal'. In the placebo

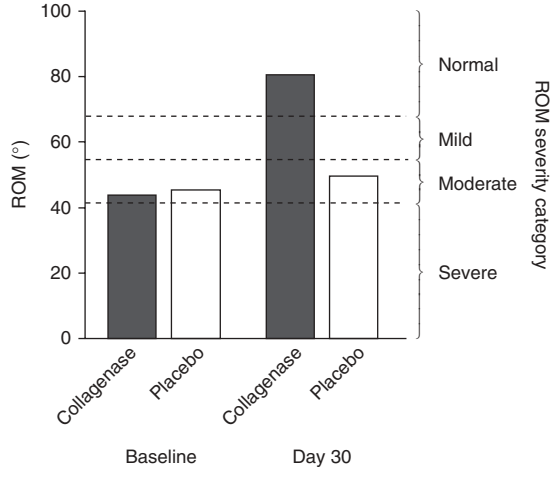

Fig. 4. Mean range of motion (ROM) assessments at baseline and after collagenase Clostridium histolyticum treatment (day 30) by treatment group superimposed on ROM severity categories.

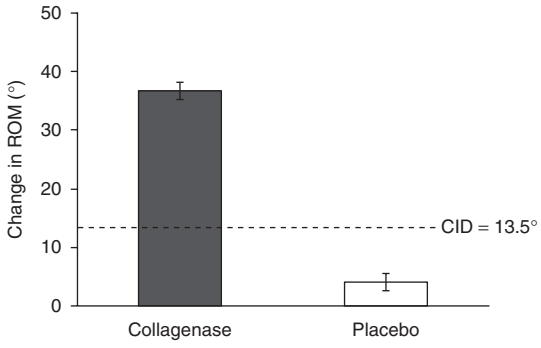

Fig. 5. Mean ± standard error treatment-related changes in range of motion (ROM) by treatment group and in relation to the estimated clinically important difference (CID) for ROM.

group, mean ROM (49.5°) was essentially unchanged, remaining consistent with the 'moderate' and 'severe' ROM categories (<54.3°). Improvements in ROM were associated with patient satisfaction, and a significantly larger percentage of patients were satisfied with collagenase than with placebo. Treatment-related improvements after collagenase (vs those after placebo) exceeded the CID, suggesting that the study results were not only statistically significant but also clinically meaningful.

It should be noted that the CID is contingent on the circumstances that produced it. That is, the estimate may vary in other situations owing to natural sampling variation, different study populations, type of anchor, time period of assessment, and other considerations. Moreover, the estimated CID defined and derived here refers to a one-category difference on an anchor and is not necessarily a *minimally* CID, as values less than this may still be meaningful and relate to a clinically relevant change that is less than a one-category difference on an anchor.

Models with each anchor (patient severity rating, patient rating of improvement in contracture, physician severity rating, physician rating of improvement) as a categorical predictor, which do not impose any functional relationship between outcome and predictor, were also investigated. The results with these models (not reported here) support the results with each anchor as a continuous predictor. The use of the anchor as a continuous predictor not only increases the sensitivity of observed relationships but also provides a simplified and meaningful interpretation of the relationship using the slope as a measure of change.

To advance the research, we made two plausible methodological assumptions. First, because no patients rated themselves as 'normal' for ROM at baseline, we used all available data to create a functional relationship to capture what the ROM would be for 'normal' subjects. Second, a common approach for CID estimation is to link the change on the target measure to a one-category change on an anchor, such as patient global impression of change, usually represented on a 7-point scale with three categories of worsening, a 'no change' category and three categories of improvement.[8,14] In following this approach, we mapped the patient improvement scale (0–100%) on the 'no change' category and the three categories of improvement. These four levels (0% 'no change', 33.3% 'minimally improved', 66.7%

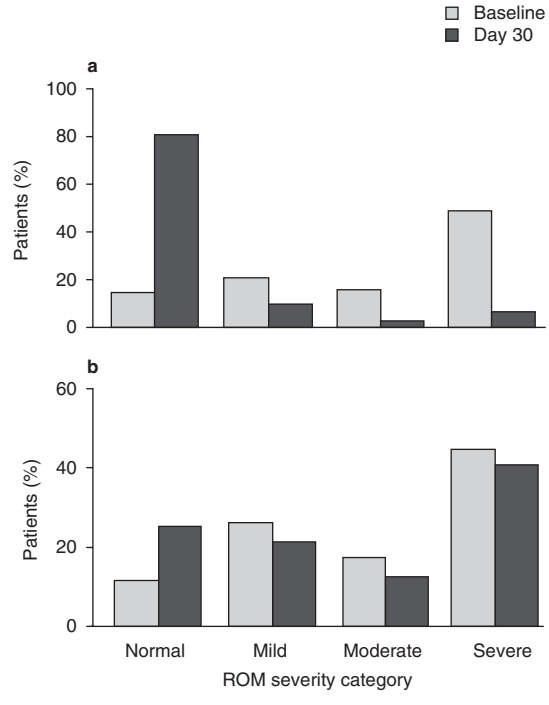

Fig. 6. Distribution of patients by range of motion (ROM) severity categories at baseline and after treatment (day 30) in (**a**) the collagenase Clostridium histolyticum group and (**b**) the placebo group.

'much improved' and 100% 'very much improved') parallel corresponding levels on the patient global impression of change, a commonly used anchor.[14]

Conclusion

Previous studies have shown that collagenase-related improvements in ROM and treatment satisfaction are statistically significant versus placebo. We have extended these findings to show that improvements in these measures are also clinically relevant. We used regression models on CORD I study data to create a ROM severity classification and estimate a CID based on physician and patient ratings. The CID for ROM is 13.5°, reflecting a one-category change in disease severity. The increase in ROM exceeded the CID in the collagenase but not in the placebo group, and the difference between collagenase and placebo also exceeded the CID. Overall, these findings suggest that the CID and severity categorization for ROM can be used to obtain a better understanding of the impact of Dupuytren's disease and the effects of treatment from the patients' perspective.

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