COMMENT

Is there a new role for oral therapy to treat peyronie's disease? Commentary on *Daily low-dose tadalafil may reduce the penile curvature progression rate in patients with acute Peyronie's Disease: a retrospective comparative analysis*

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IJIR: Your Sexual Medicine Journal (2024) 36:160–161; https://doi.org/10.1038/s41443-023-00684-7

In their article published in this months issue of *International Journal of Impotence Research*, Spirito et al. sought to evaluate the impact of low dose oral tadalafil on the rate of penile curvature progression in patients with acute phase PD [1]. Treatment for Peyronie's Disease (PD) was first described by the condition's namesake in 1743 [2]. Interesting examples of some rather esoteric treatments over the last 250 years include mercury, arsenic, electricity, and various forms of radiation [3]. Modern non-surgical approaches have involved various oral and intralesional agents with mechanisms of action that are purported to target anti-inflammatory and anti-fibrotic pathways [4]. To deliver an oral medication to a specific tissue of interest, there needs to be adequate vascularity of the target tissue. Scar vascularity has been studied in other areas of the body such as the skin after superficial burns. Neovascularization appears to happen to some extent in many scars, although the extent of neovascularization is heterogenous and this is challenging measure [5]. Thus, while from a mechanism standpoint it makes sense to consider oral medications, in practice the actual ability of that medication to travel to the target tissue (i.e. penile plaque) and exert its effects is unclear. One must also consider that most of these agents target steps along inflammation and fibrosis pathways, so there is important to get these medications delivered prior to the scar setting in. The classic dichotomy of defining PD in the acute/active and chronic/stable phases is largely based on clinical picture rather than what is happening at the cellular level, which further complicates treatment protocols and timing [6].

Among published guidelines for PD, there is nearly universal consensus that most oral agents should not be used to treat PD in either the acute or chronic phases due to the absence of any proven benefit [7]. Examples include vitamine E, tamoxifen, procarbazine, omega-3 fatty acids, and combination Vitamin E + L-carnitine. The European Association of Urology and International Society of Sexual Medicine guideline panels also recommend against potassium para-aminobenzoate, pentoxifylline, and colchicine, whereas the American Urological Association and Canadian Urological Association guidelines state that these agents have "unclear benefits" and may be considered.

I read the manuscript from Spirito et al. with great interest, given that tadalafil is the medication I prescribe most often for a variety of conditions including erectile dysfunction, bothersome lower urinary tracts, and even painful nocturnal erections and pelvic/genital pain (albeit with less robust evidence as compared to the erectile dysfunction and urinary symptoms). In their study, the authors performed a retrospective analysis comparing curvature progression in patients presenting with acute phase PD symptom, curvature <30 degrees, and self-reported ED symptoms (in the absence of prior treatment) who were treated with twelve weeks of daily tadalafil (5 mg; $n = 108$) to those who did not use tadalafil ($n = 83$). Mean baseline penile curvature in the cohort was <20 degrees and the mean symptom duration at presentation was 10-11 months. Curvature assessments were performed by a single urologist at baseline and after 12 weeks. The authors found that curve progression (defined as an increase of ≥10 degrees) was seen in 40% of the observation group compared with 26% of the tadalafil group ($p = 0.042$). Improvements were also seen in patient reported symptom scores using the validated Peyronie's Disease Questionnaire for the tadalafil group, and not surprisingly the Internation Index of Erectile function scores improved as well.

These results are interesting, and taken at first glance they would suggest that we have another candidate for oral therapy in the acute phase. From a mechanism standpoint, tadalafil and other phosphodiesterase-5 inhibitors appear to target fibrosis pathways beyond their impact on endothelial smooth muscle. Proposed mechanisms from in vitro studies involve modulation of fibroblast and myofibroblast activity through nitric oxide mediated pathways [8–10]. From a clinical perspective, there are now several reports, including that from Spirito et al., that support the utility of tadalafil to limit PD progression. For example, one often cited retrospective study from Chung et al. suggested the daily tadalafil may prevent progression and even promote regression of isolated septal scarring for those patients presenting with this variant of PD [11]. Other examples where tadalafil is used in combination with various treatment protocols also suggest a possible benefit in PD.

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Received: 11 January 2023 Revised: 26 January 2023 Accepted: 17 February 2023
Published online: 24 February 2023

However, like most of the other oral agents that have been used to treat PD, the supportive literature regarding clinical outcomes with tadalafil overall suffers from methodological flaws and a lack of high-level evidence. Spirito et al. acknowledge many limitations typical of other published protocols such as the retrospective nature and absence of randomization that may introduce bias. Another limitation is the inclusion of patients in the acute phase based only on a provider-determined clinical definition (i.e. pain and/or perceived curvature progression). The mean PD symptom duration was approximately 10 months, and many patients had symptom durations that exceeded one year. How many of these patients were truly in the acute/active phase where tadalafil and other oral agents are suggested to have their most prominent benefit? The authors performed a subgroup analysis of those patients with symptom duration < 9 months, but this is still an incomplete way to truly identify those patients who have active inflammation at the level of the PD plaque. Challenges in adequately defining the acute/active phase are not specific to this study. The definitions used across the PD literature. This makes cross-comparisons of various patient populations within study protocols more difficult [6]. Another notable limitation that was not specifically addressed in the manuscript is that a single urologist performed all of the curvature assessments, and the injection protocol involved only a single injection of intracavernosal alprostadil at a dose of 10 mcg. For those of us who regularly perform curve assessments, we know that there is variation in erection response to intracavernosal injections based on a variety of factors. Curvature progression was defined as ≥10 degrees, which is within what many would deem as the margin of error when performing a curve assessment. The true difference in the rates of progression between groups (25% versus 40%) may not actually be clinically significant. This is particularly relevant given that the authors did not perform an a prior power analysis to identify the number of patients and extent of curvature progression necessary to compare the tadalafil and observation groups.

Despite these limitations, this study adds to the limited available literature. It does not definitively answer the question: "Does tadalafil prevent curve progress in patients with acute phase PD?", but it does support the need for a more methodologically sound trial to answer that question more definitively. In the meantime, tadalafil will continue to play an important role in my treatment protocol for men with PD. Nearly half of our patients with PD present with concurrent ED, which is not surprising given that its prevalence is higher in middle and older age where the prevalence of ED is higher [12, 13]. Many of these patients also endorse bothersome lower urinary tract symptoms (LUTS). Daily tadalafil is well supported as a treatment option for both ED and LUTS [14]. It may also be cardioprotective [15]. The medication is generally well tolerated, particularly at the low daily dose. In the United States, it is now available as a generic medication and has an excellent price point for those patients paying out of pocket without insurance coverage. We use the phrase "penis protection" to describe the benefits of ensuring adequate erection rigidity in order to prevent further risk for over or subclinical penile injury (i.e. "microtrauma") that is proposed to cause PD in genetically predisposed patients. Maybe the clinical difference that Spirito et al. saw in the rate of curve progression was not due to the impact of tadalafil on the penile plaque itself, but rather the fact that patients with stronger erections were less likely to suffer ongoing injury at the level of the curvature (which may actually promote local symptom progression). Given all of the potential benefits and the low risk for significant side effects, it seems very reasonable to consider daily tadalafil as part of the protocol for those patients with PD and concurrent ED and/or LUTS. We also favor using this in conjunction with other therapies such as penile traction or intralesional therapy where we can focus on curvature improvement in addition to ensuring adequate erection rigidity.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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