Editorial

Collagenase clostridium histolyticum intralesional injections for the treatment of Peyronie's disease: a safety profile

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Peyronie's disease (PD) is a debilitating chronic condition associated with penile curvature, erectile dysfunction, pain, and emotional distress (1). The condition was first described in 1743 by Francois Gigot de la Peyronie, King Louis XV of France's physician (2). PD is a progressive condition characterised by fibrotic plaques within the tunica albuginea which can lead to pain and penile curvature (2). Non-surgical and surgical management options exist, with surgery often being offered in the most severe cases (1,3). Surgery carries the potential morbidity of penile shortening, neurovascular injury and erectile dysfunction (3).

Established non-surgical management of PD includes oral therapy, intralesional injections and mechanical traction therapy, although the efficacy of such treatments are variable and debatable (4). The levels of evidence for such studies are low and often have inherent flaws in design. For example, penile traction therapy has been suggested to improve penile curvature by 22 degrees and improvement in plaque load on ultrasonography (5). However, this study like others was a small non-randomised prospective study, with evidence for penile traction therapy being largely based on small, retrospective studies (2).

Scott & Scardino first described the use of Vitamin E as a non-surgical management of PD in the 1940s (2). Since then, studies have not shown evidence supporting the use of this as oral therapy. Hashimoto *et al.* published their retrospective study in 2006 demonstrating no statistically significant improvement in pain, penile curvature or erectile dysfunction in patients given Vitamin E compared to the placebo group (6). In 2007, Safarinejad *et al.* published their results from a double-blind randomized controlled trial, which showed no statistically beneficial effect of Vitamin E or propionyl-L-carnitine or the combination of both in treatment of PD (7). Phosphodiesterase Type 5 (PDE-5) inhibitors have also been suggested to improve penile curvature and plaque load, however, there is limited evidence for this and further level I evidence is needed to evaluate this (2).

Teasley first reported on the use of intralesional injection of corticosteroids in 1952, this has since been concluded to show no clinical benefit with low level of evidence behind it (2). Other injectable agents include verapamil and interferon alpha-2B, which have both been shown to potentially provide benefit from randomized controlled studies, although the number of patients in these studies is relatively small (2). These studies have highlighted the need for more robust clinical trials and the need for a more efficacious non-surgical treatment intervention for the treatment of PD.

More recently, Gelbard *et al.* published the results of the IMPRESS trial, reporting on the clinical efficacy of collagenase clostridium histolyticum (CCh) intralesional injections as a minimally invasive treatment option in PD (3). CCh is a purified mixture of AUX-I and AUX-II collagenases which act synergistically to enzymatically weaken the plaque in PD (3,8). CCh injections have been used in Dupuytren's contracture for some years now, which is followed by a finger extension procedure (3). This biologic agent was recently approved by the U.S. Food and

Drug Administration (FDA) for PD treatment in patients with a stable penile curvature of greater than 30 degrees and palpable plaques (8).

This trial was the largest double-blind, randomized, placebo-controlled multi-institutional trial of CCh use in PD involving 612 subjects. Subjects were stratified by degree of penile curvature (30–60, or 61–90 degrees) and randomized to the CCh or placebo group. Subjects who received anticoagulant medication, except for 165 mg aspirin daily or 800 mg of over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs) daily, during the 7 days prior to each injection were excluded (3). 0.58 mg of CCh or placebo was injected into the plaque at maximal point of curvature using a standard injection technique. A second injection was administered 24 to 72 hours later, after which investigators performed penile plaque modeling. The penis was stretched and elongated for 30 seconds (3). This treatment cycle was repeated for a further 3 times with 6-week periods in between, during which subjects were taught to perform home penile modeling 3 times a day (3).

The primary outcome reported was positive; the CCh treated group had a mean percent improvement in penile curvature of 34% (3). The placebo treated group showed a mean percent penile curvature improvement of 18.2% (3). The difference in percentage improvement was statistically significant, supporting clinical benefit with CCh (3).

With such promising results, it is important to consider the safety profile and tolerability of this non-surgical treatment, which is the first FDA-approved drug to be used in PD (9). Gelbard *et al.* reported that 84.2% (464/551) of subjects treated with up to 4 treatment cycles of CCh experienced local adverse effects; the most common ones being penile ecchymosis, penile swelling and penile pain (3). Investigators' assessment found that 79% of these local adverse effects resolved within 14 days without intervention (3). For further consideration are the treatment related serious adverse effect. Of the 551 subjects who received CCh injections, there were 3 cases of corporal rupture, all of which were repaired surgically. There were also 3 cases of penile haematomas; 1 required surgical exploration, 1 required aspiration of haematoma and 1 resolved spontaneously (3). By the end of 4 treatment cycles, at 52 weeks, the majority of subjects were found to have AUX-I and AUX-II antibodies but no systemic immunological events were reported (3). These reported complications from Gelbard *et al.* equate to a 1% risk of treatment related serious adverse effect and 0.7% risk of acquiring a serious adverse effect requiring surgical intervention.

To further explore the complications profile of this novel treatment of PD, we review the results of Yafi *et al.*'s survey published in The *Journal of Sexual Medicine* in 2016 (9). A total of 693 members of the Sexual Medicine Society of North America (SMSNA) were given an anonymous survey, with responders being asked to participate if they were prescribers of CCh (9). The survey obtained information on the prescriber's experience with CCh injections, techniques and management of treatment related serious complications.

Yafi *et al.* received 100 completed surveys from the SMSNA members; 59% of responders had performed 20 or fewer CCh injections and 41% had performed more than 20 (9). The study is questionnaire based and whilst highlighting the importance of pharmacovigilance, is limited in terms of interpretation of data but does provide some important information for the use of CCh in a community based study.

Regarding their techniques and management preference, 37% of prescribers did not apply any form of dressing to the penis following CCh injection (9). Fifty percent of responders instructed patients to remove their dressing on day 1 after the injection, with no responders instructing patients to keep dressings on for more than 2 days (9). About 54% of prescribers asked their patients to stop antiplatelets and anticoagulants prior to CCh injections but it is not stated how long prior to the injections that these medications are discontinued (9). Despite variation in dressings and antiplatelets or anticoagulant practice, all 100 prescribers stated to have encountered patients with a treatment related complication in the form of a severe haematoma (9). However, the majority of prescribers (94%) reported that a severe haematoma was rare, occurring in less than 25% of their patients (9). 65% of prescribers managed haematomas conservatively by observation, 20% of SMSNA members utilized compressive dressing alone and only a small portion of members, 2%, used haematoma drainage alone (9). Seventy nine of the 100 members would delay CCh injection when encountered by a severe haematoma (9) 89% of prescribers advised patients to perform manual modeling, in keeping with Gelbard's practice of penile plaque modeling (3,9). Of note, further analysis of prescribers responses found that the practice of dressings and discontinuation of antiplatelet and anticoagulant medications did not impact on the rates of haematoma formation (9). Therefore it is interesting to note that there was a wide variation post intervention protocols with no uniformity in practice.

Just over a third (34%) of SMSNA members encountered

corporal ruptures, which were mainly due to vigorous intercourse and nocturnal erections. This is in keeping with Gelbard *et al.*'s report of causes of corporal ruptures from CCh injections (3,9). Yafi *et al.*'s survey found that 94% of corporal ruptures occurred on the same side as the plaque or penile curvature, with 84% of ruptures found to be over the site of the plaque (9). Corporal ruptures commonly occurred after the second intralesional injection of each cycle and typically occurred 5 days following the second injection (9). Not surprisingly, many of the ruptures appeared to have occurred early after initiation of the treatment course, highlighting the need for patient counseling post treatment, although none of the ruptures occurred beyond 30 days. 67% of prescribers who encountered corporal ruptures managed them surgically; with median time from rupture to intervention being 10.5 hours (9). The majority of prescribers who surgically managed treatment related corporal rupture reported a poorer quality of tissue than expected (9).

Interestingly, there did not appear to be any ruptures beyond 30 days of treatment. The authors argue that more patients would appear to suffer from corporal rupture than previously reported, although they are unable to objectively quantify this using this type of questionnaire based study. The survey showed that there was no statistically significant difference in penile curvature or erectile function following surgical exploration of corporal rupture and observation, suggesting that rupture itself did not affect functional outcomes (9). However, there was a longer time lag for patients to resume intercourse after surgical repair when compared to conservative management of corporal rupture (9).

When compared to the IMPRESS trial results, Yafi *et al.*'s survey suggests that the occurrence of treatment related haematomas are higher than previously reported. This is also the case for corporal ruptures following intralesional injections. However, the results of the survey have not allowed us to make a direct comparison of numerical occurrences of these treatment related serious complications. There are several limitations in this study; namely the low response rate to the survey, hence size of the study and the reliability of retrospective subjective reporting. In addition, although there seems to be a higher rate of haematoma formation encountered by prescribers in Yafi *et al.*'s study, they have not defined the severe haematoma.

Established practice recommends early surgical intervention in cases of corporal rupture, or penile fracture. The meta-analysis published this year by Amer *et al.* showed that patients who underwent immediate surgical repair had a much lower risk of long term complications when compared to those who were managed conservatively (10). This was statistically significant regarding erectile dysfunction and penile curvature (10). However, when comparing emergent and delayed surgical repair, the difference in complication rate was not statistically significant. In the study of Yafi *et al.*, a significant number of patients (33%) with corporal rupture were managed conservatively and raises the issue of whether this had any deleterious long term functional effects. This of course has medical- legal implications, with the evidence within the literature advocating early surgical repair. In spite of this, most of the respondents would still manage ruptures surgically.

In our discussion here, we must consider whether the aetiology of corporal rupture, in this case following intralesional injection of CCh, affects decision-making. Yafi *et al.*'s survey found that the majority of prescribers who opted for surgical management of corporal rupture reported poor quality of tissue, which could impact on the quality of repair. Despite this, the long-term recovery between patients who underwent surgical repair compared to those who were managed by observation was not statistically different (9). From the evidence present, it is difficult to conclude whether this may be due to the fact that had those who underwent surgery been managed conservatively, their outcomes may have been less favourable.

Considering recent evidence, intralesional injection of collagenase clostridium histolyticum shows promise and hope for patients with PD as a non-surgical management option. However, like all other forms of treatment, it is not without a side effect profile (3,9). Gelbard *et al.* conducted the largest randomised controlled trial of this treatment, showing a risk of treatment related serious adverse effect of 1% but also confirming its clinical benefit. Yafi *et al.*'s smaller retrospective study suggests these serious complications may occur more frequently but there are several limitations to their study. What is also clear from this questionnaire based study is the wide variation in treatment protocols used. The reasons for this appear to be unclear and of course may be cost related.

The potential clinical benefit of intralesional CCh injection shows promise. However, the study from Yafi highlights the importance of pharmacovigilance and the need for more community based or "real world experience" of such treatments. In particular this relates to treatment emergent side effects.

Based on this study, patients should be counseled about potential complications, most importantly, the possible

increased risk of corporal rupture and haematoma (9). Patients should be warned against vigorous intercourse within the 14-day period following injection therapy and where possible, antiplatelet therapy and certainly anticoagulant medications should be ceased prior to injection. In terms of management of treatment related corporal rupture and haematomas, there is limited evidence at present but there is scope for larger studies to conclude on the best management option following CCh treatment as a significant number of patients were managed conservatively. For now, most surgeons involved with injection related corporal ruptures advocate surgical repair, in keeping with management of non-CCh related corporal ruptures.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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