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Collagenase clostridium histolyticum for the treatment of Peyronie's disease: a prospective Italian multicentric study

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SUMMARY

Peyronie's disease (PD) is a common condition which results in penile curvature making sexual intercourse difficult or impossible. Collagenase clostridium histolyticum (CCH) is the first licensed drug for the treatment of PD and is indicated in patients with palpable plaque and curvature deformity of at least 30° of curvature. However, only few monocentric studies are available in the current literature and this is the first national multicentric study focusing on this new treatment. In five Italian centres, 135 patients have completed the treatment with three injections of CCH using Ralph's shortened modified protocol. The protocol consisted of three intralesional injections of CCH (0.9 mg) given at 4-weekly intervals in addiction to a combination of home modelling, stretching and a vacuum device on a daily basis. An improvement in the angle of curvature was recorded in 128/135 patients (94.8%) by a mean (range) of 19.1 (0–40)° or 42.9 (0–67)% from baseline ($p < 0.001$). There was also a statistically significant improvement in all IIEF and PDQ questionnaires subdomains ($p < 0.001$ in all subdomains). This prospective multicentric study confirms that the three-injection protocol is effective enough to achieve a good result and to minimize the cost of the treatment.

INTRODUCTION

Collagenase clostridium histolyticum (CCH; Xiapex_ [Pfizer Inc., New York, NY, USA], Xiaflex_ [Endo Pharmaceuticals Inc., Dublin, Ireland]) was licensed by the USA Food and Drug Administration in 2013 as non-surgical treatment for Peyronie's disease (PD). Peyronie's disease is an inflammatory disorder characterized by an excessive deposition of collagen fibres within the tunica albuginea of the penis which leads to the formation of a fibrous plaque (Nehra *et al.*, 2015).

The clinical efficacy and safety of CCH were demonstrated in the randomized, placebo-controlled IMPRESS (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) which reported a mean 34% improvement in penile curvature compared with a mean 18% improvement in the placebo arm. Only three of 417 patients reported a Clavien III complication (Gelbard *et al.*, 2013; Lipshultz *et al.*, 2015). IMPRESS protocol consisted of a maximum of four treatment cycles, each cycle separated by 6 weeks at least. Each treatment cycle included two injections of 0.58 mg of CCH, approximately 24–72 h apart, which leaded to the use of maximum eight vials of CCH for each patient. As the cost of this treatment would have been very high, Ralph *et al.* evaluated the efficacy and safety of a shortened protocol that aimed to reduce the number of injections and the patient visits needed, therefore reducing the total cost of the treatment (Abdel Raheem *et al.*, 2017a). This new protocol consisted of three injections given at 4-weekly intervals. In between injections, patients used a combination of home modelling, stretching and a vacuum device on a daily basis. Despite the

reduced number of injections, the clinical efficacy of the injections remained unchanged (Abdel Raheem *et al.*, 2017b).

At the present time, excluding the initial IMPRESS, there are only single-centre clinical trials that validate the current literature (Abdel Raheem *et al.*, 2017b). This study is the first national multicentric study on the efficacy of CCH for PD using Ralph's protocol.

MATERIALS AND METHODS

This is a prospective, non-randomized multicentric study on patients with PD who received treatment with CCH injections using Ralph's protocol. Patients were recruited in outpatient clinics of University of Florence, University Federico II of Naples, University of Turin, University of Catania. Exclusion criteria were as follows: penile curvature <30°, patients with ventral plaque, completed calcified plaque, acute phase of the disease. All patients signed a written fully informed consent statement and voluntarily entered the trial.

The parameters assessed included (i) the angle of curvature; (ii) the International Index of Erectile Function (IIEF-15); (iii) Peyronie's disease questionnaires (PDQ). The IIEF-15 scale considered the severity of ED, classified as follow: severe (IIEF-15 ≤ 10), moderate (IIEF-15 between 11 and 16) and mild (IIEF-15 between 17 and 25). The IIEF-15 subscores were valued, including IIEF-erectile function (IIEF-EF), IIEF-orgasmic function (IIEF-OF), IIEF-sexual desire (IIEF-SD), IIEF-intercourse satisfaction (IIEF-IS) and IIEF-overall satisfaction (IIEF-OS). The PDQ is a 15-question self-reported survey that measures the impact and severity of PD symptoms in three domains: psychological and physical symptoms (PS symptom severity score; PDQ question 1–6), penile pain (penile pain score; PDQ question 7–9) and bother symptoms (bother score; PDQ question 10–15). Patients were asked to complete the PDQ scale only if they had had vaginal intercourse with a female partner within the previous 3 months. All parameters and questionnaires were evaluated before treatment (baseline) and at the end of treatment cycle (1 month after the injection of the last vial).

After the recruitment process, each patient was evaluated by medical history, physical examination, intracavernous alprostadil injection (ICI) test plus Doppler ultrasound scan and patient self-administered questionnaires. The curvature was evaluated with the use of a goniometer. The point of maximal curvature was marked when the penis was fully erect and the distance from the corona was recorded, and subsequently used for the injection without inducing an erection every single time.

The ICI penile duplex was also performed to exclude patients with complete calcified plaques. A penile block with 10 mL of lidocaine 1% was performed before each injection, to minimize the discomfort during the injection. The protocol consisted of three intralesional injections of CCH (0.9 mg),and each injection was given at 4-weekly intervals. The whole vial was injected at the point of maximal curvature, which was recorded for each patient during the first visit. The only difference with Ralph's protocol was the slight compression applied after the injection to be held for 24 h. Patients were instructed to remove the compression the day after and to perform home modelling manoeuvres, straightening manoeuvres and to use Rapport Classic Vacuum system (OwenMumford, Inc, West Oak Common Court, USA, distributed by Medis, Rozzano, Italy) twice a day. Straightening and modelling manoeuvres started 24 h after the injection, whilst the vacuum pump was started 48–72 h after the treatment when the swelling had subsided. Treatment emergent adverse events (TEAEs) were collected, including any patient-reported event that began or worsened after the first dose of study drug until study completion or early withdrawal. All data were collected and analysed with the software program SPSS, version 23.0 (SPSS, Chicago, IL, USA).

RESULTS

One hundred and thirty-five (135) patients completed the treatment with the modified protocol, thus each of them received three CCH injections in 12 weeks. The mean age of the population was 54.4 years (range 23–74), and duration of PD was 13.0 months (range 1–36). The mean baseline curvature was 48.9° (range 30–90°) (Table 1). The types of curvature registered were dorsal, lateral or dorsolateral in direction (Table 2). Of the 135 patients in the study, 128 patients(94.8%) had an improvement in the angle of curvature by a mean of 19.1° (range 0–40°) or 42.9% (range 0–67%) from baseline after three CCH injections. The final mean curvature was 29.3° (range 0–65°; $p < 0.001$; Fig. 1). There was a statistically significant improvement in all IIEF questionnaire subdomains ($p < 0.001$; Fig. 2). Likewise, PDQ subscores significantly changed from baseline to final follow-up ($p < 0.001$; Fig. 3). Ecchymosis and haematoma were

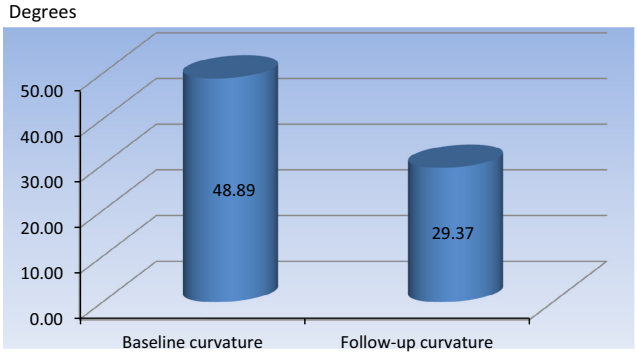
Table 1 Descriptive statistics of the population

	Descriptive statistics			
	Min	Max	Mean	Std. Dev
Age	23	74	54.37	12.886
Age of the partner	22	75	49.82	11.685
Duration of PD	1	36	12.96	4.479
Baseline curvature	30	90	48.89	22.291

Table 2 Direction of the curvature

	Direction of the curvature		
	Frequency	Percentage	Cumulative percentage
Dorsal	121	89.6	89.6
Lateral	9	6.7	96.3
Dorsolateral	5	3.7	100.0
Total	135	100.0	

Figure 1 Improvement after three injections of CCH. [Colour figure can be viewed at wileyonlinelibrary.com]



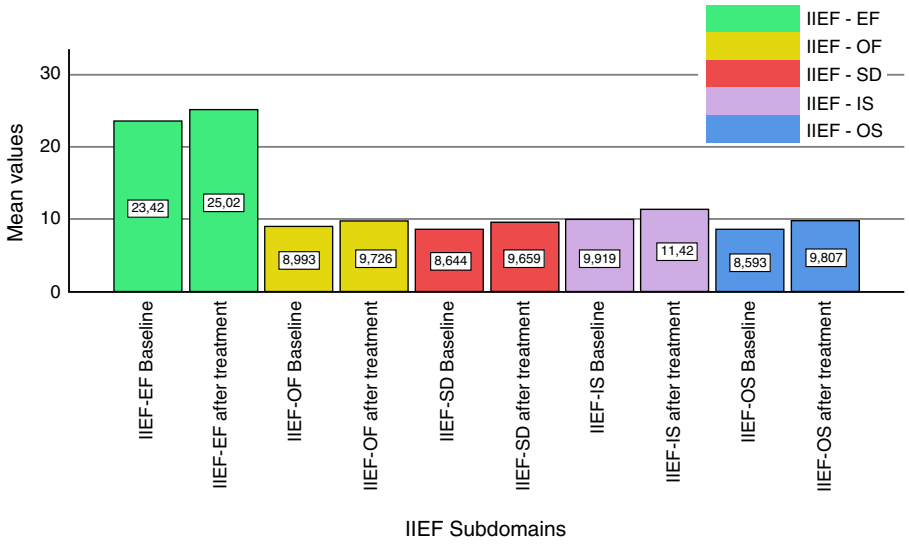
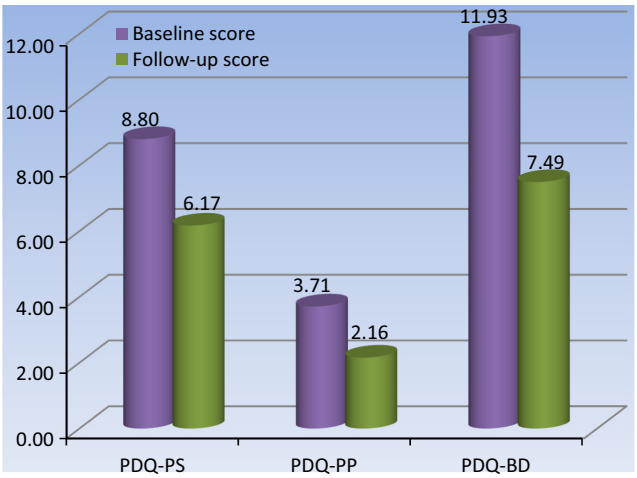


Figure 2 Improvement in IIEF subdomains after treatment. [Colour figure can be viewed at wileyonlinelibrary.com]

Figure 3 Improvement in PDQ subdomains after treatment. [Colour figure can be viewed at wileyonlinelibrary.com]



recorded in 125/135 patients (92.6%), but no Clavien Dindo III complications were seen (0%).

DISCUSSION

Nowadays, PD continues to be a disease under the magnifying glass for its attractive modality of minimally invasive treatments (Gabrielson *et al.*, 2017). CCH is the only licensed drug for the treatment of PD. The safety and efficacy of CCH for the treatment of PD has already been described in phase III and non-randomized single-centre studies (Gelbard *et al.*, 2013; Lipshultz *et al.*, 2015; Abdel Raheem *et al.*, 2017a,b). Post-approval clinical trials continue to become available and to discover new factors in order to optimize clinical outcomes (Nguyen *et al.*, 2017)

According to the European Association of Urology (EAU) Guidelines on penile curvature, the results of the studies on conservative treatment for Peyronie's disease are often contradictory making it difficult to provide recommendations in the everyday, real-life setting (Hatzimouratidis *et al.*, 2017). However, all the studies recently published have proved the efficacy and the safety of the treatment with CCH. Moreover, this multicentric analysis confirms that three-injection protocol is effective enough to achieve a good result and to minimize the cost of the treatment. Interestingly, the development of the new protocol has given results comparable to the eight-injection protocol of the IMPRESS, which could give the andrologist the option of increasing the number of injections to achieve greater improvement, if the initial response is favourable. This might be due to the fact that in Ralph's protocol, 0.9 mg of Xiapex is injected into the plaque, whereas in the IMPRESS, only 0.58 mg has been used for each injection. On the other hand, the use of the whole vial of Xiapex in comparison with the injection of half of it (0.9 vs. 0.58 mg) results in higher percentage of ecchymosis and haematoma (92.6% vs. 65.5%, respectively).

Furthermore, in our records the overall number of surgical procedures to correct PD's curvature has dramatically reduced after the release of CCH, although at the present time, all the centres are not able to present any data regarding this aspect. It is clear that a change in the management of the disease is needed in the nearest future and further studies focusing on the identification of the correct patients are essential.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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None

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