REVIEW PAPER

FUNCTIONAL UROLOGY

Current drug therapy of patients with BPH-LUTS with the special emphasis on PDE5 inhibitors

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Introduction Benign prostatic hyperplasia (BPH) is the most common cause of lower urinary tract symptom (LUTS) development in men [1]. The intensity of the symptoms may vary from mild to severe, significantly affecting the quality of life. Erectile dysfunction (ED) is one of the most challenging issues in modern urology that significantly influences the quality of life in men worldwide. The objective of this literature review was to analyze the current drug therapies of patients with BPH-LUTS, with the special emphasis on PDE5 inhibitors.

Material and methods The authors searched the literature for the period from 2000 until 2015 in MEDLINE and PubMed.

Results Twenty-three articles were selected based on their reliability. A detailed analysis of the selected papers was performed. Primary attention was given to articles describing the use of PDE5. Works describing the use of different groups of drugs in patients with BPH-LUTS were also selected.

Conclusions The current literature analysis suggests that the introduction of PDE5 inhibitors in clinical practice for the treatment of patients with BPH-LUTS will allow for significant expansion of the therapeutic options for the treatment of this disease.

Key Words: benign prostatic hyperplasia (BPH) ‹› erectile dysfunction (ED) ‹› PDE5 inhibitors ‹› lower urinary tract symptoms (LUTS)

INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common cause of lower urinary tract symptom (LUTS) development in men [1]. The intensity of the symptoms may vary from mild to severe, significantly affecting the quality of life (QoL). Approximately 40% of men older than 50 years and 80% older than 80 years are known to have BPH [1]. They report various LUTS, such as weak urine stream, stuttering urination, need to strain during urination, urinary spillage, feeling of incomplete bladder emptying, frequent urination, urination at night (nocturia) and urgency [1].

According to the guidelines AUA and EAU, the first-line therapy for BPH after non-drug treatment is the drug therapy, including alpha-adrenergic antagonists and 5-alpha reductase inhibitors or their combination and PDE-5 inhibitors, as well as other pharmacological groups [2, 3]. Unfortunately, patients develop a significant number of sexual side effects resulting in limited administration of the aforementioned drugs, in many cases, at the expense of efficacy.

Erectile dysfunction (ED) is one of the most challenging issues in modern urology that significantly influences the QoL in men worldwide. Erection as a complex phenomenon involves arterial dilatation, trabecular smooth muscle relaxation and corporal veno-occlusive mechanism activation [4]. ED is a persistent inability to attain and maintain penile erection sufficient to permit sexual performance [5]. The results of the study conducted in 1948 by Kinsey et al. [6] showed that approximately 10 million American men (1 in 10) have ED. Another large-scale epidemiological study was completed in 1994 (Massachusetts Male Aging Study). The authors reported the presence of ED in 52% of men aged 40 to 70 years [7]. In 2012,

an epidemiological study was conducted to assess the prevalence of ED in the population of 20- to 75-year-old men in the Russian Federation [8]. The results of the survey showed that 10.1% of responding men had no ED signs, whereas 71.3% had mild, 6.6% had moderate and 12% had severe ED. Therefore, 1101 of 1225 respondents had ED symptoms [8]. A series of studies determined the main predisposing factors of ED development, including hypertensive disease, cardiovascular diseases and diabetes mellitus [9].

Possible mechanisms of LUTS include decreased activity of cyclic guanosine monophosphate (cGMP), RhoA-kinase hyperactivity, chronic ischemia of pelvic organs and hyperactivity of the autonomic nervous system [10]. Administration of PDE5 inhibitors may positively affect all aforementioned proposed mechanisms of LUTS development, resulting in symptoms improvement [11]. Phosphodiesterase type 5 is primarily located in the muscular layer of the urinary bladder neck, prostatic urethra and prostate [12]. Administration of PDE5 inhibitors results in the increase of intracellular cGMP concentration, smooth muscle relaxation and vasodilatation in the urogenital tissues [13].

The objective of this review is to determine the place of PDE5 inhibitors in the individualized approach to only BPH-LUTS treatment with concurrent ED treatment, based on the literature review and personal experience.

MATERIAL AND METHODS

Two authors (K.K. and G.K.) independently searched the literature for the period from 2000 until 2015 in MEDLINE and PubMed using the following keywords in English: "enlarged prostate, benign prostatic hyperplasia, lower urinary tract symptoms, phosphodiesterase type 5 inhibitors, alpha-adrenergic antagonists, 5-alpha reductase inhibitors and erectile dysfunction". The discovered works were evaluated and analyzed for feasibility for inclusion in the current review. Primary attention was given to the articles describing the use of PDE5 inhibitors as monotherapy in various groups of patients: patients with BPH-LUTS and patients with concurrent BPH-LUTS and ED. Works describing the use of different groups of drugs in patients with BPH-LUTS were also selected.

Twenty-three articles of highest reliability (inclusion criteria was maximal level of evidence) were selected, 6 of which were dedicated to the monotherapy with PDE5 inhibitors in patients with BPH-LUTS and concurrent BPH-LUTS and ED [18–23]; 4 articles reported monotherapy with alpha-adrenergic antagonists in patients with BPH-LUTS [24–27]; 5 were dedicated to monotherapy with 5-alpha reductase inhibitors in men with BPH-LUTS [28–32]; 7 reported combined therapy with alpha-adrenergic antagonists and PDE5 inhibitors in patients with BPH-LUTS [33–39]; 1 reported combined therapy with alpha-adrenergic antagonists and 5-alpha reductase inhibitors in patients with BPH-LUTS [40]. Thirty- one articles – retrospective works, clinical cases and low reliability publications were excluded from the analysis. The current authors chose tadalafil as the only PDE5 inhibitor registered for BPH treatment, a long-acting drug, to assess the effect of PDE5 inhibitors. As mentioned before, PDE5 is present in the tissue and vessels of the urinary bladder neck, prostatic urethra, prostate and cavernous bodies of penis [12]. Therefore, this enzyme may have significant effect on the pathogenesis of BPH-LUTS. In addition, there is information stating that PDE5 expression in the spinal cord area is responsible for urination control [14]. Tadalafil administration appeared to increase the amount of cyclic nucleotides in the urinary bladder, prostate and cavernous bodies of penis. Such conclusions support the hypothesis about the ability of tadalafil to improve erectile function *via* the increase in the cGMP level and relaxation of vascular smooth muscle. In addition, the increased cGMP level results in relaxation of the urinary bladder, urethra and prostate, improvement of oxygenation and inhibition of the proliferation of prostate stromal cells [15, 16, 17].

RESULTS

Monotherapy with PDE5 inhibitors

Several clinical studies were conducted to assess the efficacy of PDE5 inhibitor administration in patients with concurrent LUTS and ED [18, 19, 20]. International Prostate Symptom Score (IPSS), BPH Impact Index, International Index of Erectile Function (IIEF) scores and Qmax value were used for efficacy assessment. Gacci et al. [21] performed a meta-analysis of the studies comparing PDE5 inhibitor administration and placebo, combined therapy with PDE5 inhibitors and alpha-adrenergic antagonists and monotherapy with alpha-adrenergic antagonists. Dong et al. [18] presented the results of tadalafil monotherapy comparison with placebo. The studies included patients with isolated LUTS and with concomitant ED. Both studies demonstrated significant improvement of IPSS and IIEF scores compared to placebo. Dong et al. [18] noted a significant decrease of total IPSS score by 2.19 points compared to the placebo, in addition to statistically significant improvement of irritative and obstructive domains of IPSS, BPH Impact Index and QoL param-

eter. No significant improvement of Qmax was noted in any work [21]; however, Dong et al. [18] described a statistically significant change of this parameter in patients receiving tadalafil 5 mg. In this case, different patient enrollment criteria for administration of tadalafil 5 mg (patients with concurrent BPH-LUTS and ED and sexually active patients) were used. Such differences in patient enrollment may explain the different results obtained for Qmax. The lack of the treatment effect on the urodynamic parameters of the urinary bladder contractility during long-term treatment with tadalafil was also demonstrated in the randomized study by Dmochowski et al. [20]. In addition, no significant changes in residual urine was reported during study drug administration [20]. The obtained results suggest other mechanism of LUTS improvement during PDE5 inhibitor administration than mechanic changes. This is well known and allows for the acknowledgement of the complex, yet not completely understood, mechanism of the influence of PDE5 inhibitors on LUTS *via* increasing the vascularization and reducing ischemia as a result of nitrogen oxide interaction with cGMP, as well as, a decrease in inflammatory and proliferative changes due to RhoA/RhoA-kinase activity [20].
Baseline patient characteristics also influenced the final result of the treatment with PDE5 inhibitors. Gacci et al. [21] performed the regression analysis, which showed that patient age, baseline body mass index and baseline IPSS score significantly influenced the treatment effect. Younger age, low body mass index and higher baseline IPSS score led to a better effect of the treatment with PDE5 inhibitors. Therefore, the ideal patients for treatment with PDE5 inhibitors are young men with high IPSS scores [21]. Porst et al. [19] proved the absence of prostate specific antigen (PSA) level influence on the effect of the treatment with PDE5 inhibitors [19].
The literature data analysis suggests some common pathophysiological mechanisms of LUTS and ED development, in many cases related to the patient age. PDE5 inhibitors block cGMP degradation, thus allowing for excessive relaxation of the smooth muscle of the urinary bladder, prostate and urethra. Administration of tadalafil 5 mg daily as monotherapy is justified in patients with BPH-LUTS with or without concurrent ED [22–23].

Monotherapy with alpha-adrenergic antagonists

Now, most publications dedicated to the administration of alpha-adrenergic antagonists in patients with LUTS focus on the use of silodosin because this drug is the youngest selective alpha-adrenergic antagonist introduced in clinical practice.

Novara et al. [24] analyzed the results of silodosin registration studies. Data of 1494 patients involved in three 3-month randomized, controlled studies (RCSs) were pooled. Silodosin was more active when compared to the placebo according to the total IPSS score, QoL and Qmax values. The most common side effect was retrograde ejaculation (22%, silodosin group; 0.9%, placebo group). Incidence of dizziness and orthostatic hypotension demonstrated no statistically significant differences between the groups [24]. Further studies showed a moderate positive effect on nocturia in patients with more than 2 episodes of nighttime urination (urination frequency decreased in 61% of cases in the silodosin group *vs.* 49% in the placebo group) [25].
A well-known concept of the treatment of patients with acute urinary retention without a urethral catheter was checked by Kumar et al. [26]. The authors included 60 patients with acute urinary retention in the randomized study. Patients received 8 mg of silodosin daily. The effect of the administered treatment was reported in 77% of patients in the silodosin group and 37% in the placebo group. The presence of more than 800 mL of urine and an IPSS score greater than 25 in patients with acute urinary retention were considered the risk factors of treatment failure [26].
In a 12-week RCS involving 532 patients conducted in Korea, similar efficacy and safety profiles were reported in the patients receiving silodosin 8 mg/day and 2 4 mg/day [27].
It can be concluded that silodosin is effective in the treatment of patients with LUTS. It has an excellent safety profile with respect to cardiovascular complications and significant incidence of retrograde ejaculation.
Administration of alpha-adrenergic antagonists in patients with moderate-to-severe BPH-LUTS is a first-line drug treatment due to its fast onset of action, good efficacy and favorable side effect profile.

Monotherapy with 5-alpha reductase inhibitors

Safety of dutasteride administration was questioned in the CombAT study due to the high risk of cardiovascular complications reported in dutasteride group when compared to placebo. This fact motivated Locke et al. [28] to conduct a meta-analysis of 12 RCSs (18,802 patients; duration: 6-208 weeks). Dutasteride administration was not associated with increased incidence of heart failure, myocardial infarction or stroke. The authors reported the absence of an apparent relationship between the development of cardiovascular complications and dutasteride administration [28].

The relationship between dutasteride administration and high-risk prostate cancer development is a debatable issue. The Prostate Cancer Prevention Trial study pointed out the increase in the prostate cancer incidence in men consuming a significant volume of alcohol in the group of therapy with 5-alpha reductase inhibitors [29]. Fowke et al. [30] investigated the aforementioned hypothesis using the REDUCE study data. The study enrolled 6374 patients; 25% were not consuming alcohol, 49% were consuming 1 to 7 glasses per week and 26% had severe alcohol dependence (>7 glasses per week). In this study, alcohol intake by the patients in the dutasteride and placebo groups was not associated with the increased incidence of low- and high-risk prostate cancer. However, incidence of high-risk prostate cancer in patients with severe alcohol dependence in the dutasteride group was 86% higher than in non-drinkers. Patients not consuming alcohol demonstrated a reduced incidence of high-risk prostate cancer development. A similar tendency was not reported in the group of patients with severe alcohol dependence. Alcohol consumption had negative effect on the relationship between dutasteride administration and high-risk prostate cancer development [30].
Dutasteride's effect on nocturia was investigated in several 24-month, phase III studies involving 4321 patients. By the 24th month of drug administration, most patients demonstrated a decrease in nighttime urination frequency when compared to the placebo group ($p < 0.05$). The most significant effect was noted in patients with more than 2 episodes of nighttime urination at baseline [31].
Wada et al. [32] studied the effect in 52 patients receiving dutasteride, in addition to alpha-adrenergic antagonists, if they were not satisfied with their treatment. The authors concluded that long-term dutasteride administration as the adjunct therapy resulted in moderate improvement of the obstructive symptoms.
According to the recommendations of the EAU, 5 -reductase inhibitors should be administered to men with moderate-to-severe LUTS and enlarged prostates (>40 mL) as well as with high PSA level (>1.4–1.6 ng/mL). Due to the slow onset of action, they are suitable for long-term treatment only (many years) [3].

Combined therapy with alpha-adrenergic antagonists and PDE5 inhibitors

Administration of alpha-adrenergic antagonists is the first-line therapy in patients with BPH-LUTS. Several works suggested the feasibility of therapy with PDE5 inhibitors and alpha-adrenergic antagonists [33–39]. However, administration of this combination seems questionable, considering the potential drug interactions leading to critical blood pressure (BP) lowering. This aspect was studied in several works. Kloner et al. [33] studied the safety of tadalafil combined with 2 different alpha-adrenergic antagonists in a double-blind, placebo-controlled, randomized crossover study. The authors investigated hemodynamic effects during administration of doxazosin 8 mg for 7 days followed by the addition of tadalafil 20 mg and during the administration of tamsulosin 0.4 mg for 7 days followed by the addition of tadalafil 10 and 20 mg. In the first part of the study, patients receiving concomitant doxazosin and tadalafil reported significant lowering of the mean maximum systolic BP compared with placebo. In addition, 3 patients had significant dizziness not correlated with BP values. In the second part of the study (tamsulosin administration in combination with tadalafil), no significant BP lowering was noted after adding tadalafil. Gualiano et al. [34] also did not show significant hemodynamic changes in patients receiving the combination of tadalafil 20 mg and alfuzosin 10 mg daily.
Singh et al. [37] studied the efficacy of combined therapy with tamsulosin 0.4 mg/day and tadalafil 10 mg/day *vs.* monotherapy with each drug. This randomized study included 133 patients with BPH-LUTS. The efficacy of combined therapy (IPSS score) appeared to be higher when compared to monotherapy with tadalafil ($p < 0.05$), but not monotherapy with tamsulosin. Moreover, the efficacy of combined therapy with regard to the ED symptoms (IIEF scale) was higher than in the tamsulosin group.
The aforementioned studies and some others [38, 39] demonstrated the efficacy of combined therapy with PDE5 inhibitors and alpha-adrenergic antagonists in patients with LUTS. Although daily combined therapy with tadalafil 5 mg and alpha-adrenergic antagonist is promising, no results of any randomized, double-blind study, in which conduct is very important, have been published.
Thus, the concomitant administration of tadalafil and the nonselective alpha-adrenergic antagonist doxazosin is contraindicated, whereas concomitant administration of tadalafil and selective alpha-adrenergic antagonists is possible in certain clinical cases (with necessary precautions).

Combined therapy with alpha-adrenergic antagonists and 5-alpha reductase inhibitors

The role of combined therapy with alpha-adrenergic antagonists and 5-alpha reductase inhibitors is well studied, and the combination is recommended

for the treatment of moderate-to-severe BPH-LUTS in patients with an apparent risk of progression by all main clinical guidelines.

MTOPS was the first study to assess combined therapy with alpha-adrenergic antagonists and 5-alpha reductase inhibitors, for which the results were published over 10 years ago. Fwu et al. analyzed the results of this study in 2013. In their work, they studied the effect of monotherapy and combined therapy based on the results from various QoL tools and the effect on sexual function using Brief Male Sexual Function Inventory within the 4-year study [40]. Treatment with finasteride and combined therapy resulted in sexual function worsening, whereas doxazosin administration had minimal negative effect.

These data support EAU recommendations for dutasteride and tamsulosin combination administration in patients at high risk for disease development (higher prostate volume, low Qmax and high PSA) [3].

There are some limitations including the brief discussion of different combinations for BPH therapy, silodosin as the only discussed alpha-blocker and absence in this review of some drug groups (muscarinic receptor antagonists and beta-3 agonists). This was done due to the strong limitation of the text size.

CONCLUSIONS

Specialists can evaluate various factors to choose a particular drug treatment for patients with BPH-LUTS, including the degree of the symptom severity, concurrent diseases, the possibility of therapeutic effect on the symptoms and patient's QoL and the potential development of side effects associated with certain drugs. Despite the fact that no new drug for the treatment of LUTS was registered during the past 24 months, studies conducted within this period make us take a fresh look at the old principles. The performed analysis suggests the possibility for implementation of individualized medicine principles, allowing for the selection of the most effective drug or drug combination in each specific case.

The current literature analysis suggests that the introduction of PDE5 inhibitors in clinical practice for the treatment of patients with BPH-LUTS will allow for significant expansion of the therapeutic options for the treatment of this disease.

CONFLICTS OF INTEREST

Diana Priymak is an employee of Eli Lilly and Company. No other authors have any conflicts of interest to disclose.

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