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Intralesional interferon-alpha-2b for the treatment of Peyronie's disease

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Peyronie's disease can best be described as a localized connective tissue disorder that primarily affects the tunica albuginea of the penis. The disease may be attributed to repetitive vascular trauma that initiates an inflammatory process and ultimately leads to the formation of a fibrous penile plaque. The plaque consists mainly of collagen and can significantly alter penile anatomy and function. Patients with Peyronie's disease will most often present with penile curvature, pain on erection, a palpable nodule most commonly located on the dorsal shaft of the penis, and erectile dysfunction. There is no definitive treatment for Peyronie's disease and the treating physician has many options. They may wait for spontaneous resolution of the plaque, choose medical therapy (which includes both oral and intralesional regimens), or opt for surgical management. The main purpose of this article is to discuss the advances in medical therapy for Peyronie's disease, in particular intralesional injection of interferon-alpha-2b (IFN-α-2b). Several studies have concluded that IFN-α-2b can be an effective modality of treatment and that many patients placed on a regimen of IFN-α-2b experienced a significant reduction in penile curvature, diminished pain with erection, and decreased size of the plaque. Further clinical studies are currently being undertaken to determine the precise quantity and frequency of administration of IFN-α-2b that is most effective with the least amount of side effects.
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Introduction

Francois Gigot de la Peyronie was the first to report a clinical series on penile curvature in 1743. More than 250 y later, the exact etiology and mechanism of the well-recognized symptom complex still remain unclear. Peyronie's disease has been reported to affect more than 3% of the male population and is most commonly found in men aged between 40 and 70 y.[1,2] This condition is characterized by local changes in the collagen composition of the tunica albuginea of the penis. The result is a fibrous plaque that contains an excessive amount of collagen, alterations in the elastin framework, and fibroblastic proliferation. Consequently, the anatomy and function of the penis can be greatly altered. The most frequent clinical signs and symptoms of Peyronie's disease include penile curvature, pain on erection, palpable nodule most commonly found on the dorsal shaft of the penis and always on the side to which curvature is directed, and complications with sexual intercourse. Erectile dysfunction is known to occur in 40% of men with Peyronie's disease and this condition is recognized to affect quality of life, with 77% of men with the disease demonstrating significant psychological effects.[3,4]

Many theories have been proposed as to the origin of Peyronie's disease. However, most authorities now believe that Peyronie's disease is a result of repetitive trauma that incites an inflammatory process with a subsequent low-level autoimmune response.[5–9] This inflammatory process causes an increased deposition of collagen (types I and III) and glycosaminoglycans, which ultimately leads to fibrosis of the tunica albuginea. Thus, Peyronie's disease may be classified as a wound-healing disorder, similar to keloids, hypertrophic scars, or Dupuytren's contractures, all of which may be coinciding findings in this condition.[9–13]

Because of spontaneous plaque resolution recognized in 13–40% of Peyronie's patients, the standard of care is a 'conservative' approach to treatment for at least the first 12 months.[3,14] Symptoms will not resolve spontaneously in most patients, hence medical therapy should be imple-

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mented. It has been shown that patients with early stage Peyronie's disease benefit most from medical therapy. Many oral medicines have been reported as having limited success in treating Peyronie's disease. These treatment options include oral therapy with vitamin E, potassium aminobenzoate (Potaba), tamoxifen, or colchicine.[5,15–17] Intralesional injection of various agents has also been proposed as a minimally invasive treatment option for Peyronie's disease. The benefit of modern intralesional therapy can be attributed to Gelbard and colleagues, who injected purified collagenase into Peyronie's plaques.[18,19] The benefit of intralesional verapamil was then introduced by Levine in 1994.[10,20] Recently, Rehman and colleagues further demonstrated the benefit of intralesional verapamil, concluding it was a reasonable approach to the treatment of Peyronie's disease.[21] Finally, many studies have also confirmed that intralesional injection of interferon-alpha-2b can be a successful option for the treatment of this condition. The remainder of this article will be focused on the discussion of IFN-α-2b and its use in the treatment of Peyronie's disease.

Interferon-alpha-2b

The interferons are a group of naturally occurring, low molecular weight proteins and glycoproteins that play an integral role in the immune system. They were first recognized for their anti-viral properties. Research has also shown that interferons possess other diverse biological properties including: anti-tumorigenesis, growth regulatory activities, regulation of cell differentiation, and immunoregulatory effects. There are at least three recognized types: alpha, beta and gamma interferons.[22] Alpha interferons have been used clinically to treat patients with hepatitis B and C, Kaposi's sarcoma in HIV and certain dermatological conditions (such as hemangiomas) because of their ability to augment or depress immune reactions.

Duncan and colleagues first demonstrated the potential use of intralesional interferons in 1991. They reported on the *in vitro* effects of interferons-α-2b and -γ on the production of collagen in Peyronie's disease-derived human fibroblasts.[23] They documented that the interferons inhibited fibroblast proliferation, which diminished collagen production. In addition, they documented that interferon-α-2b stimulated the activity of the enzyme collagenase. Ahuja *et al*, using an *in vitro* model of corpora cavernosal-derived myofibroblasts, demonstrated stimulation of collagen production with exposure to oxygen-free radicals and diminished collagen production in the presence of interferon-α.[24] Furthermore, IFN-α-2b is recognized to effectively decrease keloid scars and scleroderma.[25]

Intralesional interferon-α-2b in the treatment of Peyronie's disease

Based on the success of intralesional collagenase and verapamil and the recognized *in vitro* effects of INF-α-2b, investigators began to look at intralesional INF-α-2b as a possible treatment for Peyronie's disease. Many researchers recommend that prior to beginning intralesional therapy, appropriate consent should be obtained and erectile response and plaque size need to be evaluated. All patients are informed that the use of IFN-α-2b at much higher levels has been associated with side effects such as a 'flu-like' syndrome, anorexia, rashes, hypotension and cardiac arrhythmias. For pre-therapy assessment patients generally undergo intracavernosal injection of prostaglandin E and penile duplex doppler ultrasonography is then used to measure cavernosal blood flow. At the same time the number of plaques, plaque dimensions and penile tumescence are recorded. The presence and degree of penile curvature and pain is always documented for comparison purposes. During patient follow-up, reduction in pain, plaque size, and improvement in curvature and sexual function are followed as end points of therapy. The area in which there has been some discrepancy among researchers is regarding how much IFN-α-2b is administered and how often it is injected. Moreover, the site of injection is another debate. Most studies involve injecting the medication directly into the Peyronie's plaque after anesthetic circular blockade of the penis (Figure 1). However, other studies have employed injection of the interferon subcutaneously next to the plaque.

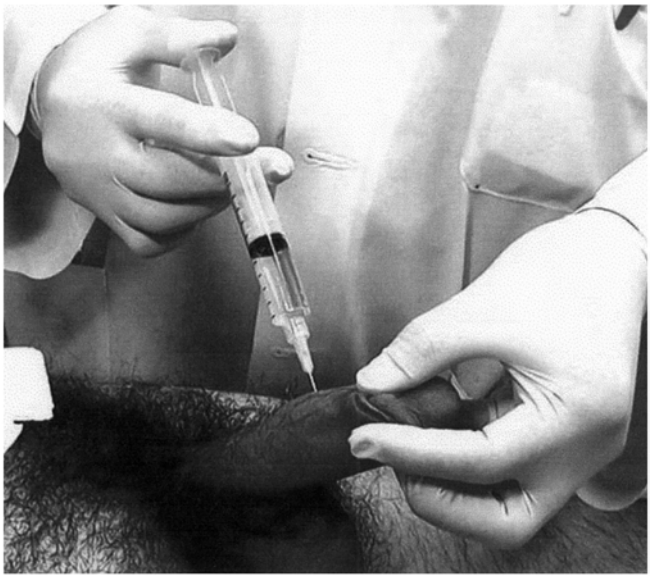

Figure 1 Demonstration of IFN-α-2b injected directly into a

Initial enthusiasm for intralesional IFN-α-2b therapy arose when Benson *et al* reported significant plaque softening, diminished curvature (50%) and total pain relief in all 10 patients in a study published as an abstract.[26] However, no further data emerged as a result of this study.

The next studies were done by Wegner *et al* in 1995 and 1997. These researchers injected 25 patients subcutaneously adjacent to the plaque once a week for 5 weeks at a dose of 1×10^6 units. Patients were assessed after 1 and 6 months and a decrease in plaque size in 28% of non-calcified or minimally calcified plaques was reported as well as pain subsiding in all but one patient.[27] In a subsequent follow-up study Wegner *et al* used 3×10^6 units of IFN-α-2b and injected 30 patients subcutaneously adjacent to the plaque once a week for 3 weeks. Patients were assessed after 6 months and no decrease in plaque size was reported and the appearance of new plaques in seven patients as well as an 82% incidence of side effects ('flu-like' symptoms) was observed. There was pain relief in 97% of the patients. They ultimately concluded that intralesional therapy with IFN-α-2b was not effective.[28] However, this study appears to present a surgical bias and lacks the inclusion of a placebo control group.

In 1997, a study by Judge and Wisniewski showed promise for IFN-α-2b. They investigated 13 patients suffering from Peyronie's disease. Three men were given intralesional saline as a control, while the remaining 10 underwent injection with 1.5×10^6 units of IFN-α-2b three times a week for 3 weeks. There were no changes noted in the control subjects, but the study drug patients reported resolution of pain, decreased penile curvature, plaque softening, and decreased plaque size.[29]

Further support for the use of intralesional IFN-α-2b was recently provided by Ahuja *et al*. They reported that nine of 10 patients (90%) who were given this medical treatment and who initially reported penile pain on erection had resolution of their phallagia. They also demonstrated that 65% of their study patients had significant improvement in the curvature of their penis, ranging from 20 to 90% reduction in curvature, and that 85% had an objective decrease in plaque size. In their study Ahuja *et al* used 1×10^6 units of IFN-α-2b in 10 ml of normal saline, injected biweekly for 6 months. They hypothesized that a larger volume of fluid within the plaque may exert a hydrostatic pressure that actively remodels the plaque more effectively.[30] The major limitation of this study was the lack of a placebo control group.

In the most recent report, Brake *et al* performed subcutaneous injections adjacent to the plaque at a dose of 2×10^6 units three times a week for 3 weeks. Total resolution of phallagia was reported in patients with pain prior to treatment. Penile deviation was reduced in only one patient and plaque size remained unchanged in all patients. Sexual function improved in 30% of the patients.[31]

The preceding studies have demonstrated that intralesional IFN-α-2b is a reasonable option for the treatment of Peyronie's disease. In the studies where the conclusions were not in favor of using IFN-α-2b, it appears that the authors opted to inject the therapy into the tissue adjacent to the plaques rather than into the plaques themselves. Furthermore, multi-center trials using a placebo-control cross-over design are currently underway.[32] These studies will hopefully bring greater understanding as to what quantity and which frequency of administration of IFN-α-2b is most efficacious and where the therapy should be injected. When the results of these studies are reported, it will be possible to make more definitive conclusions regarding the efficacy of using IFN-α-2b for the treatment of Peyronie's disease.

Conclusion

Peyronie's disease represents a challenging problem faced in urologic practice, which unfortunately is being encountered at an ever-increasing rate by today's urologist. The disease is well recognized for its adverse anatomical and functional effects on the penis, but the damaging psychological effects are often overlooked. Although surgical correction is ultimately successful in the majority of cases, the investigation for less invasive therapeutic alternatives should continue to be a high priority in the study of Peyronie's disease because there are many patients who either cannot tolerate or do not desire surgery. At this time, intralesional IFN-α-2b injection therapy appears to demonstrate an objective reduction of penile curvature and plaque size. It also offers a subjective improvement in penile pain on erection and in the overall quality of erections.

As continued research into Peyronie's disease brings us a better understanding of its pathophysiology, more targets for intervention will become available. The goals of any treatment modality should include pain reduction and normalization of penile anatomy and function such that sexual intercourse is feasible and comfortable. Interventions should be individualized to each patient based on the timing and severity of the disease, the patient's desires, and the aforementioned goals of therapy.

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