Injection Therapy for Peyronie's Disease

22

Eric Shaw, Faysal A. Yafi, Premsant Sangkum, and Wayne J.G. Hellstrom

Introduction

Peyronie's disease (PD) is a sensitive topic for many patients and the medical community still lacks basic knowledge about this condition. PD is not a rare condition, as it has been reported that anywhere from 3.2 to 8.9 % of adult men have PD [1–3]. Similarly, it is not a novel condition, as it was named after the French surgeon Francois Gigot de LaPeyronie (LaPeyronie, fittingly, translates to "the little stone"), who lived in the 17th and 18th centuries and described PD in a treatise on ejaculatory failure [4]. For these reasons, PD has not received the medical attention it fully deserves.

PD is categorized into an early or acute phase, characterized by pain and progressive deformity, and a stable or chronic phase, characterized by diminished pain, organization of a plaque, and penile deformity with erection [5]. Any surgical correction should be postponed until there is stabilization of the deformity so that multiple interventions are not needed; theoretically, non-surgical treatment in the acute phase (e.g., with oral agents, traction therapy and intralesional injections) may prevent plaque organization and lessen eventual erectile deformity [6]. This chapter discusses intralesional injection therapy (ILI), which is one of many modalities in the treatment of PD. Focus is placed on the mechanism of action of the different pharmacologic agents described, the history of their use, specific indications or contraindications if applicable, common injection regimens, the most frequent and serious side effects, and the efficacy of particular treatments (Table 22.1).

Corticosteroids

While the exact pathophysiology of PD is yet to be elucidated, one proposed mechanism is that an inciting event (trauma or microtrauma to the penis, e.g., during sexual intercourse) causes local inflammation within the tunica albuginea, which in genetically susceptible men leads to abnormal wound healing characterized by fibrous plaque formation, and the physical manifestation of the disease [7, 8]. Corticosteroids were the first known ILI agent employed in the treatment of PD, with documented use as early as 1952 by Teasley [9]. Their use is rational when one

E. Shaw, MD • F.A. Yafi, MD
W.J.G. Hellstrom, MD, FACS (✉)
Department of Urology, Tulane Medical Center, 1430 Tulane Avenue, 86-42, New Orleans, LA 70112, USA
e-mail: eshaw@tulane.edu; faysalyafi@gmail.com; whellst@tulane.edu

P. Sangkum, MD
Department of Urology, Ramathibodi Hospital, 270 Rama VI Road, Bangkok 10400, Thailand
e-mail: premsanti@gmail.com

© Springer International Publishing Switzerland 2016

T.S. Köhler, K.T. McVary (eds.), *Contemporary Treatment of Erectile Dysfunction*, Contemporary Endocrinology, DOI 10.1007/978-3-319-31587-4_22

Table 22.1 Selected large single-agent intralesional injection therapy studies for Peyronie's disease

Authors	Year	Design	Therapy	*N*	Duration	Findings
Levine et al.	2002	Nonrandomized prospective	Verapamil 10 mg in 10 cc normal saline, ILI q 2 weeks × 12 injections	156	6 months	140 patients completed study. 62 % of patients with decrease in penile curvature (mean 31°, range 5–90), 8 % increase in penile curvature (mean 20°, range 20–45), and 30 % with no change in curvature.
Hellstrom et al.	2006	Randomized single blind, placebo controlled	Interferon a-2B 5 MU ILI q 2 weeks × 12 injections	117	3 months	Statistically significant improvement in patient's penile curvature (27 % mean curvature improvement in treatment arm vs. 9 % in placebo), plaque size (mean decrease of 55 % in treatment arm vs. 20 % in placebo), and pain with erections (68 % resolution of pain in treatment arm vs. 28 % in placebo) with interferon a-2B treatment. No statistically significant improvement in IIEF score (mean increase of 13 % in treatment arm vs. 6 % in placebo).
Gelbard et al.	2013	Randomized double blind, placebo controlled	Collagenase clostridium histolytiucm 0.58 mg ILI q24–72 h × 2 injections, every 6 weeks (maximum 8 injections total)	832	52 weeks	Statistically significant improvement in penile curvature in the treatment group (mean 34 %, corresponding to a $-17.0 \pm 14.8°$) as compared to control group (mean 18 % improvement in curvature, corresponding to a $-9.3 \pm 13.6°$ ($p < 0.001$)). Statistically significant improvement in the PD symptom bother domain score (treatment group mean improvement PD bother score is -2.8 ± 3.8 points), superior (statistically significant, $p = 0.0037$) to the control group (mean improvement -1.8 ± 3.5 points).

ILI intralesional injection therapy, *IIEF* International Index of Erectile Function, *PD* Peyronie's disease

considers steroids' long-known anti-inflammatory properties and their ability to suppress collagen formation [10]. In 1954, Teasley published a retrospective study of 24 patients that were treated with corticosteroids administered by ILI with promising results [11]. A number of subsequent studies, by Bodner in 1954 [12], Furey in 1957 [9], Desanctis in 1967 [13], Toksu in 1971 [14], Winter in 1975 [15], and Williams in 1980 [16], all described the use of corticosteroid by ILI in the treatment of PD. While these studies showed varying levels of improvement, these studies were small, nonrandomized, and, in general, of poor level of evidence [6]. Presently, ILI of corticosteroids is not recommended due to its unproven efficacy in treatment, and because it

causes local atrophy of tissue planes within the penis that makes subsequent surgical intervention more difficult [10].

Verapamil

After corticosteroids, the next pharmacologic agent utilized for ILI therapy of PD was the calcium channel blocker (CCB) verapamil. Fibrous PD plaques are composed of extracellular matrix (ECM) macromolecules such as collagen, glycosaminoglycans (GAGs), and fibronectin [17]. CCBs like verapamil have been shown to inhibit the secretion of these molecules, forming the theoretical basis of their use in treating PD [17]. They also have been hypothesized to increase the proteolytic activity of collagenase, the enzyme responsible for breaking down the collagen that characterizes PD plaques [18].

Verapamil was first used in 1994 on 14 patients in a dose-escalating study, starting with 1 mmol solution injected biweekly into the plaque via 100–150 plaque punctures with a 25 gauge needle (multi injection technique). The concentration of the drug was then doubled every month until a 10-milligram (mg) dose was achieved. The authors of the study noted subjective improvement in pain, penile curvature, and sexual performance in 91 %, 42 %, and 58 % of patients, respectively. Furthermore, the authors concluded that ILI of verapamil was safe, with no serious adverse events, with the only noted side effect being temporary ecchymosis at the injection site [17].

Subsequent studies of verapamil ILI were able to reproduce these early promising findings. In 1997, Levine published a follow-up study of 46 men with PD who were treated with 10 mg verapamil diluted to 10 cubic centimeters (cc) every other week for a total of 12 injections over 24 weeks. Importantly, this study not only demonstrated an objective improvement in curvature in 54 % of patients, but also an improvement in the ability to engage in coitus in 72 % of patients [19].

The first randomized placebo-controlled trial with ILI of verapamil took place in 1998 when Rehman et al. treated 14 men with either weekly injections of 10–27 mg verapamil ILI, or with a saline solution placebo [20]. At the end of 6 months the authors noted a statistically significant improvement in plaque volume, and a trend towards improvement in penile curvature, in the verapamil group as compared to placebo [20].

Levine et al. then published an uncontrolled study of 156 men with PD (140 of whom completed the therapy), treated again with injections of 10 mg verapamil in 10 cc saline solution injected every other week for 24 weeks. Again, a little over half of all patients who completed therapy had objective decrease in penile curvature [21].

Subsequent trials with verapamil ILI therapy, however, were less conclusive in their results. In 2007, Bennett et al. published an uncontrolled study of 94 patients with predominantly dorsal plaques who were treated with a course of six verapamil ILIs. They found that only 18 % of study subjects experienced improvement in their penile deformity, while 60 % had unchanged curvature, and 22 % experienced worsening of penile curvature. The only finding that proved statistically significant in the study was an improvement in penile rigidity adequate for intercourse [22]. The authors concluded verapamil injections were beneficial in stabilizing lesions, but that patients' expectations regarding treatment benefits need to be tempered.

In 2007, Cavallini et al. published a study of 77 patients randomized to receive different dilutions of verapamil ILI, concluding that the most dilute (and greatest volume) of verapamil solution (10 mg diluted in 20 cc solution) was more efficacious than the 10 mg given in 10 or 4 cc of solution. The study noted a statistically significant decrease in plaque area in all three groups, and a statistically significant improvement in penile curvature in the patients receiving the greatest volume of verapamil (i.e., the most dilute concentration of verapamil), though not in the other two groups receiving smaller volumes of less concentrated drugs [23].

In 2009, Shirazi et al. published a randomized controlled trial of 80 men with PD who were

treated in the same fashion as in Levine's original studies (10 mg verapamil in 10 cc normal saline (NS), given every other week for 24 weeks) and found no significant difference between the verapamil and NS control groups with regard to penile curvature, plaque size, or erectile dysfunction [24].

In 2010, Soh et al. published the first study looking at the ILI of a CCB other than verapamil in the treatment of PD. Specifically, the study utilized nicardipine, a dihydropyridine (DHP) CCB that, in vitro, was more effective than non-DHP CCB (e.g., verapamil) in reducing extracellular matrix production. The study was single-blind, placebo-controlled, and treated 37 men with PD to ILI of 10 mg of nicardapine dissolved in 10 cc of NS every other week for 12 weeks, and 37 men to ILI of 10 cc of NS in the same fashion. The authors found statistically significant improvement in pain score, International Index of Erectile Function (IIEF) score and decrease in plaque size at 48 weeks in the treatment arm versus placebo, but no significant difference in improvement in penile curvature between the two groups [25].

In 2011, Moskovic et al. published an uncontrolled study of 131 patients who received six injections of 10 mg of verapamil in 5 cc solution, examining baseline characteristics that could be used to predict efficacy of ILI therapy. The authors concluded that younger age and larger baseline curvature were significantly correlated with improvement in curvature with therapy [26].

While the above trials have treated men with PD with dorsal plaques, in 2015 Berookhim et al. described their institution's use of ILI of verapamil on 154 men with PD, of which 10 were treated with ventral plaques. They reported a similar efficacy of therapy in the patients treated with ventral plaques as those with dorsal plaques, with 40% of patients with ventral plaques reporting at least 10° improvement in curvature, 50% reporting stable curvature, and 10% reporting worsening of curvature. The authors conclude that verapamil ILI is safe to use for ventral plaques, so long as special attention is given to avoiding midline injections into the urethra [27].

Interferon

In 1991, Duncan et al. published a report on the effect of human recombinant interferons (IFNs) on cells cultured from PD plaques. The authors stated that these cells resembled myofibroblasts observed in wound healing and were responsible for collagen deposition and other ECM components including GAGs. They further hypothesize how these cells cultured from PD plaques are similar to fibroblasts seen in scleroderma and keloid lesions that are also postulated to cause excessive deposition of ECM components [28].

While Duncan et al. provided the theoretical basis for the use of IFN in the treatment of PD, in 1995 Wegner et al. was the first to perform ILI with IFN [29]. A total of 25 patients were treated with interferon a-2B (IFN a-2B), 1 million units (MU) given weekly for 5 weeks. The authors demonstrated improvement in plaque size in 7 patients, stability of plaque size in 12 patients, and increase in plaque size in 6 patients. They concluded the drug was safe, with the most common side effects being myalgia and fever seen in 4 of the 25 patients. They also noted that the treatment appeared to be more efficacious in early plaque lesions and in patients without evidence of calcifications, and suggested that further dosing studies were needed [29].

In 1997, Wegner published a new series involving 30 additional men with early PD treated with ILI INF a-2B 3 MU weekly for 3 weeks, and concluded that their regimen was not an effective treatment, since approximately 25% of men had progression of the disease with IFN therapy, and an intolerable side effect profile that caused fevers greater than 38 °C after 74 of the 90 total injections [30].

That same year, however, Judge et al. published a series of 13 men treated with either INF a-2B 1.5 MU, three times weekly for 3 weeks (10 of 13 patients), or treated with same regimen of NS ILI (3 of 13 patients). The authors found 6 of the 10 patients treated with IFN had reduction in their pain with erections and had improvement in their degree of curvature (mean improvement 20°), while none of the patients treated with NS had improvement in these respective categories.

They also noted the most common side effect in the treatment group was a transient flu-like illness, though stated it lessened with each subsequent injection, and was often controlled by taking 1 g of oral paracetamol after receiving the injection [31].

Subsequent small-scale studies continued to produce more promising results. A study by Ahuja et al. in 1999 reported on 21 patients treated with IFN a-2B 1 MU biweekly for 6 months, and found statistically significant reduction in pain, penile curvature, and plaque size in treated patients [32]. Another study by Dang et al. in 2004 looked at 21 patients treated with injections of IFN a-2B 2 MU twice weekly for 6 weeks. Of these 21 patients, 7 patients received a 6-week course of NS ILI twice weekly prior to starting IFN a-2B ILI therapy. The authors found significant improvements in penile pain and curvature in the majority of patients after treatment with IFN a-2B ILI therapy. They also noted that subjective improvements in pain and erectile curvature were not seen in the saline control group prior to beginning IFN therapy [33].

In 2005, Kendirci et al. published the first randomized, placebo-controlled trial with intralesional IFN on 39 patients, of which 19 were treated with IFN a-2B 5 MU every other week for six injections, and 20 patients with 10 cc NS ILI every other week for six injections. The study is notable not only for the increased dose of IFN a-2B that subjects received (5 MU per injection as compared to 3 MU or less in previous studies), but also in that it examined the effect that IFN a-2B ILI therapy had on penile hemodynamic parameters. The authors observed that, in addition to improving penile curvature, decreasing plaque size, and decreasing pain with erections, IFN a-2B ILI therapy also improved penile hemodynamics (31.5 % of patients with nonvascular penile blood flow prior to ILI therapy versus 57.8 % after treatment). This improvement in penile blood flow did not, however, correspond with a significant improvement in erectile function in the treatment group [34].

In 2006, the largest IFN a-2B study to date was published. Hellstrom et al. performed a single-blind, placebo-controlled, randomized study of IFN a-2B ILI, with 55 patients receiving IFN a-2B ILI 5 MU in 10 cc NS every other week for 12 weeks, versus 62 patients randomized to receive the same dosing of NS ILI control. Not only was this trial notable for its size, but also for its comprehensiveness. Patients were evaluated for pre- and post-intervention penile curvature, plaque size, pain with erections, as well as erective function, as measured by the patient's IIEF score. Again, there was statistically significant improvement in patient's penile curvature (27.01 % mean curvature improvement in treatment arm versus 8.87 % in placebo), plaque size (mean decrease of 54.6 % in treatment arm versus 19.8 % in placebo), and pain with erections (67.7 % resolution of pain in treatment arm versus 28.1 % in placebo) with IFN a-2B treatment. The study did not find a statistically significant improvement in IIEF score after 12 weeks of injections (mean increase of 13.53 % in treatment arm versus 5.96 % in placebo). Hellstrom et al. concluded IFN a-2B was an effective minimally invasive, and generally well-tolerated, intervention in the treatment of PD [35].

More recently, Trost et al. published a series reviewing 127 patients treated with IFN a-2B ILI from 2001 to 2012 at a single institution. Patients were treated with IFN a-2B 2 MU biweekly for a median number of 12 injections. Again, erectile function and penile hemodynamics were studied before and after receiving IFN a-2B ILI therapy. Of the 127 patients, 54 % responded to therapy with an average improvement in erectile curvature of 9°, while 10.2 % of patients had progression of their disease while on IFN therapy, and 18.9 % of patients had stability of their disease. The trial was significant in that it showed equivalent outcomes regardless of when therapy was initiated (acute setting versus chronic), and in that it showed no improvement in patients treated with two courses of IFN a-2B ILI injections as opposed to one course of 12 injections with IFN a-2B. In addition, the trial reproduced the results from previous trials showing that IFN a-2B ILI improved penile hemodynamics without a corresponding improvement in erectile function [36]. It is also worth noting that at our institution, IFN a-2B ILI has been safely used on patients with ventral PD plaques with rates of efficacy similar as to patients treated with dorsal PD plaques.

Collagenase

Although ILI of collagenase clostridium histolyticum (CCH) was only FDA approved for the treatment of PD in 2013, its potential role in the treatment of PD was first examined almost 30 years prior. In 1982, Gelbard et al. published in vitro studies of CCH applied to tunica albuginea and PD plaque tissue samples. The authors concluded that CCH was effective in the dissolution of both normal tunica albuginea and the intended PD plaques. However, they went on to state that there was very limited dispersion of the enzyme from its applied site, and that elastic tissues were preserved. Most importantly, CCH did not digest vascular smooth muscle cells, a property that protects all penile vasculature with the exception of the small venules. This same property also prevents nerve axons from being degraded, as their myelin sheaths are comprised of lipids not digested by CCH [37].

First used in the treatment of PD in 1980s, CCH was not pursued again in the treatment of PD until quite recently. In 1985, Gelbard et al. published a report of 31 patients treated with 420–920 U of purified CCH enzyme given in 1 cc solution. As this was the first time CCH was used in the treatment of PD, its immunologic affects were unknown and the researchers decided to administer the drug on 3 consecutive days in order to limit the risk of a theoretical hypersensitivity reaction. Gelbard et al. concluded that 65 % of the patients had objective improvement in the deformity of their disease, and pain with erection was eliminated in 93 % of patients. They also noted that the injections appeared safe for use without systemic side effects, with the most serious side effect being a small corporeal wall rupture at the site of injection that occurred in one patient [38].

The first randomized, double-blind, placebo-controlled trial using intralesional CCH was published in 1993 by Gelbard et al. Subjects were injected with a one-time dose of 6000–14,000 U of CCH depending on the severity of their erection deformity, and were followed for 3 months to assess treatment response. The researchers discovered the injections to be safe, but only able to improve penile curvature by approximately 20°, and thus concluded CCH to be most effective for patients with less severe curvatures [39].

In 1998, Jordan published a study of 25 men with PD treated with three injections of 10,000 U of collagenase given over 7–10 days, and repeated with three additional ILI at 3 months. The authors found statistically significant improvement in penile deformity (mean improvement of 12.7° at 3 months), and again noted the injection to be generally well tolerated, with the most common adverse events being penile pain, edema and ecchymosis at the site of injection [40].

In 2010, intralesional CCH was approved for the treatment of Dupuytren's contracture in patients with a palpable cord, and there was renewed interest in using CCH in the treatment of PD [41]. As such, in September 2010 a number of centers in the USA began accruing patients for two large, identical, phase 3 studies (randomized, double-blind, placebo-controlled) named IMPRESS I and II (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) with 417 and 415 patients enrolled, respectively. The treatment arm of the studies involved a maximum of four treatment cycles of CCH ILI 0.58 mg, each cycle consisting of two ILI given 24–72 h apart, followed by penile plaque modeling 24–72 h after the last injection. Therapy was discontinued if the penile curvature was decreased to less than 15°, or if the investigator deemed further treatment to be not clinically indicated. Exclusion criteria in IMPRESS I and II were patients with calcified plaques and/or ventral lesions. In addition, patients were required to have at least a 30° curvature with erections to be eligible for the trial [42].

The study reported a mean improvement in penile curvature in the treatment group of 34 %, corresponding to a $-17.0 \pm 14.8°$. This was found to be significantly superior to the control group, who on average saw an 18.2 % improvement in curvature, corresponding to a $-9.3 \pm 13.6°$ ($p < 0.001$). In addition, the researchers observed a statistically significant improvement in the PD symptom bother domain score, which is comprised of four questions and whose total score can range from 0 to 16. In the treatment group the average PD bother score improvement was

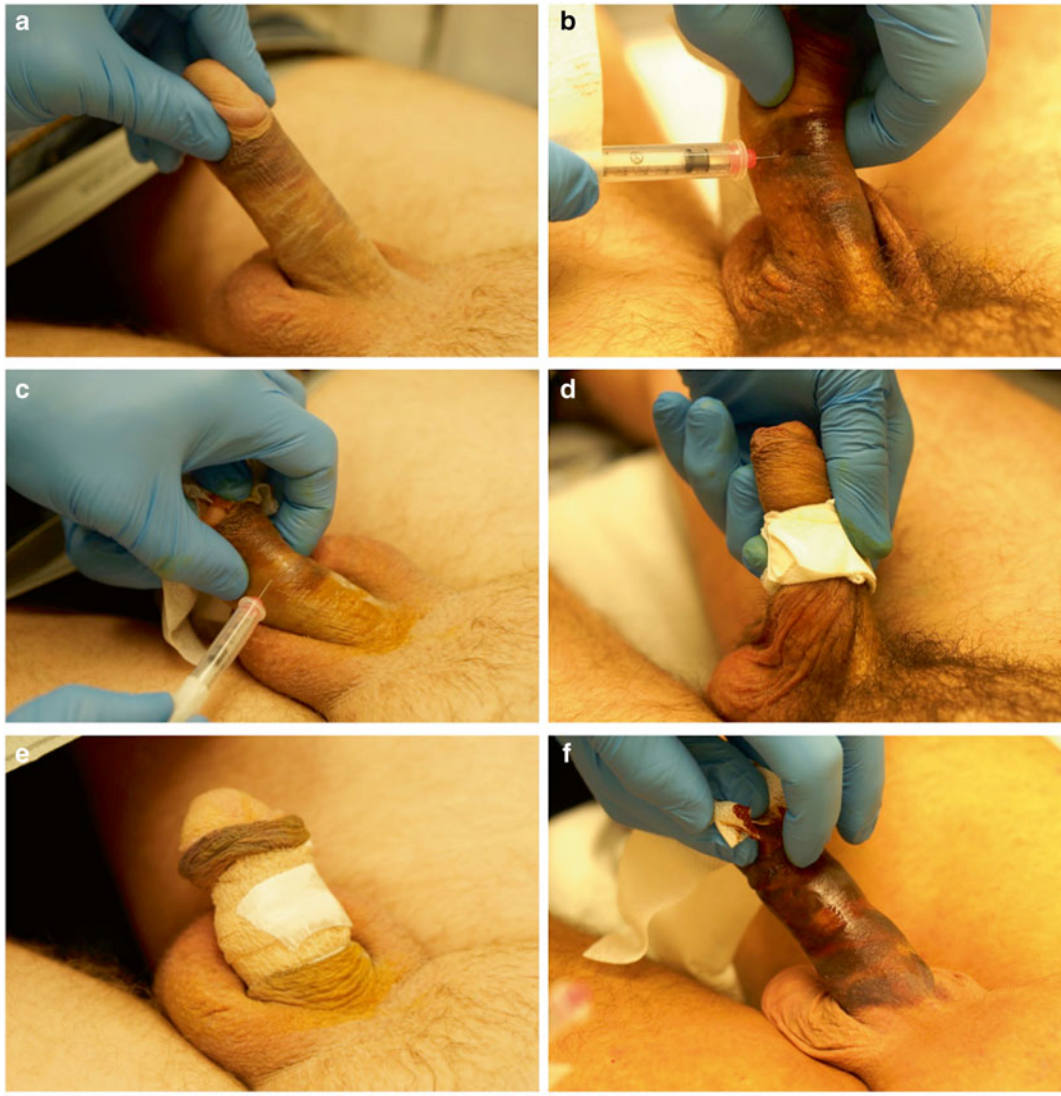

Fig. 22.1 (**a**–**f**) Intralesional injection of collagenase clostridium histolyticum for Peyronie's disease. (**a**) Penis is held in straight position and prepped in a sterile manner. (**b** and **c**) Using a 27-gauge 1⁄2-in. needle, 0.58 mg CCH (0.25 ml) is injected into the Peyronie's plaque in alignment with the point of maximal concavity. The needle should not go beneath the plaque or perpendicularly towards the corpora cavernosa. (**d**) Following injection, the penis is first wrapped with sterile gauze. (**e**) Then wrapped with a Coban dressing. (**f**) Example of a penile hematoma that can occur after injection

−2.8 ± 3.8 points, which was superior (statistically significant, $p = 0.0037$) to the control group that changed −1.8 ± 3.5 points [42].

As a result of the study, on December 6, 2013 the FDA approved collagenase for the treatment of PD with the above indications and contraindications [43]. Figure 22.1a–f shows photos of ILI of CCH for PD.

Penile Traction Therapy with ILI

While this chapter focuses on intralesional therapies in the treatment of PD, there are a number of trials that use combination of intralesional, oral, and penile traction therapies (PTT), among other treatment modalities. This section aims to focus

on PTT, which has been used in combination with a number of ILI studies.

In 2008, Abern and Levine published a pilot study looking at verapamil ILI with and without concurrent PTT. They described treating 44 patients with verapamil ILI alone, and 27 patients who received the same regimen of verapamil ILI and who, in addition, elected to wear a FastSize Penis Extender (FastSize LLC, Aliso Viejo, CA, USA) 2–8 h per day. The authors looked at subjective improvements in curvature, and found a trend toward benefits in the combination therapy, though without statistical significance. They concluded future studies with post-treatment Doppler ultrasound were needed to objectively assess the added utility of PTT to verapamil ILI [44].

Abern et al. published such a study investigating the added utility of PTT in 2012, in which 74 men were treated with verapamil 10 mg dissolved in 10 cc NS ILI administered every other week for 24 weeks. In addition, patients were treated with oral L-arginine 1 g twice daily and oral pentoxifylline 400 mg three times daily. Finally, all patients were offered PTT, of which 39 patients decided to pursue as part of their treatment. Patients receiving PTT obtained an external penile extender (US PhysioMED, Irvine, CA, USA) and were instructed to wear the device anywhere from 2 to 8 h per day, in sessions no longer than 2 h at a time with at least 15 min between sessions. They were also instructed to add 0.5 centimeter (cm) spacers to the device every 2–3 weeks as tolerated [45].

At the end of 24 weeks, the researchers found that the patients in the PTT group, on average, wore the device for 3.3 h per day. While both groups of patients had statistically significant improvement in degree of curvature from baseline, the PTT also had a trend towards increased stretched penile length (SPL) from baseline (on average 0.3 cm, $p=0.06$), which was not observed in the non-PTT group. The authors acknowledge that selection bias and the nonrandomized nature of the study may have influenced results of the trial, and suggest a future study comparing ILI alone, to PTT alone, to ILI with PTT, would show whether ILI and PTT are synergistic in nature [45].

A retrospective review of patients treated with IFN a-2B evaluated the concomitant use of PTT (Andropenis®, [Andromedical, Spain]) with ILI-a2B. Yafi et al. examined 112 patients who had documented information regarding use of PTT. Of those patients, 31 % reported using PTT at least 2 h per day on a "regular basis." They were able to show a statistically significant gain in SPL in those patients who used PTT for greater than 3 h per day as compared to those not using PTT (4.4 mm versus 1.3 mm, $p=0.04$), concluding that PTT may offer a small but meaningful improvement in SPL if used diligently [46].

Other Therapies

One of the challenges in deciphering the numerous trials for treating PD is the large variety of combination therapies that have been employed. This highlights the fact that a definitive minimally invasive or oral treatment for the disease is yet to be discovered. Combination therapies generally combine different modalities of treatment, including oral therapies, iontophoresis, extracorporeal shock wave therapy, PTT, transdermal electromotive therapy, and topical administration therapy. Trials using multimodal therapy have generally been small, often are not randomized, and thus make it difficult to attribute benefits of therapy to a particular agent used in the treatment regimen, especially considering the natural history of the disease that can at times improve without any treatment at all. Table 22.2 lists some of the combinations therapies that have been employed.

Future Therapies

The intralesional therapies outlined in this chapter offer patients minimally invasive treatment options for treating their disease with minimal risk and beneficial, reproducible results. To this day, the gold standard for treating PD is surgery, which comes with its own set of risks both during the actual procedure (e.g., risk of anesthesia, bleeding, and infection) and in its aftermath (e.g., disease recurrence, erectile dysfunction, loss of

Table 22.2 Selected combination therapy studies for Peyronie's disease

Authors	Year	Design	*N*	Therapy	Duration	Outcomes
Paulis et al.	2013	RCT- unblinded, placebo controlled	70	Vitamin E 600 mg po daily + verapamil 10 mg ILI q 2 weeks (5 mg ILI given for the first ILI) + 5 mg verapamil iontophoresis daily + blueberry extract 160 mg po daily (36 % anthocyanosides) + propolis 600 mg po daily + topical diclofenac sodium 4 % gel bid versus above treatment without vitamin E	6 months	Statistically significant improvement in plaque size, curvature, and IIEF score (in patients with comorbidities and ED) in patients receiving vitamin E
Paulis et al.	2013	RCT- unblinded, placebo controlled	64	Peironimev-plus oral 1 tab daily + verapamil 10 mg ILI q 2 weeks + verapamil iontophoresis 5 mg 3 × week versus above treatment without oral therapy	6 months	Statistically significant improvement in penile curvature and symptom bother score in treatment arm
Mehrsai et al.	2012	RCT- unblinded	60	10 mg verapamil and 4 mg dexamethasone in 2 mL DW ILI weekly versus 10 mg verapamil and 4 mg dexamethasone in 2 mL DW TEA	6 weeks	No statistically significant improvement in plaque size, penile curvature, or erectile dysfunction. Statistically significant improvement in pain in the TEA group, greater than ILI group
Cavallini et al.	2012	RCT- single blind, placebo controlled	43	Verapamil 10 mg in 20 cc NS ILI q 2 weeks + testosterone 30 mg buccal patch bid versus verapamil ILI without testosterone replacement	6 months	Greater improvement in plaque area and penile curvature when ILI associated with testosterone supplementation
Abern et al.	2011	Nonrandomized trial- unblinded, placebo controlled	74	Verapamil 10 mg in 10 cc solution q 2 weeks + L-arginine 1 g po bid + pentoxifylline 400 mg po tid + PTT versus above with no PTT	6 months	No statistically significant improvement in PTT group versus control. Trend toward improved stretched penile length in PTT group

RCT randomized controlled trial, *ILI* intralesional injection therapy, *TEA* transdermal electromotive administration, *PTT* penile traction therapy, *IIEF* International Index of Erectile Function

sensation, loss of penile length, and device failure or erosion). The advent of stem cell therapy in the treatment of PD may someday obviate the need for surgical correction of the disease. And while "future therapies" at the time of this publication will quickly become dated, the following section aims to give readers a brief history of regenerative medicine as it pertains to PD, and, in doing so, hopefully some idea of where the field may be headed in the future.

While the promise of stem cell therapy is great, there are still many obstacles to its implementation. One basic problem is the lack of a universally accepted animal model to use in its research [47]. To date, most studies have utilized a murine model, and have used an injection of thrombin, thrombin and fibrin, or transforming growth factor beta-1 (TGF-β1) into the tunica albuginea of the study animal in order to recreate the disease [47–49]. However, researchers readily

admit that PD in humans is not completely understood and likely much more complex than our current animal models, and thus findings in these animal studies may not perfectly translate into human therapies [50].

With that being said, exciting research is taking place with regard to adipose tissue-derived stem cells (ADSCs) in the treatment of PD. ADSCs are one type of multipotent stromal cells (MSC), which can be derived from numerous other tissue sources including bone marrow, liver, muscle, amniotic fluid, placenta, umbilical cord blood, and dental pulp [51]. MSC are thought to be at least in part responsible for the regeneration of their respective tissues, a desirable property in treating a disease state characterized by abnormal tissue [48]. Specific advantages to adipose-derived MSCs (aka. ADSCs) are their abundance, their ease of harvesting, and their low processing costs [52]. In addition, ADSCs are not burdened by the ethical issues that surround the use of embryonic stem cells [48]. Finally, they have immunosuppressant properties that allow for allogeneic or even xenogeneic transplantation without creating a graft-versus-host disease [53].

An early study involving ADSCs did not pertain to PD specifically, but instead looked at how the intracavernosal injection of ADSCs may improve the endothelial and neural abnormalities responsible for hyperlipidemia-associated ED. In 2010, Huang et al. fed 28 Sprague-Dawley rats a high-fat diet that had been previously shown to induce impaired penile hemodynamics mimicking an ED state. The authors then harvested paragonadal fat in these rats, procured ADSC from this tissue, cultured it, and reinjected it into the corpus cavernosa of the treatment group of rats. They found improved erectile function in the rats treated with ADSCs, concluding that future studies were needed to look at the exact mechanism of action of the therapy, as well as the dosing, safety (especially with respect to possible increased risk of tumor formation), and durability of treatment, before human trials could even be considered [54].

In 2013, Castiglione et al. published a study evaluating the use of ADSCs in the treatment of the active phase model of PD in 12-week-old Sprague-Dawley rats. The authors separated 27 male rats into three groups, one group a sham PD model receiving ADSC treatment, one group the active PD model (via injection of TGF-β1) receiving ADSC treatment, and one group the active PD model without ADSC treatment. The authors concluded that the local injection of ADSCs prevents formation of fibrosis and elastosis in an animal model of PD. Self-described limitations to their study include an imperfect animal model, and the fact that they examined the treatment of PD in its active, inflammatory phase as opposed to the chronic state most commonly seen on presentation [52].

Also in 2013, Gokce et al. published a report looking at the use of ADSC in a rat model of PD. Again Sprague-Dawley rats (24 in total) were used, and again TGF-β1 was injected into the rat tunica albuginea in order to simulate the PD condition. The study was unique in that it had studied ADSC therapy both in the prevention and in the treatment of PD. In addition, the authors correlated their results with histological findings from tunica albuginea specimens from the sacrificed rats, concluding that in severe penile fibrosis there is increased gene expression of profibrotic tissue inhibitors of metalloproteinases (TIMPs), and decreased gene expression of antifibrotic matrix metalloproteinases (MMPs). Gokce et al. concluded that ADSCs were beneficial both in the prevention and the treatment of tunica albuginea fibrosis and erectile dysfunction in an animal model of PD [50].

AUA Update on Peyronie's Disease

In April 2015, the AUA approved new guidelines for the diagnosis and treatment of PD [55]. Within the guidelines, there were six statements specific to injection therapy of PD. Guideline Statements 8, 10, and 12 refer to the use of intralesional collagenase, interferon alpha, and verapamil in the treatment of PD, respectively. Guideline Statements 9, 11, and 13 address the need for clinicians to counsel their patients regarding the side effects of these treatments.

Guideline Statement 8 states that intralesional collagenase clostridium histolyticum may be used to treat patients with stable PD with curvature between 30° and 90°, and intact erectile function. It notes that the drug has only been studied in patients with dorsal plaques, and emphasized that collagenase does not treat pain associated with PD, or treat erectile dysfunction. It also recommends that patients be counseled regarding expectations of treatment. Specifically, the guidelines cited the IMPRESS I and II trials in which the average reduction in curvature in the collagenase treatment arm at 1 year was 17°, while the average decrease in the placebo arm at 1 year was 9.7°. The statement evidence strength of Guideline Statement 8 was Grade B, as it was based on high quality randomized controlled trials (RCTs), but the findings of the trial have yet to be reproduced.

Guideline Statement 10 deals with the use of IFN a-2b in the treatment of PD. It reads that clinicians, "may administer intralesional IFN a-2b" to PD patients, noting that, based on the single RCT, it was used on patients with stable curvature greater than 30° and without calcified plaques. It also states that IFN a-2b may be beneficial in treating curvature, plaque size, pain, and some vascular outcomes. Finally, it emphasizes that patients should be advised that average improvement in penile curvature was 13.5°. The strength of the evidence was Grade C, as the panel noted there was only one RCT of "moderate" quality and "somewhat divergent" findings in the other studies looking at treatment with interferon.

With regard to verapamil, Guideline Statement 12 gives intralesional therapy with the drug a conditional recommendation. The panel emphasizes that the majority of trials using intralesional verapamil failed to have appropriate control groups, especially considering the natural history of PD with spontaneous resolution in a minority of cases. It states clinicians should, "carefully consider" the appropriateness of this treatment modality given its uncertain efficacy and availability of other treatment that are "clearly more effective." It rates the strength of evidence Grade C, based on the conflicting findings from the two RCTs with intralesional verapamil, the lack of appropriate control groups in many of the studies, and the lack of replicated studies confirming results from the published trials.

Guideline Statements 9, 11, and 13 all consider the potential complications of the above treatments. The statements instruct clinicians to counsel patients regarding the risks of specific adverse events particular to each intralesional therapy. With regard to intralesional collagenase, Guideline Statement 9 describes common adverse events to include penile ecchymosis, penile swelling, and penile pain. These events occurred in 80.0 %, 55.0 %, and 45.4 % of patients, respectively, during the IMPRESS I and II trials. Serious adverse events occurred in 1.1 % of collagenase-treated patients during these trials, in the form of penile hematoma and corporal rupture.

The most common adverse events associated with intralesional interferon treatment include sinusitis, flu-like symptoms (e.g., fevers, chills, arthralgia), and minor penile swelling and ecchymosis. Guideline Statement 11 states these adverse events occur in 40–100 % of patients, and are self-limiting. It suggests these adverse events can be mitigated with oral hydration, and treated with over-the-counter, nonsteroidal, anti-inflammatory medications.

Finally, the potential adverse events of intralesional verapamil are perhaps the least severe and most vague. Guideline Statement 13 states that patients should be counseled regarding possible penile bruising, dizziness, nausea, and pain at the injection site.

Summary

There is much to learn about Peyronie's disease. Its true prevalence, detailed pathophysiology, and best combination of treatment even among existing therapies are all yet to be defined. Intralesional injection therapy with calcium antagonists, interferon, or collagenase clostridium histolyticum is a minimally invasive treatment modality that is proven safe and reasonably effective in the treatment of PD. Intralesional injection therapy with stem cells, while still in its infancy, offers hope for a more targeted treatment of the disease in the future.

References

1. Mulhall JP, Creech SD, Boorjian SA, Ghaly S, Kim ED, Moty A, et al. Subjective and objective analysis of the prevalence of Peyronie's disease in a population of men presenting for prostate cancer screening. J Urol. 2004;171(6):2350–3.
2. Schwarzer U, Sommer F, Klotz T, Braun M, Reifenrath B, Engelmann U. The prevalence of Peyronie's disease: results of a large survey. BJU Int. 2001;88(7): 727–30.
3. Rhoden EL, Teloken C, Ting HY, Lucas ML, Teodósio da Ros C, Ary Vargas Souto C. Prevalence of Peyronie's disease in men over 50-y-old from Southern Brazil. Int J Impot Res. 2001;13(5):291–3.
4. Dunsmuir WD, Kirby RS. Francois de LaPeyronie (1678–1747): the man and the disease he described. Br J Urol. 1996;78(4):613–22.
5. Mulhall JP, Schiff J, Guhring P. An analysis of the natural history of Peyronie's disease. J Urol. 2006;175(6):2115–8. discussion 2118.
6. Russell S, Steers W, McVary KT. Systematic evidence-based analysis of plaque injection therapy for Peyronie's disease. Eur Urol. 2007;51(3):640–7.
7. Moreland RB, Nehra A. Pathophysiology of Peyronie's disease. Int J Impot Res. 2002;14(5): 406–10.
8. Taylor FL, Levine LA. Non-surgical therapy of Peyronie's disease. Asian J Androl. 2008;10(1): 79–87.
9. Furey CA. Peyronie's disease: treatment by the local injection of meticortelone and hydrocortisone. J Urol. 1957;77(2):251–66.
10. Levine LA. Review of current nonsurgical management of Peyronie's disease. Int J Impot Res. 2003;15 Suppl 5:S113–20.
11. Teasley GH. Peyronie's disease; a new approach. J Urol. 1954;71(5):611–4.
12. Bodner H, Howard AH, Kaplan JH. Peyronie's disease: cortisone-hyaluronidase-hydrocortisone therapy. J Urol. 1954;72(3):400–3.
13. Desanctis PN, Furey CA. Steroid injection therapy for Peyronie's disease: a 10-year summary and review of 38 cases. J Urol. 1967;97(1):114–6.
14. Toksu E. Peyronie's disease: a method of treatment. J Urol. 1971;105(4):523–4.
15. Winter CC, Khanna R. Peyronie's disease: results with dermo-jet injection of dexamethasone. J Urol. 1975;114(6):898–900.
16. Williams G, Green NA. The non-surgical treatment of Peyronie's disease. Br J Urol. 1980;52(5):392–5.
17. Levine LA, Merrick PF, Lee RC. Intralesional verapamil injection for the treatment of Peyronie's disease. J Urol. 1994;151(6):1522–4.
18. Roth M, Eickelberg O, Kohler E, Erne P, Block LH. Ca^{2+} channel blockers modulate metabolism of collagens within the extracellular matrix. Proc Natl Acad Sci U S A. 1996;93(11):5478–82.
19. Levine LA. Treatment of Peyronie's disease with intralesional verapamil injection. J Urol. 1997;158(4): 1395–9.
20. 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(4): 620–6.
21. Levine LA, Goldman KE, Greenfield JM. Experience with intraplaque injection of verapamil for Peyronie's disease. J Urol. 2002;168(2):621–6.
22. Bennett NE, Guhring P, Mulhall JP. Intralesional verapamil prevents the progression of Peyronie's disease. Urology. 2007;69(6):1181–4.
23. Cavallini G, Modenini F, Vitali G. Open preliminary randomized prospective clinical trial of efficacy and safety of three different verapamil dilutions for intraplaque therapy of Peyronie's disease. Urology. 2007;69(5):950–4.
24. Shirazi M, Haghpanah AR, Badiee M, Afrasiabi MA, Haghpanah S. Effect of intralesional verapamil for treatment of Peyronie's disease: a randomized single-blind, placebo-controlled study. Int Urol Nephrol. 2009;41(3):467–71.
25. Soh J, Kawauchi A, Kanemitsu N, Naya Y, Ochiai A, Naitoh Y, et al. Nicardipine vs. saline injection as treatment for Peyronie's disease: a prospective, randomized, single-blind trial. J Sex Med. 2010;7(11): 3743–9.
26. Moskovic DJ, Alex B, Choi JM, Nelson CJ, Mulhall JP. Defining predictors of response to intralesional verapamil injection therapy for Peyronie's disease. BJU Int. 2011;108(9):1485–9.
27. Berookhim B, Chevinsky M, Jakubowski C, Larish Y, Nelson CJ, Mulhall JP. Ventral intralesional verapamil injections for Peyronie's disease: feasibility and safety. Abstract accepted for 20th Annual Fall Scientific Meeting of SMSNA, Miami, FL; November 20–23, 2014.
28. Duncan MR, Berman B, Nseyo UO. Regulation of the proliferation and biosynthetic activities of cultured human Peyronie's disease fibroblasts by interferons-alpha, -beta and -gamma. Scand J Urol Nephrol. 1991;25(2):89–94.
29. Wegner HE, Andresen R, Knipsel HH, Miller K. Treatment of Peyronie's disease with local interferon-alpha 2b. Eur Urol. 1995;28(3):236–40.
30. Wegner HE, Andresen R, Knispel HH, Miller K. Local interferon-alpha 2b is not an effective treatment in early-stage Peyronie's disease. Eur Urol. 1997;32(2):190–3.
31. Judge IS, Wisniewski ZS. Intralesional interferon in the treatment of Peyronie's disease: a pilot study. Br J Urol. 1997;79(1):40–2.
32. Ahuja S, Bivalacqua TJ, Case J, Vincent M, Sikka SC, Hellstrom WJ. A pilot study demonstrating clinical benefit from intralesional interferon alpha 2B in the treatment of Peyronie's disease. J Androl. 1999; 20(4):444–8.
33. Dang G, Matern R, Bivalacqua TJ, Sikka S, Hellstrom WJG. Intralesional interferon-alpha-2B injections for the treatment of Peyronie's disease. South Med J. 2004;97(1):42–6.
34. Kendirci M, Usta MF, Matern RV, Nowfar S, Sikka SC, Hellstrom WJG. The impact of intralesional

interferon alpha-2b injection therapy on penile hemodynamics in men with Peyronie's disease. J Sex Med. 2005;2(5):709–15.
35. Hellstrom WJG, 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 α-2b for minimally invasive treatment for Peyronie's disease. J Urol. 2006;176(1):394–8.
36. Trost LW, Ates E, Powers M, Sikka S, Hellstrom WJG. Outcomes of intralesional interferon-α2B for the treatment of Peyronie disease. J Urol. 2013; 190(6):2194–9.
37. Gelbard MK, Walsh R, Kaufman JJ. Collagenase for Peyronie's disease experimental studies. Urol Res. 1982;10(3):135–40.
38. Gelbard MK, Lindner A, Kaufman JJ. The use of collagenase in the treatment of Peyronie's disease. J Urol. 1985;134(2):280–3.
39. Gelbard MK, James K, Riach P, Dorey F. Collagenase versus placebo in the treatment of Peyronie's disease: a double-blind study. J Urol. 1993;149(1):56–8.
40. Jordan GH. The use of intralesional clostridial collagenase injection therapy for Peyronie's disease: a prospective, single-center, non-placebo-controlled study. J Sex Med. 2008;5(1):180–7.
41. Traynor K. Enzyme product approved for rare hand disorder. Am J Health Syst Pharm. 2010;15:416.
42. Gelbard M, Goldstein I, Hellstrom WJG, 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(1):199–207.
43. Rojo M, Iribarren IM, Rodriguez JC. Experience in the use of collagenase clostridium histolyticum in the management of Peyronie's disease: current data and future prospects. Ther Adv Urol. 2014;6(5): 192–7.
44. Abern MR, Levine LA. Intralesional verapamil injections with and without penile traction and oral therapies for management of Peyronie's disease. J Urol. 2008;179(4):408.
45. Abern MR, Larsen S, Levine LA. Combination of penile traction, intralesional verapamil, and oral therapies for Peyronie's disease. J Sex Med. 2012;9(1):288–95.
46. Yafi FA, Pinsky MR, Stewart C, Sangkum P, Ates E, Trost LW, et al. The effect of duration of penile traction therapy in patients undergoing intralesional injection therapy for Peyronie's disease. J Urol. 2015; 194(3):754–8.
47. Cerruto MA, DElia C, Molinari A, Cavicchioli FM, D'Amico A, Artibani W. Animal experimental model of Peyronie's disease: a pilot study. Arch Ital Urol Androl. 2013;85(1):28–33.
48. Davila HH, Ferrini MG, Rajfer J, Gonzalez-Cadavid NF. Fibrin as an inducer of fibrosis in the tunica albuginea of the rat: a new animal model of Peyronie's disease. BJU Int. 2003;91(9):830–8.
49. El-Sakka AI, Hassan MU, Nunes L. Histological and ultrastructural alterations in an animal model of Peyronie's disease. Br J Urol. 1998;81(3):445–52.
50. Gokce A, Abd Elmageed ZY, Lasker GF, Bouljihad M, Kim H, Trost LW, et al. Adipose tissue-derived stem cell therapy for prevention and treatment of erectile dysfunction in a rat model of Peyronie's disease. Andrology. 2014;2(2):244–51.
51. Albersen M, Kendirci M, Van der Aa F, Hellstrom WJG, Lue TF, Spees JL. Multipotent stromal cell therapy for cavernous nerve injury-induced erectile dysfunction. J Sex Med. 2012;9(2):385–403.
52. Castiglione F, Hedlund P, Van der Aa F, Bivalacqua TJ, Rigatti P, Van Poppel H, et al. Intratunical injection of human adipose tissue-derived stem cells prevents fibrosis and is associated with improved erectile function in a rat model of Peyronie's disease. Eur Urol. 2013;63(3):551–60.
53. Lin C-S, Lin G, Lue TF. Allogeneic and xenogeneic transplantation of adipose-derived stem cells in immunocompetent recipients without immunosuppressants. Stem Cells Dev. 2012;21(15):2770–8.
54. Huang Y-C, Ning H, Shindel AW, Fandel TM, Lin G, Harraz AM, et al. The effect of intracavernous injection of adipose tissue-derived stem cells on hyperlipidemia-associated erectile dysfunction in a rat model. J Sex Med. 2010;7(4 Pt 1):1391–400.
55. Nehra A, Alterowitz R, Culkin DJ, Faraday MM, Hakim LS, Heidelbaugh JJ, et al. Peyronie's disease. J Urol. 2015;194(3):745–53.