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***Clostridium histolyticum* collagenase – is this a revolutionary medical treatment for Peyronie’s disease?**

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Peyronie’s disease (PD) was described by Francois de la Peyronie in 1743, a battlefield surgeon and Commander of the Medical Corps of Louis XIV. The prevalence in the general population varies from 0.39% to 3.4%, but increases to 7.1% in patients aged 50–69 years, with a reported prevalence rate of 20.3% in men with diabetes. The disease has two distinct clinical phases; the acute and stable or chronic phases. The acute phase is characterised by painful erections with increasing penile deformity usually lasting between 3 and 12 months. The chronic phase is usually pain-free and characterised by stabilisation of the plaque and penile deformity. The aetio-pathogenesis of the disease remains largely unknown with local trauma, genetic, and vascular factors being implicated.

PD presents a challenging problem for both clinicians and patients. The development of a plaque and deformity in the penis has a significant psychological impact on patients, with impairment of sexual function. Treatment of the condition aimed at correcting the penile deformity is primarily surgical.

The European Medicine Agency has not previously approved any conservative therapy for the treatment of PD, whilst the European Association of Urology (EAU) guidelines state that studies on the conservative treatment for PD are often contradictory, making it difficult to provide recommendations in the everyday, real-life setting, with studies mostly uncontrolled, with limited numbers, short-term follow-up, and with different outcome measures used in assessment of efficacy [1].

Surgery is indicated when the disease has stabilised for at least 6 months and secondly if the deformity is severe enough to interfere with sexual activity. The aim of surgery is to correct

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Conflicts of Interest

Dr. Poullis has no conflicts to report. Dr. Eardley reports personal fees from LILLY, personal fees from ALLERGAN, personal fees from PFIZER, personal fees from MENARINI, personal fees from RECORDATI, outside the submitted work. Dr. Shabbir has received honoraria and funding for medical education from Lilly. Dr. Minhas received an honorarium from SOBI pharmaceuticals for his attendance at an educational symposium on Xiapex. Dr. John Mulhall has a consultant/advisor role in Lilly, Nexmed, Absorption Pharmaceuticals, AMS, Meda, and Vivus.

the curvature and allow penetrative intercourse. The two main surgical techniques used are penile shortening procedures, such as the Nesbit procedure or plication, and penile lengthening procedures, such as plaque incision and grafting, although both are associated with significant morbidity. The choice of surgical intervention is based on penile length assessment, nature and severity of the deformity, as well as erectile function. However, the potential risks with surgery (Nesbit and grafting) are penile shortening, erectile dysfunction, penile hypoaesthesia, risk of recurrent curvature, the potential for palpation of suture knots underneath the skin, and the need for circumcision at the time of surgery.

While surgery is effective at straightening the penis, it does not return it to its pre-morbid state. In view of the significant risks and morbidity associated with surgery, the search for an effective alternative non-invasive treatment has proved challenging. Over the decades, numerous treatments have been tried and tested; however, none of these has proven to be an effective or a reliable alternative to surgery.

The concept of directly treating the PD plaque has always been an attractive approach, although previous attempts have had mixed responses. In 1963, Keller and Mandl [2] identified collagenase purified from cultures of *Clostridium histolyticum* (CCH), as a cleaving enzyme of native collagen under physiological temperature and pH. Intralesional collagenase is the first USA Food and Drug Administration (FDA) approved drug for the treatment of PD and has recently been licensed in Europe and the UK. It selectively degrades collagen types I and III in connective tissues. As early as 1982, an open label trial reported that CCH significantly reduced the size of PD plaques, sparing elastic fibres, vascular smooth muscle, and axonal sheaths [3]. In the first prospective, randomised, double-blind, placebo-controlled trial of intralesional CCH, 49 men with PD were treated with CCH, resulting in significant improvements in plaque size and penile deformity [4]. All patients with a deformity of 30° and/or palpable plaque of <2 cm responded (three patients); 36% of patients with a penile curvature of 30 – 60° and/or a 2–4 cm palpable plaque improved; 13% with curvature $>60^\circ$ and/or plaque size >4 cm improved. Intralesional CCH was well tolerated, with no allergic reactions and no significant changes in laboratory parameters.

Over 15 years later, studies emerged on the use of CCH in Dupuytren's contracture including the Collagenase Option for Reduction of Dupuytren's (CORD) trial, published in the *New England Journal of Medicine* in 2009 by Hurst et al. [5]. This study demonstrated that the range of motion in joints was significantly improved after injection with collagenase when compared with placebo (from 43.9° to 80.7° vs from 45.3° to 49.5° respectively, $P < 0.001$). The most commonly reported adverse events were localised swelling, pain, bruising, pruritus, transient regional lymph-node enlargement, and tenderness. Three treatment-related serious adverse events were reported including two tendon ruptures and one case of complex regional pain syndrome.

A phase II trial reported on 25 patients with PD receiving three intra-lesional injections of 10 000 units of CCH over 7–10 days, with a repeat of injections and assessment at 3 months to review the change from baseline in penile deviation and plaque size [6]. A decrease in angulation of 25% was achieved in 58% of patients and 95% of patients had a reduction in

plaque size. More than 50% of patients in this series were ‘very much improved’ or ‘much improved’ at all-time points in the study. However, about one-third had minimal improvement or no change, and were reported as being ‘worse’.

In a further phase IIb trial, 147 patients with PD enrolled in a randomised, double-blind, placebo-controlled trial of CCH or placebo injection with a second randomisation to modelling or non-modelling [7]. Patients in the CCH plus modelling arm had a significant change in penile curvature compared with placebo, of 32.4% and 2.5%, respectively ($P < 0.001$). Those treated with CCH who underwent modelling also showed improved PD symptom bother scores ($P = 0.004$). However, in patients without modelling there were minimal differences noted between the active and placebo cohorts.

More recently, the phase III Investigation for Maximal Peyronie’s Reduction Efficacy and Safety Studies (IMPRESS) I and II trials examined the clinical efficacy and safety of CCH intra-lesional injections in comparison with placebo injection [8]. In all, 417 and 415 patients, respectively, were treated with a maximum of four cycles, each separated by 6 weeks. Men received four cycles of 0.58 mg CCH, two injections per cycle separated by ≈ 24 –72 h. After the second injection, penile plaque modelling was performed. Men were stratified by baseline penile curvature and randomised to CCH or placebo 2:1 in favour of active drug. A meta-analysis of IMPRESS I and II data revealed that men treated with CCH showed a mean 34% improvement in penile curvature, representing a mean (SD) change of -17.0 (14.8)° per patient, compared with a mean change of -9.3 (13.6)° per patient in the placebo group ($P < 0.001$). The mean (SD) overall change in PD symptom score was significantly greater in treated men vs placebo, at -2.8 (3.8) vs -1.8 (3.5) ($P = 0.004$). Maximal curvature reduction was seen in the 21–30° and 30–45° groups, with a percentage reduction of 42.7% and 25.5%, respectively. In contrast, the patients with 45–60° deformity had a 21% reduction of curvature, and in the 61–90° curvature group a 35.0% reduction versus 23.3% in placebo; ($P = 0.008$). However there was no statistical significance in the Peyronies Disease symptom bother.

Although serum antibodies to CCH developed in virtually all patients studied, there were no hypersensitivity or anaphylactic reactions. The most frequently noted side-effects were ecchymosis and local penile bruising. Serious adverse events were corporal rupture in three patients and penile haematoma in three patients. All corporal ruptures and one of the three penile haematomas were treated surgically, with a further haematoma drained percutaneously, although these patients may have had sex within the 2 week abstinence period.

Whilst these results are promising, the question is whether a mean curvature of reduction of 17° is functionally significant for the patient. It is generally accepted that a curvature of >30 –45° will inhibit penetrative intercourse and is an indication for surgical intervention. It could therefore be argued that at this degree of curvature, the collagenase injection could convert a curvature that prevents penetrative intercourse to one where intercourse is possible, assuming a mean curvature reduction of 17°. Furthermore, it may have a role in those men with more mild curvatures, that are not severe enough to justify surgery, but which do cause

cosmetic or psychological concerns for the patient. The degree of improvement in relation to initial curvature is shown in Fig. 1 [9].

A more difficult group are those with more severe curvatures ($> 60^\circ$). In these men, it could be argued that a curvature reduction of 17° may not be functionally significant and will not reduce the number of patients requiring surgical intervention. The range of curvature improvement in some patients was as high as 28° and those with high International Index of Erectile Function scores before treatment seem to achieve better results.

However, an interesting concept is whether a mean curvature reduction of 17° in men with more severe curvatures, who would normally be treated with plaque incision and grafting (according to the EAU guidelines) may be sufficient to allow the less morbid plication procedure to be performed, e.g. a Nesbit or plication procedure.

Intralesional CCH has a grade B recommendation by the EAU guidelines for the treatment of PD in men with a palpable plaque and a curvature deformity of $> 30^\circ$ at the start of therapy. CCH is available in the USA only through a restricted programme under a Risk Evaluation and Mitigation Strategy (REMS). CCH should be administered by a healthcare professional, who is experienced in the treatment of male urological diseases. The REMS requires participating healthcare professionals to be certified within the programme by enrolling and completing training in the administration of CCH treatment for PD. The REMS also requires healthcare facilities to be certified within the programme and ensure that CCH is used by certified healthcare professionals.

For overall costs to the NHS, the injections are £650 pounds (€850) per vial. Adding the £366 (soon to be £405 in 2016) per clinic attendance for injectable treatment and the cost of at least four injections, the sum is $>£4\,000$ (€5 600). If the whole course of eight injections is used, the cost would be $>£8\,000$ (€11 200). This is more than double compared with a tariff of £1 856 for a Nesbit procedure according to National Tariff 2015/16 (NHS England).

It may be that the treatment regimen will evolve with time and experience, especially as the maximum reduction in curvature in the IMPRESS trial was noted to occur after the first two treatments. Reducing the number of treatment cycles needed would make the treatment significantly more cost effective, although further clinical studies are needed to evaluate the cost benefits of this.

It therefore remains to be seen whether CCH will be introduced to the NHS, although the overall costs may be prohibitive. However, for those of us treating this difficult group of patients, it is clear that most patients will initially prefer to try a medical therapy with relatively low morbidity rather than a surgical intervention with its associated complications. CCH is currently the only alternative treatment to surgery in men with PD and in carefully selected patients appears to be of functional benefit.

Appendix

Item	Company	Applies to	Financial	Relationship type	Begin date	End date
1	Lily	Self	Yes	Consultant or advisor	01/01/2013	Present
2	Alliance for fertility preservation	Self	No	Leadership position	01/02/2013	Present
3	Nexmed	Self	Yes	Consultant or advisor	03/01/2012	Present
4	Absorption pharmaceuticals	Self	Yes	Consultant or advisor	01/01/2012	Present
5	AMS	Self	Yes	Consultant or advisor, scientific study or trial	01/01/2012	Present
6	Meda	Self	Yes	Consultant or advisor	01/01/2012	Present
7	Vivus	Self	Yes	Consultant or advisor, scientific study or trial	01/01/2012	Present
8	Association of Peyronie's disease advocates (APDA)	Self	No	Leadership position	01/01/2012	Present
9	Pfizer	Self	No	Scientific study or trial	01/01/2012	Present

Abbreviations

CCH	collagenase <i>Clostridium histolyticum</i>
EAU	European Association of Urology
PD	Peyronie's disease
REMS	Risk Evaluation and Mitigation Strategy

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Fig. 1.
Outcome in relation to degree of curvature (from Lipshultz et al. [9]).