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Non-hormonal pharmacotherapies for benign prostatic hyperplasia: The Role of Tadalafil Monotherapy

Aamir Jalal Al-Mosawi
Advisor doctor and expert trainer
Baghdad Medical City and Iraqi Ministry of Health Baghdad, Iraq
Corresponding Author: Aamir Jalal Al-Mosawi, Advisor doctor and expert trainer, Baghdad Medical City and Iraqi Ministry of Health Baghdad, Iraq

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Abstract

Many medications have been used in the treatment of benign enlargement of the prostate during the 1960s, 1970s, and 1980s, including progestational agents, amino acids, spironolactone, candicidin, nystatin, flutamide, bromocriptine, alpha-adrenergic blockers, Serenoa repens (Saw palmetto extracts), and mepartricin.

Finasteride and dutasteride are 5-alpha reductase inhibitors decrease levels of dihydrotestosterone, which contributes to prostate enlargement, have been increasingly used in the treatment of benign prostatic hyperplasia.

There is some evidence suggesting that non-hormonal therapies (i.e., medication that do not directly affect male hormones like testosterone or dihydrotestosterone) can reduce prostate volume, particularly in the context of benign prostatic hyperplasia**.**

In recent years, the use of tadalafil (Phosphodiesterase type 5 inhibitor), as monotherapy for benign prostatic hyperplasia-related lower urinary tract symptoms has gained increasing attention. Tadalafil has demonstrated potential benefits in improving both the symptoms and the underlying pathology of benign prostatic hyperplasia. The aim of this paper is to highlight the role of tadalafil monotherapy in the treatment of benign prostatic hyperplasia.

Keywords: Benign prostatic hyperplasia, tadalafil.

Introduction

Many medications have been used in the treatment of benign enlargement of the prostate during the 1960s, 1970s, and 1980s, including progestational agents, amino acids, spironolactone, candicidin, nystatin, flutamide, bromocriptine, alpha-adrenergic blockers, Serenoa repens (Saw palmetto extracts), and mepartricin.

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There is some evidence suggesting that non-hormonal therapies (i.e., medication that do not directly affect male hormones like testosterone or dihydrotestosterone) can reduce prostate volume, particularly in the context of benign prostatic hyperplasia [1].

In recent years, the use of tadalafil (A long acting phosphodiesterase type 5 inhibitor), as monotherapy for benign prostatic hyperplasia-related lower urinary tract symptoms has gained increasing attention. Tadalafil has demonstrated potential benefits in improving both the symptoms and the underlying pathology of benign prostatic hyperplasia. A series of studies over the years have demonstrated its efficacy not only in improving symptoms like urinary frequency, urgency, and weak flow, but also in potentially reducing prostate volume.

Clinical Evidence Supporting Tadalafil Monotherapy in Benign Prostatic Hyperplasia

Clinical studies have shown that tadalafil, when administered in a daily dose of 5 mg, effectively alleviates the symptoms of benign prostatic hyperplasia and improves urodynamic parameters.

The first large-scale study by Kevin T McVary from the United States and his research team in 2007 highlighted that tadalafil can markedly reduced lower urinary tract symptoms in males with benign prostatic hyperplasia , with improvements in urinary flow rate and symptoms such as urgency and frequency [2].

Subsequent studies confirmed these findings, showing that tadalafil's once-daily administration leads to improvements in both objective urodynamic measures (e.g., peak urinary flow rate) and subjective patient-reported symptoms.

In 2010, Claus G Roehrborn from the United States and his

research team reported a placebo-controlled study which included1058 males who had benign prostatic hyperplasia and lower urinary tract symptoms. The patients were treated with either tadalafil (2.5, 5, 10, or 20 mg) for 12 weeks or placebo.

The study showed that tadalafil was associated a deleterious effect and resulted in dose-dependent improvements. Although treatment was associated with minimal changes in uroflowmetric measures, tadalafil was associated with clinically meaningful and statistically marked improvements in the obstructive symptoms of benign prostatic hyperplasia [3].

In 2015, Osamu Nishizawa from Japan and his research team reported a placebo-controlled study which included1199 Japanese, Korean, and Taiwanese males who had lower urinary tract symptoms. 601 were treated with tadalafil (5 mg once-daily) for 12 weeks, 598 were given placebo. Treatment was associated with marked symptomatic improvement and was not associated with adverse effect [4].

Moreover, tadalafil's benefits have been observed across diverse patient populations, including those with chronic prostatitis and chronic pelvic pain syndrome, where tadalafil has been reported to improve both pain and urinary symptoms.

In 2017, Yoshinori Nishino from Japan and his research team reported a study which included 23 Japanese male patients who had a benign prostatic hyperplasia (Prostate volume: 25. 2 ml) and associated with chronic pelvic pain syndrome and lower urinary tract symptoms.

The patients were treated with tadalafil (5 mg once daily) for four weeks. Treatment was associated with marked Symptom improvement. Therefore, the author suggested that tadalafil is a useful new option for the treatment of benign prostatic hyperplasia associated with chronic pelvic pain [5].

In 2018, Yoshihisa Matsukawa from Japan and his research team reported a study which included seventy-one patients (Mean age: 70.2 years) who had enlarged prostate (Mean volume: 45.6 mL). The patients were treated with tadalafil (5 mg daily) for 12 weeks.

Treatment was associated with marked symptomatic improvement and a marked increase mean maximum bladder capacity by about 35 mL ($P < 0.001$).

Detrusor overactivity improved in 15 (39.5%) of 38 patients who had detrusor overactivity at baseline ($P < 0.001$). Treatment also increased mean maximum flow rate from 7.1 to 9.1 mL/s ($P < 0.001$), and markedly decreased the mean bladder outlet obstruction index from 61.3 to 47.1 ($P < 0.001$).

Therefore the author suggested that tadalafil can improve storage and voiding function, detrusor overactivity and bladder outlet obstruction in benign enlargement of the prostate [6].

Also in 2018, Andrea Benelli from Italy and his research team reported a study which included 14 patients who had chronic prostatitis, and were treated with tadalafil (5 mg once-daily). Treatment was associated with symptomatic improvement and improved quality of life in patients which were not associated statistically important improvement of uroflowmetry parameters [7].

In 2019, Yoshihisa Matsukawa and his research team reported a study which included ninety-four patients (Mean age: 70.7 years) who had enlarged prostate (Mean prostate volume: 44.5 ml). The patients were treated with tadalafil (5 mg daily) for 1 year. Treatment was associated with marked symptomatic improvement and improvements in storage and voiding functions after 3 months.

Forty-nine patients had detrusor overactivity revealed by cystometry, 15 (30.6%) patients experienced improvement after three months ($p = 0.02$), and 22 (44.9%) patients experienced improvement after one year of treatment ($p < 0.001$).

Treatment also resulted in marked increase in mean maximum flow rate by 2.9 mL/s during the one year of treatment ($p < 0.001$), and marked reduction in mean bladder outlet obstruction index from 59.5 to 45.7 at 3 months ($p = 0.001$), and to 42.9 at one year ($p < 0.001$) [8].

Additionally, tadalafil has been found to be well-tolerated, with a favorable safety profile in both elderly and younger patients.

In 2019, Keiichiro Hayashi from Japan and his research team studied the safety of tadalafil in Seventy-one, above 75-year old patients who had enlarged prostate (Prostate volume : 41.2±24.3 ml) and lower urinary tract symptoms. Treatment was associated with marked symptomatic improvement. Adverse effect were observed in nine patients (10.7%), and five patients (6.0%) stopped treatment. Therefore, the authors considered tadalafil to be effective and safe medication [9].

Reduction in Prostate Volume

While the primary clinical benefit of tadalafil in benign prostatic hyperplasia has been its symptomatic relief, several studies suggested that tadalafil may also exert effects on prostate volume.

The exact mechanism by which tadalafil might decrease prostate size is not entirely understood, but it is thought to involve the ability to improve blood flow to the prostate and decrease inflammation.

Preclinical studies in animal models have shown that phosphodiesterase 5 inhibition can reduce prostate hyperplasia, likely through its effects on the smooth muscle and microcirculation of the prostate. It is hypothesized that its action on smooth muscle relaxation and improved blood flow could indirectly reduce the mechanical pressure that contributes to prostate enlargement.

In 2016, Yuko Kawai from Japan and her research ream reported an experimental study on a rat model of surgically induced partial bladder outlet obstruction. Treatment with tadalafil considerably prevented the increase in the frequency micturition and the reduction in mean micturition volume. The beneficial effect of tadalafil was attributed to preventing the decrease in bladder blood flow and thus improving urinary function [10].

These findings have been supported by clinical observations in patients with benign prostatic hyperplasia, where tadalafil has been associated with modest reductions in prostate volume.

In 2014, Claus G Roehrborn from the United States and his research team reported a placebo-controlled study which included 1,197 patients (Mean age: 63.1 years). Treatment with tadalafil (5 mg) markedly increased maximum urinary flow [11].

In the context of benign prostatic hyperplasia, several studies have investigated tadalafil's impact on prostate size. McVary et al. (2007) initially found that tadalafil could provide significant

symptom relief in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia, though it did not directly address prostate volume. However, subsequent research, such as that by Roehrborn et al. (2010, 2014), indicated improvements in peak urinary flow rate and voiding efficiency with tadalafil, suggesting a potential secondary effect on prostate size or the ability to reduce obstruction.

However, while the evidence for tadalafil's effect on prostate size is promising, it remains less robust than its impact on symptoms and flow rates.

Potential Benefits beyond Symptomatic Relief

In addition to improving urinary flow and reducing symptoms, tadalafil's role in addressing other aspects of benign prostatic hyperplasia, such as nocturia and bladder function, is noteworthy.

In 2020, Ryosuke Takahashi from Japan and his research team demonstrated that tadalafil can markedly improve nocturia and quality of life in patients suffering from nocturia related to benign prostatic hyperplasia, a common and bothersome symptom of the condition.

They reported a study which included 31 patients (Mean age: 74 years) with a mean prostate volume of 31 ml. Tadalafil treatment (5 mg once daily) markedly improved nocturia after 4 weeks, and treatment was not associated with serious adverse effects. The authors suggested that tadalafil can offer a clinically meaningful treatment option for benign prostatic hyperplasia patients having nocturia [12].

Moreover, tadalafil has been shown to enhance endothelial function, potentially addressing some of the underlying vascular components of benign prostatic hyperplasia.

In 2017, Kazuhiko Fukumoto from Japan and his research team reported a study which included twenty patients 20 patients (Median age: 65 years) who had enlarge prostate (Mean volume: 36.2 ml) and didn't respond to a α1-blocker. They responded to tadalafil (5 mg daily) with a marked symptomatic improvement with improvement in symptoms of bladder overactivity.

Treatment was associated with marked improvements in vascular function and vascular endothelial function. The authors suggested that the improvement in intrapelvic blood flow improved vascular endothelial function and voiding symptoms [13].

Mechanism of Action

Tadalafil works by inhibiting the enzyme phosphodiesterase type 5, which leads to increased levels of cyclic guanosine monophosphate (cGMP) in smooth muscle cells. This action facilitates smooth muscle relaxation in the prostate and the bladder, improving the voiding function and potentially reducing bladder outlet obstruction. Additionally, tadalafil improves endothelial function and has been suggested to exert anti-inflammatory and anti-fibrotic effects in the lower urinary tract (Fukumoto et al., 2017). These mechanisms of action support the rationale for tadalafil's efficacy in alleviating lower urinary tract symptoms associated with benign prostatic hyperplasia [13, 14].

Conclusion

Tadalafil monotherapy represents a promising and effective treatment option for patients with benign prostatic hyperplasia, providing relief from urinary symptoms, improving peak urinary flow rates, and possibly even reducing prostate volume.

Research has shown that long-term use of tadalafil can improve benign prostatic hyperplasia symptoms and may have a mild effect in reducing prostate volume, but these results are not as dramatic as those observed with hormonal treatments like finasteride or dutasteride.

Although its effects on prostate size remain an area for further investigation, its efficacy in managing lower urinary tract symptoms is well-established, and it offers an attractive alternative to other pharmacologic therapies.

Given its favorable safety profile, ability to improve endothelial function, and benefits in nocturia and quality of life, tadalafil is a valuable treatment option for many patients with benign prostatic hyperplasia benign prostatic hyperplasia.

Conflict of interest: None.

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