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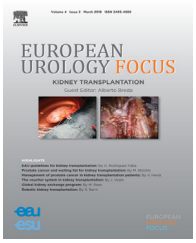

Clinical Case Discussion

Xiaflex for Treatment of Peyronie's Disease

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Peyronie's disease (PD) is a symptom complex that may include penile pain, curvature, shortening, narrowing, hinge deformity, and palpable plaque sometimes associated with erectile dysfunction (ED) [1]. The exact etiology of PD is unknown; however, it is thought to stem from disorganized, excessive deposition of collagen leading to formation of a plaque within the penile tunica albuginea [2]. The prevalence of PD varies among countries and institutions, ranging from 2% to 8.9% [3]. Alterations in the function and appearance of the penis can lead to psychosocial and emotional consequences such as depression and relationship difficulties [4]. For a 56-yr-old patient with PD who does not have any evidence of ED and no prior interventions for PD, it is prudent to provide a well-tolerated treatment with minimal side effects aimed at improving the penile curvature and dissipating any emotional or psychosocial distress.

In the active phase of PD, patients should be offered anti-inflammatory medications for pain management [4]. Absence of current pain and the stability of the curvature indicate that this patient is no longer in the active phase of the disease. Once PD has stabilized, for men with persistent bothersome curvature, several treatment options are available. In the past, oral treatments such as Vitamin E, tamoxifen, and omega-3 fatty acids were offered as initial therapies. However, such oral therapies are no longer recommended. In addition, use of topical therapies, such as low-intensity shock wave therapy and topical verapamil and iontophoresis, have not been supported in the literature [3]. The current recommended treatment options include intralesional injections with collagenase (Xiaflex), interferon or verapamil, or surgical management [2].

While surgical management may provide immediate correction of penile deformities, patients often are not ready to undergo an invasive procedure as first-line therapy. Subsequently, intralesional injections are a more suitable form of therapy for most patients since it provides satisfactory improvements in curvature with minimal side effects. Even when complete resolution does not occur, any improvement in the deformity after intralesional therapies can often simplify future surgical intervention. The patient in this clinical scenario is an ideal candidate to undergo intralesional injections, specifically with Xiaflex. The use of Xiaflex in treating PD is a Grade B recommendation according to the American Urological Association (AUA) PD Guidelines, the highest grade recommendation in the AUA PD Guidelines. Although intralesional interferon and verapamil may also be considered, these are Grade C recommendations since there is less convincing evidence-based literature available to support the efficacy of these therapies [2].

Xiaflex or collagenase *Clostridium histolyticum* is an enzyme produced by the bacterium *C. histolyticum.* Xiaflex selectively degrades collagen types I and III in connective tissues despite the presence of tissue inhibitors of metalloproteinases, which have been shown to be elevated in PD as well as to increase apoptosis of fibroblasts [5]. While the idea of using collagenase for PD is not new, the landmark IMPRESS I and IMPRESS II clinical trials were the definitive trials that established the current United States Food and Drug Administration-approved intralesional collagenase plus modeling protocol for stable PD [4]. Briefly, the protocol includes two 0.58 mg Xiaflex injections, separated by 1–3 d, followed by in-office penile modeling 1–3 d after the second injection. This cycle can be repeated up to four times with at least 6 wk in between cycles with at home penile modeling [6].

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The IMPRESS I and IMPRESS II trials were prospective, double-blinded, placebo controlled studies with over 400 participants in each study. Inclusion criteria were patients with stable disease, >30 degrees and <90 degrees of curvature, no proximally located plaque at base of the penis, and those with erectile function (with or without medications). In both studies, the average reduction in curvature was 17 degrees with Xiaflex and modeling, a statistically significant difference in curvature reduction when compared to placebo or Xiaflex alone [7].

The patient in the presented clinical scenario fits the typical profile of a patient who may benefit from Xiaflex and modeling. He has a 45-degree curve, stable disease for 2 yr without pain or ED, and has a mid-shaft dorsal plaque. Although extensive calcification was an exclusion criterion in the IMPRESS I and II studies, plaque calcification is not a contraindication for Xiaflex injections. Accordingly, this patient may still undergo Xiaflex injections rather than proceeding directly to surgery. Should intralesional therapy not be entirely successful, he may still undergo corrective surgery at a later date as Xiaflex is not a contraindication to future surgical treatment for PD [8]. The importance of post-injection modeling after each cycle should be emphasized as a simple and well-tolerated step that will positively impact curvature reduction [7].

Upon undergoing Xiaflex treatment with modeling the patient can expect an average reduction in curvature of 17 degrees $\pm$ 14.8 degrees over the course of 1 yr. Our patient can also expect significant improvement in the PD Questionnaire Symptom Score of -2.8 ± 3.8 [7]. Common adverse events that often resolve without intervention include penile hematoma (50.2%), penile pain (33.5%), penile swelling (28.9%), injection site pain (24.1%), and injection site hematoma (19.6%). Xiaflex is generally well tolerated with only a 0.9% chance of treatment-related serious adverse events such as corporal rupture and significant penile hematoma [9]. Given that Xiaflex is generally well tolerated, it should be offered as the initial therapy for PD prior to surgical treatments, which could be associated with more serious adverse events such as loss of penile sensation, penile shortening, ED, and glans ischemia or necrosis [3].

In conclusion, it is the authors' belief that the 56-yr-old patient presented in this case is an excellent candidate for Xiaflex treatment. With the exception of the plaque calcifications, he precisely fits the criteria used during the IMPRESS I and IMPRESS II trials: stable disease, curvature >30 degrees and <90 degrees, no proximally located plaque at base of the penis and good erectile function. In summary, Xiaflex is a safe, effective medication that can significantly help our case patient improve penile curvature and his psychosocial and emotional health while avoiding more aggressive surgical intervention.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Ralph D, Gonzalez-Cadavid N, Mirone V, et al. The management of Peyronie's disease: evidence-based 2010 guidelines. J Sex Med 2010;7:2359–74.
[2] Brock G, Hsu GL, Nunes L, et al. The anatomy of the tunica albuginea in the normal penis and Peyronie's disease. J Urol 1997;157:276–81.
[3] Chung E, Ralph D, Kagioglu A, et al. Evidence-based management guidelines on Peyronie's disease. J Sex Med 2016;13:905–23.
[4] Nehra A, Alterowitz R, Culkin DJ, et al. Peyronie's Disease. American Urological Association; April 2015. 2015 http://www.auanet.org/guidelines/male-sexual-dysfunction-peyronies-disease-(2015)
[5] Levine LA, Larsen S. Diagnosis and management of Peyronie disease. In: Wein AJ, Kavoussi LR, Partin AW, Peters CA, editors. Campbell-Walsh Urology. ed. 11. Philadelphia, PA: Elsevier; 2016. p. 722–48.
[6] Levine LA, Cuzin B, Mark S, et al. Clinical safety and effectiveness of collagenase *Clostridium histolyticum* injection in patients with Peyronie's disease: a phase 3 open label study. J Sex Med 2015;12:248–58.
[7] Gelbard M, Goldstein I, Hellstrom WJ, 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;190:199–207.
[8] Levine LA, Larsen SM. Surgical correction of persistent Peyronie's disease following collagenase *Clostridium histolyticum* treatment. J Sex Med 2015;12:259–64.
[9] Carson III CC, Sadeghi-Nejad H, Tursi JP, et al. Analysis of the clinical safety of intralesional injection of collagenase *Clostridium histolyticum* (CCH) for adults with Peyronie's Disease (PD). BJU Int 2015;116:815–22.