

## Re: Minimally Invasive Therapy Using Intralesional OnabotulinumtoxinA in Peyronie's Disease

Peyronie's disease (PD) is a benign condition of unclear etiology. It results in penile deformities such as penile curvature, dimple, and shortening. The incidence of this disease has increased dramatically during the last decade, especially in younger men. More and more young people are affected by PD. In our community most of the affected men are in their 30s and 40s, and unlike PD in older men, the prognosis in these younger men is very poor, and the natural history of PD in these young patients mostly is rapid progression with resultant severe erectile dysfunction. Younger patients are predominantly vulnerable to emotional, psychosexual, and relationship problems. Most of my patients are men under 40. The onset of PD in men under 40 is often much more acute.<sup>(1)</sup> I believe that, this disease will become a health problem in most communities in the next decade, and a public health action plan is needed to determine the prevalence and causes for this disease. The reported prevalence of PD in some studies is up to 7%.<sup>(2-4)</sup> Yet in my opinion, these reported prevalence are under estimated. Researches are needed to better understand many known and potential causes of PD.

Medical and surgical treatment options are limited in number and efficacy for PD.<sup>(5-13)</sup> Therefore addressing new treatment modalities (oral medication, intralesional injection, and surgery) is of utmost importance. Development of novel therapeutic modalities is hampered by lack of standardized definition for PD and its complications. In addition the exact cause of PD is unknown and usually treatment focuses on the causative disorder. Though two questionnaires, namely Peyronie's Disease Symptom Bother Domain (PDSBD) and the Peyronie's Disease Questionnaire (PDQ), have been developed, but they are not sufficient. Usually the results of different treatment approaches in different studies are not reproducible. Because, PD has a wide range of presentation and different disease stages. The methods for plaque and penile curvature measurements have not been yet standardized. Assigning patients into different stage of disease is mostly by physician desertion. As I mentioned above, PD is somewhat prevalent in our community. I have not seen any benefits from intralesional therapy (verapamil, interferon, collagenase and etc.). Indeed in some cases intralesional therapy have resulted in catastrophe. Multiple injections into multiple plaques are very traumatizing. I saw many patients who developed a short bony penis without any erection due to multiple injections. In these patients penile ultrasonography revealed a calcified plaque that involved the entire tunica albuginea of both corpora cavernosal. Most of the existing pharmacological and other treatment regimens have not demonstrated consistent results in clinical trial.<sup>(14-16)</sup> The principal problem in PD is the plaque formation in the tunica albuginea of the penis. The plaque(s) prevent normal expansion of the penile tunica albuginea, resulting in penile curvature, deformity, and narrowing with a hinge effect. Therefore every effective treatment modality should result in plaque disappearance or at least significant reduction in plaque(s) volume. The aim of intralesional pharmacotherapy in the treatment of PD is to direct delivery of large doses of pharmacologic agents into the plaque. Multiple agents have been used, including corticosteroids, verapamil, collagenase, and interferon, among others.<sup>(5,7)</sup> In present study, the authors aimed to address this issue with new intralesional therapeutic agent. In present study the authors reported significant improvement with a single dose intralesional onabotulinumtoxinA administration. OnabotulinumtoxinA (Botox®, Allergan, Inc., Irvine, CA) is a potent neurotoxin derived from the anaerobic bacteria *Clostridium botulinum*. Of the seven known toxin serotypes (A-G), only serotypes A and B are used in medicine. OnabotulinumtoxinA was first approved by the U.S. Food and Drug Administration (FDA) in 1989 for two therapeutic indications: blepharospasm and strabismus.<sup>(17)</sup> Haubner and colleagues examined patient-specific keloid tissue in a cell culture model to clarify the effects of onabotulinumtoxinA incubation on cell proliferation and the expression of cytokines and growth factors such as TGF- $\beta$ , vascular endothelial growth factor (VEGF), and IL-6.<sup>(18)</sup> They demonstrated that none of the examined variables were affected by onabotulinumtoxinA incubation and concluded that there was no enough evidence to suggest a significant therapeutic effect for intralesional onabotulinumtoxinA injections in the treatment of keloids.<sup>(18)</sup> Studies addressing the safety and efficacy of onabotulinumtoxinA for treatment of wound scar, fibrotic tissue and keloid are very scarce and inconclusive.

In present study, the authors reported beneficial effects from single dose intralesional injection of onabotulinumtoxinA. But the reported results might be hampered due to following reasons. The study has no control group, the sample size and as a result the study power is low, the stage of disease in which the recruited patients were, is not clear, the follow-up period is short and standard questionnaires for PD such as PDSBD and PDQ, have not been used. It is important to monitor both the subjective and objective response to any PD treatment. Although there is no standard subjective questionnaire, some tasks should be employed to evaluate the patient's perception of changes resulted from treatment. With the fact that erectile function may worsen over time and the penile plaque and curvature may relapse, the results at long-term follow-up should be considered.

Given the potential complications and possible recurrence of disease following intralesional therapy, the assessment of patient expectations and beliefs about the proposed treatment option and the determining and correction of mistaken beliefs are essential components prior to intralesional therapy.

Intralesional therapy is an invasive treatment with questionable benefits and potential complications. The European Association of Urology (EAU) guidelines provided recommendations for the diagnosis and treatment of PD penile curvature.<sup>(19)</sup> But, this will be beneficial on patients in the early stage of the disease. In addition, the EAU recommends intralesional clostridial collagenase use with a level of evidence 2b and recommendation grade C, based on two small studies, with poor samples of patients and insufficient follow-up periods.<sup>(20,21)</sup> Many of the studies have had design

flaws, which means more researches are required to confirm or disprove the results. Yet, there is no effective treatment for PD when the plaque is densely fibrotic or calcified.

Despite a vague therapeutic benefit, off-label intralesional injection therapy has become the principal treatment for PD in different stages. When evaluating efficacy and safety, considering specific endpoints, which are, penile curvature, plaque volume, erectile function, and relationship with partner, need to be analyzed in a critical, evidence-based fashion. The sentence "surgical correction is ultimately successful in the majority of patients with PD",<sup>(22)</sup> is not true. The majority of patients with advanced PD, have extensive "T" shape plaque formation. The plaque involved the entire tunica albuginea of both corpora cavernosum extending into raphe. This extensive involvement of tunica albuginea, severely deteriorate penile hemodynamics. The ultimate goal of every surgical procedure for PD, should be removing and restoring normal penile hemodynamics. Correction of only penile curvature, will not treat PD and will not result in improved penile hemodynamics. It is important to monitor both the subjective and objective response to any PD treatment.

The take home message is that treatment modalities for PD have a low success rate in advanced stage, usually are not reproducible, and that standardization for patient selection is crucial. PD is yet debilitating condition with increasing prevalence and morbidity. For introducing effective treatment option we need to completely understand the etiology and underlying pathophysiology of PD. If further studies are needed to determine the role of intralesional onabotulinumtoxinA in the treatment of PD, I can't recommend it. But additional basic science studies are needed to devise more effective treatments for this difficult condition.

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## Reply by Author

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We appreciate the pertinent editorial comments to our manuscript. Certainly, the incidence of Peyronie's disease (PD) is increasing in male population, and the illness' prognosis is unfavorable in many patients, particularly in sexual function.

Since the early description of the disease by Peyronie, many treatments have been tested, achieving disconcerting results, as established in the different treatment guidelines recently published.

The pathophysiology of the disease still remains unknown, so the gold standard treatment has not been described yet. According with the observations of common molecular and biological pathways of PD with hypertrophic scars, keloid scars and Dupuytren's contracture, some reports using botulinum toxin have demonstrated to have a slight-to-mild beneficial therapeutic effect.

We designed this prospective cohort study with favorable results, but we clarified in our manuscript that the design of a prospective clinical trial is encouraged to demonstrate any therapeutic benefit. Currently, a protocol is running at Baylor College of Medicine, entitled "H-22411: BOTOX® for Peyronie's Disease", with the identifying No. NCT00812838 by Mohit Khera and colleagues, waiting for final results in January 2016.

The authors would appreciate our article to be referred in the editorial comment as an accepted manuscript, since our results constitute the first literature report of treatment of PD with onabotulinumtoxinA.

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