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REVIEW

Collagenase clostridium histolyticum: a novel medical treatment for Peyronie's disease

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ABSTRACT

INTRODUCTION: Peyronie's disease (PD) affects up to 9% of the male population. PD causes scarring of the tunica albuginea of the penis which leads to penile deformity making sexual intercourse difficult or impossible. PD also causes significant psychological, emotional and relationship difficulties for both patient and partner. Up until the licencing of Collagenase clostridium histolyticum (CCH) (Xiapex®, Xiaflex®), surgical correction of the penile deformity was the mainstay of treatment. Many conservative treatment options had been previously tried, however, the safety and efficacy of these options has not been demonstrated in large well-designed clinical trials. Intra-lesional CCH is now the gold standard option for the non-surgical management of PD. It is the first and only treatment approved by the Food and Drug Administration and the European Medicines Agency for PD. In this review article, we will discuss the pharmacology, clinical efficacy, safety and future of CCH intralesional injection.

EVIDENCE ACQUISITION: MEDLINE and PubMed search (from 1946). The search terms ("Collagenase Clostridium Histolyticum" OR "Xiapex" OR "Xiaflex") AND "Peyronie's disease" were used.

EVIDENCE SYNTHESIS: The safety and efficacy of intra-lesional CCH in the management of PD has been demonstrated in 2 large-scale multicenter, randomized, double-blind placebo-controlled clinical trials; the investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies I and II (IMPRESS I and IMPRESS II). A new study published by our group suggests a new modified shortened protocol that will reduce the cost and duration of treatment without compromising the safety or efficacy of treatment.

CONCLUSIONS: CCH is the gold standard non-surgical option in the management of PD. The safety and efficacy of CCH has been demonstrated in large well-designed clinical trials. The new modified protocol, developed by our group, reduces the cost and inconvenience to patients whilst maintaining the efficacy. This will allow more men to benefit and will reduce the number of men undergoing surgical correction for their PD.

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KEY WORDS: Penile induration - Clostridium histolyticum collagenase VII-S - Xiapex - Dupuytren contracture.

Introduction

Peyronie's disease (PD) is a connective tissue disorder characterized by localized collagen plaque formation of the tunica albuginea. The pathophysiology of PD is not fully understood. However, it is currently accepted that repetitive coital micro-trauma results in an inflammatory process. This in turn results in formation of a collagen plaque in men with a genetic predisposition. The fibrotic plaque reduces the elasticity of the tunica albuginea causing curvature and deformity during penile erection. Alongside the physical symptoms, these men (and their partners) also experience significant psychological and emotional symptoms associated with their disease.[1]

Given the nature of PD, the incidence is likely to be underreported. Current estimates suggest that between 7-9% of men are affected, with the

incidence increasing with age. PD typically presents in men during their 5th decade, however can affect men of all ages. The prevalence of PD is higher in men with diabetes mellitus, erectile dysfunction, Dupuytren's contracture and following radical prostatectomy.[2] The natural course of PD initially involves an acute phase that is characterized by plaque formation with a progressive penile deformity (in most cases a curvature), usually with pain on erection and during sexual intercourse. Following this, the disease enters a quiescent or chronic phase in which the penile curvature stabilizes and the pain subsides.[3]

Historically, the mainstay of the management of PD has been surgical correction. Surgery is indicated in men with stable disease whose curvature is adversely affecting sexual intercourse. It is well documented that surgery is effective at straightening the penis, however it is associated potential complications and morbidity. Nesbit or plication procedures are associated with penile shortening and men often complain being able to palpate the sutures. Incision and grafting procedures are able maintain penile length, however, are associated with erectile dysfunction (ED). Men with poor erections often elect for a penile prosthesis, however these are associated with infection/malfunction and the possibility of a urethral injury.[4]

There have been several non-surgical options investigated in the management of PD. Based on data from randomized controlled trials (RCT), the oral options of potaba, vitamin E, tamoxifen, colchicine, carnitine and pentoxifylline have all failed to reach significance when compared with placebo.[5, 6] Intralesional injection with Verapamil has been found to significantly reduce the plaque volume in a small (N.=14) single blind study. Unfortunately, this did not result in a significant reduction in penile curvature.[7] More recently, intralesional Interferon α-2b has been found to be safe and effective at reducing penile curvature and reducing plaque volume. The investigators demonstrated a mean improvement in curvature from baseline of 13°. This study unfortunately was single-blinded so there may have been a degree of investigator bias.[8] The role of penile traction remains unclear, as much of the data is provided from non-controlled studies and the benefit still appears to be minimal.[9]

Collagenase clostridium histolyticum (CCH) (Xiapex®, Xiaflex®) intralesional injection is now the gold standard option for the non-surgical management of PD. It is the first USA Food and Drink Administration (FDA) and European Medicines Agency (EMA) approved treatment for PD. These men are often devastated by the physical effects of PD and prior to CCH were faced with either surgical correction (and the associated morbidity) or would have to live with their penile deformity. Throughout, this review we will discuss the pharmacology, clinical efficacy, safety and future of CCH intralesional injection.

Evidence acquisition

Scientific papers for inclusion in this review article were obtained by searching MEDLINE (from 1946) and PubMed (from 1946) medical databases. We used the search terms ("Collagenase Clostridium Histolyticum" OR "Xiapex" OR "Xiaflex") AND "Peyronie's disease." The bibliographies of the articles identified were also screened for additional relevant papers. Well-designed large clinical trials in men with PD receiving CCH were included in the clinical efficacy section. Also, those with relevant pharmacological data and novel uses of CCH in PD were also included.

Evidence synthesis

Pharmacology of CCH

Collagenases are biological enzymes that hydrolyze fibers of collagen. CCH is formed of a mixture of Class I and Class II Collagenases produced by the bacteria clostridium histolyticum. Class I and Class II Collagenases work synergistically by acting on different parts of the collagen molecule. The Class I collagenases produce large protein fragments, whereas Class II act on the interior of the molecule producing smaller protein fragments. CCH acts selectively on collagen types (I and III) which predominate in the plaques of men with PD. CCH also selectively spares the collagen type (IV) that predominate in neurovascular structures. This reduces the likelihood of damage to important adjacent structures.[10]

There systemic absorption of intralesional CCH has been found to be minimal and short-lived. The plasma concentrations of all the participants was found to be unquantifiable 30 minutes after CCH injection. There have been no formal drug interactions identified with intralesional CCH. Where possible, men should stop their anticoagulants prior to CCH injection. Those men that are anticoagulated or have a clotting disorder are at greater risk of hematoma and bruising. The use of concomitant phosphodiesterase inhibitors is not contraindicated with CCH. Concomitant use with tetracycline antibiotics is not recommended, as they inhibit collagen breakdown and is theorized that the effect of CCH may be reduced.[10]

Clinical efficacy of CCH

There have been 3 large well-designed studies investigating the use of CCH and PD (two RCTs and one open-label trial) (Table I). They all used the same ("classic") protocol, consisting of 4 treatment cycles separated by an interval of 6 weeks. Each treatment cycle consists of two CCH intralesional injections (0.58 mg), 24-72 hours apart with investigator modelling 24-72 hours after the second the injection.

The majority of the evidence is provided by, The Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies I and II (IMPRESS I and IMPRESS II). These 2 prospective multi-institutional double-blind RCTs are identically designed and recruited 417 and 415 participants respectively. They included men with a curvature of ≥30° and ≤90° dorsal or lateral curvature and stable disease for more than 12 months. Ventral curvatures and men with a completely calcified plaque were excluded.[11, 12] The mean age of participants in the IMPRESS trials was 57.7 years. They had a mean duration of PD of 4.1 years. The participants were stratified based on the severity of their curvature 30-60° (77.3%) or 60-90° (22.7%) and randomized into intervention and control groups in a ratio of 2:1. The intervention arm received the "classic" CCH protocol and the control group where injected with a placebo of 10 mmol/L tris and 60 mmol/L sucrose.[11, 12]

There was significant improvement in the following two co-primary endpoints at 52 weeks: 1) mean reduction in curvature; 2) Peyronie's Disease Questionnaire (PDQ) bother score. There was a mean reduction in curvature of 17°±14.8° (34%) compared to 9.3°±13.6° (18.2%) in the control group (P≤0.0001*)*. There was also a significant improvement in PDQ bother score of -2.8±3.8 in the intervention group compared with -1.8±3.5 in the control group.[11, 12] There were 7 secondary end-points examined in the IMPRESS trials. Of these 7 endpoints, the following 5 reached significance; PDQ physical and psychological symptoms domain scores, mean International Index of Erectile Function overall satisfaction domain score, plaque consistency, global responder and composite responder. A global responder is defined as a participant with an improvement of ≥1 on the PDQ bother domain score. A composite responder was defined as someone with a 20% or greater improvement in curvature and an improvement of 1 or more on the PDQ bother domain score. There was no significant difference in penile length and PDQ penile pain in the intervention group compared to control.[11, 12]

Levine *et al,* conducted a large open-label clinical trial using the same primary end-points (Mean change in curvature and PDQ bother score) and protocol as the IMPRESS trials. They found a mean reduction in curvature of -18.3°±14.02° (34%) and an improvement of -3.3 (95% CI: 2.8-3.7) in PDQ bother score. These results are comparable with the IMPRESS trial

TABLE I.—*Clinical efficacy outcomes of collagenase clostridium histolyticum for the treatment of Peyronie's disease.*

Study	Duration (weeks)	N. participants	Baseline curvature (mean)	End of study curvature (mean)	Improvement in curvature (mean)
IMPRESS I and II[11, 12]	52	401	50.1°	33.1°	34%*
Open-label studies[13]	36	238	53.0°	34.7°	34.4%*
Modified protocol[14]	24	53	54.1°	36.9°	31.4%*

*Statistically significant difference.

data. A sub-group analysis was also preformed which showed that those men with a larger curvature showed a greater improvement. In the 30-60°group, there was a mean improvement of 33%, whereas in the 60-90° there was a mean improvement of 37%.[13]

Treatment-related adverse effects

Within the IMPRESS trials, 84.2% of the participants (464/551) that received four cycles of CCH experienced adverse effects. These where most commonly mild, localized and short-lived; penile swelling, bruising and pain were the most commonly reported side effects. Of these adverse effects, 79% of these had resolved within 14 days and had not required intervention. Of the 551 men recruited in the IMPRESS trial, 6 experienced a serious adverse event; there were three episodes of corporal rupture requiring surgical intervention and three episodes of penile hematoma; one requiring surgical drainage, one requiring aspiration and one was treated conservatively. This equates to a 0.7% chance of having a serious adverse event requiring intervention (Table II).[11, 15]

More recently, Yafi *et al.* published questionnaire data completed by providers of CCH injection therapy. They found that one in three providers had experienced at least one case of corporal rupture. From their data the incidence of corporal rupture and corporal hematoma appears to be greater than the incidence reported in the IMPRESS trials. Unfortunately, given the methodological differences between the two studies, a direct comparison cannot be made. Furthermore, imaging was not performed in 49% of the cases and there may well be an over diagnosis of corporal rupture because the side effects following CCH injection resemble corporal rupture especially that swelling, bruising and small hematomas around the injection site occur in most patients.[16]

Antibodies to CCH were identified in almost all of the men having received CCH, however no allergic and anaphylactic reactions were noted.[10]

TABLE II.—*Adverse events occurring in the pooled analysis from IMPRESS I and IMPRESS II Clinical trials.*[11]

Adverse event	CCH group	Control group
Penile bruising (including hematoma)	80%	26%
Penile swelling	55%	3.2%
Penile pain	45.4%	9.3%
Blood blister	4.5%	0%
Penile blister	3.3%	0%
Penile erythema	3.1%	3%
Genital pruritis	3.1%	0%
Painful erection	2.9%	0%
Erectile dysfunction	1.8%	0.4%
Skin discoloration	1.8%	0%
Procedural pain	1.6%	0.7%
Injection site vesicles	1.3%	0%
Localized edema	1.3%	0%
Dyspareunia	1.1%	0%
Injection site pruritis	1.1%	0%
Nodule	1.1%	0%
Suprapubic pain	1.1%	0%

Future for CCH

Raheem *et al.* have recently made an alteration to the CCH protocol that may reduce the cost and inconvenience to patients without reducing the efficacy (Figure 1). They propose that each cycle can consist of 1 CCH injection of 0.9 mg (one full vial), followed by home modeling with a vacuum device. The use of a vacuum device has been deemed safe to use in PD.[17] Compared with

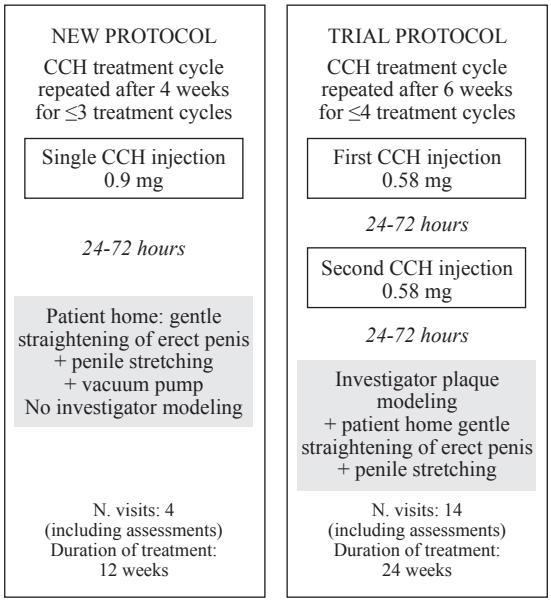

Figure 1.—Alteration to the CCH protocol that may reduce the cost and inconvenience to patients without reducing the efficacy.

the IMPRESS trials of 2 CCH injections (0.58 mg) 24-72 hours apart followed by a further visit for investigator modeling. They recommend injecting the full vial into 3 areas around the point of maximum curvature. This may allow for better distribution and accuracy, as the resultant inflammatory process following the first injection makes palpation of plaque during the second injection more difficult.[14]

Overall, in the modified protocol the patients need to attend clinic on four occasions and will require three vials of CCH compared with 14 times and 8 vials of CCH in the classic protocol. Taking both factors into consideration, the savings on cost and convenience are considerable. They found comparable efficacy in the modified protocol compared with classic protocol. There was a significant ($P<0.001$) reduction in the mean curvature of the 53 men recruited. There was a 17.36° or 31.4% improvement in penile curvature of these men. Furthermore, there was also an improvement in stretched penile length, improved IIEF questionnaire domains and an improvement in PDQ scores (bother, pain, psychological, and physical symptoms domains). There were no cases of corporal rupture and the side effects were local, transient and self-limiting.[14]

Currently, CCH is licensed in men with stable PD with a dorso-lateral penile curvature of >30° and <90°. There are however significant number of men that do not fall within these constraints and/or have atypical PD, such as, ventral curvature, hourglass deformity, shortened penis and multi-planar curvature. The safety and effectiveness of CCH needs to be determined in these patient groups.

Men with a curvature of <30° where not included in the IMPRESS Trials and those men whose curvature improved during the trial to <30° did not receive any further intralesional CCH injections. There is recent evidence that has found no significant difference in the serious treatment-related adverse effects between men with a curvature of <30° and men with a curvature of >30°. There was however a significant increase in minor side effects between the 2 groups (including penile swelling, penile bruising and skin hyperpigmentation) in the <30° curvature group compared to the >30° group. This suggests that CCH is safe to use in men with a smaller curvatures.[18] Although, men with a smaller curvature achieve a smaller improvement following CCH injection. Therefore, careful consideration between the risks and benefits needs to be made.

There is a small case series of two men with atypical ventral curvature treated with intralesional CCH injection. Ventral curvatures pose additional risk of urethral injury and injection of CCH is technically more difficult than that of dorsal curvatures. They found an improvement in the curvature of both men with neither experiencing urethral side effects.[19]

The use of CCH during the active phase of the disease has the potential for disease modification and a prevention of a worsening penile curvature. One study has injected intralesional CCH into the plaques of men with active disease. They demonstrated a mean reduction in curvature of 20°.[20] Additional research needs to be conducted to fully evaluate the safety and efficacy in men with active or atypical disease.

Conclusions

CCH is the gold standard non-surgical option in the management of PD. It is the first treatment option that is licensed by the FDA and EMA for use in men with stable disease. PD significantly and adversely effects the psychological and emotional wellbeing of the men affected. They find themselves "between a rock and a hard place" — terrified by the thought of surgical correction, however have little other choice given their deformity. The safety and efficacy of CCH has been demonstrated in large well-designed clinical trials. The new modified protocol reduces the cost and inconvenience to patients whilst maintaining the efficacy. This will allow more men to benefit and will reduce the number of men undergoing surgical correction for their PD. The use of CCH in men with atypical PD and during the active phase of the disease needs to be further investigated.

Reference

1. Gabrielson AT, Spitz JT, Hellstrom WJ. Collagenase Clostridium Histolyticum in the Treatment of Urologic Disease: Current and Future Impact. Sex Med Rev 2018;6:143–56.

2. Langston JP, Carson CC 3rd. Peyronie's disease: review and recent advances. Maturitas 2014;78:341–3.

3. Anaissie J, Hellstrom WJ, Yafi FA. Collagenase Clostridium Histolyticum for the Treatment of Peyronie's Disease: A 'Real World' Clinical Perspective. Drugs 2016;76:1523–8.

4. Poullis C, Shabbir M, Eardley I, Mulhall J, Minhas S. Clostridium histolyticum collagenase - is this a revolutionary medical treatment for Peyronie's disease? BJU Int 2016;118:186–9.

5. Garaffa G, Trost LW, Serefoglu EC, Ralph D, Hellstrom WJ. Understanding the course of Peyronie's disease. Int J Clin Pract 2013;67:781–8.

6. Safarinejad MR, Asgari MA, Hosseini SY, Dadkhah F. A double-blind placebo-controlled study of the efficacy and safety of pentoxifylline in early chronic Peyronie's disease. BJU Int 2010;106:240–8.

7. Rehman J, Benet A, Melman A. Use of intralesional verapamil to dissolve Peyronie's disease plaque: a long-term single-blind study. Urology 1998;51:620–6.

8. Hellstrom WJ, Kendirci M, Matern R, Cockerham Y, Myers L, Sikka SC, *et al.* Single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralesional interferon alpha-2B for minimally invasive treatment for Peyronie's disease. J Urol 2006;176:394–8.

9. Gontero P, Di Marco M, Giubilei G, Bartoletti R, Pappagallo G, Tizzani A, *et al.* Use of penile extender device in the treatment of penile curvature as a result of Peyronie's disease. Results of a phase II prospective study. J Sex Med 2009;6:558–66.

10. Dhillon S. Collagenase Clostridium Histolyticum: A Review in Peyronie's Disease. Drugs 2015;75:1405–12.

11. Gelbard M, Goldstein I, Hellstrom WJ, McMahon CG, Smith T, Tursi J, *et al.* Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of peyronie disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. J Urol 2013;190:199–207.

12. Gelbard M, Hellstrom WJ, McMahon CG, Levine LA, Smith T, Tursi J, *et al.* Baseline characteristics from an ongoing phase 3 study of collagenase clostridium histolyticum in patients with Peyronie's disease. J Sex Med 2013;10:2822–31.

13. Levine LA, Cuzin B, Mark S, Gelbard MK, Jones NA, Liu G, *et al.* Clinical safety and effectiveness of collagenase clostridium histolyticum injection in patients with Peyronie's disease: a phase 3 open-label study. J Sex Med 2015;12:248–58.

14. Abdel Raheem A, Capece M, Kalejaiye O, Abdel-Raheem T, Falcone M, Johnson M, *et al.* Safety and effectiveness of collagenase clostridium histolyticum in the treatment of Peyronie's disease using a new modified shortened protocol. BJU Int 2017;120:717–23.

15. Yan S, Yap T, Minhas S. Collagenase clostridium histolyticum intralesional injections for the treatment of Peyronie's disease: a safety profile. Transl Androl Urol 2017;6:123–6.

16. Yafi FA, Anaissie J, Zurawin J, Sikka SC, Hellstrom WJ. Results of SMSNA Survey Regarding Complications Following Intralesional Injection Therapy With Collagenase Clostridium Histolyticum for Peyronie's Disease. J Sex Med 2016;13:684–9.

17. Raheem AA, Garaffa G, Raheem TA, Dixon M, Kayes A, Christopher N, *et al.* The role of vacuum pump therapy to mechanically straighten the penis in Peyronie's disease. BJU Int 2010;106:1178–80.

18. Hellstrom WJ, Tan RB, Liu G. Safety Profile of Collagenase Clostridium Histolyticum Stratified by Degree of Penile Curvature in Patients With Peyronie Disease. Urology 2017;106:237.e9–14.

19. Kuhlmann PK, DeLay KJ, Anaissie J, Hellstrom WJ, Yafi FA. Collagenase Clostridium histolyticum in the treatment of Peyronie's disease: patient selection and perspectives. Patient Prefer Adherence 2017;11:431–48.

20. Aliperti LA, Mehta A. Expanding the role of injectable collagenase clostridium histolyticum for the treatment of active phase Peyronie's disease. Transl Androl Urol 2017;6:114–5.

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