Benign prostatic hyperplasia (BPH/LUTS) is one of the most common urinary disorders in elderly men. The symptoms of the disease include prostate gland enlargement, bladder outlet obstruction, and lower urinary tract symptoms (LUTSs) (1). BPH predisposes patients to bladder infections and bladder stone formation and increases their risk of urinary retention, which in turn causes renal failure (2). The disease is becoming an important diagnostic-therapeutic and socioeconomic problem, considering the increase in the life expectancy of men. BPH often requires surgical treatment (3); however, in recent years, the number of surgical interventions performed has significantly decreased because of the high efficacy of pharmacotherapy, including combination treatment mostly with 2 drug classes, namely, 5-α-reductase inhibitors and α-1-adrenolytics with a different pharmacological activity (4). α-1-Adrenolytics contribute to decreasing urinary symptoms, by improving objective parameters, increasing maximum urine flow rate, and decreasing urine retention after miction (1). Noradrenaline acts at α-1-adrenergic receptors (α-1-ARs) in the neck and sphincter of the urinary bladder. It promotes contraction and urinary retention, and controls the smooth muscles in the prostate capsule and prostate urethra. The selective α-1-AR blockers relieve obstruction by relaxing the smooth muscle in the prostate and bladder neck (1). The most common drugs available from this class are doxazosin, tamsulosin, alfuzosin, and terazosin (Fig. 1).

Alfuzosin known chemically as N-[3-[(4-amino-6,7-dimethoxyquinazolin-2-yl)-methylamino]propyl]tetrahydrofuran-2-carboxamide, is a quinazoline derivative α-adrenergic blocking agent active after oral administration. It is a selective antagonist of postsynaptic α-1-ARs located in the prostate gland, at the base of the urinary bladder and...
in the prostatic urethra. Inhibition of these adrenoceptors leads to the relaxation of smooth muscle in the bladder neck and prostate, resulting in the improvement of urine flow and a reduction in symptoms in BPH. Alfuzosin also inhibits the vasoconstrictor effect of circulating and locally released catecholamines (epinephrine and norepinephrine), resulting in peripheral vasodilation (5). Alfuzosin is rapidly absorbed from the alimentary tract, reaching peak plasma concentrations on average 1.5 h after intake. Food does not impact alfuzosin bioavailability. In patients over 75 years of age, this drug has a faster absorption rate and reaches higher blood plasma concentrations. Alfuzosin metabolites are not pharmacologically active. The half-life is about 4.8 h, and it is not significantly prolonged in patients with renal failure. Alfuzosin undergoes extensive metabolism by the liver using CYP3A4 as the principal hepatic enzyme isoform, and is metabolized by 3 metabolic pathways: oxidation, O-demethylation,
Clinical evaluation of α1-adrenolytics in patients diagnosed with BPH

and N-dealkylation. Only 11% of the administered dose is excreted unchanged in the urine (5). Doxazosin known chemically as 1-(4-amino-6,7-dimethoxy-2-chinazolinyl)-4-(2,3-dihydro-1,4-benzodioxixin-2-ylcarbonyl)piperazin is a selective α1-AR antagonist. Doxazosin acts by inhibiting postsynaptic α1-ARs in vascular smooth muscles. Doxazosin competitively antagonizes the pressor effects of phenylephrine (an α1-AR agonist) and the systolic pressor effect of noradrenaline. The antihypertensive effect of doxazosin results from a decrease in systemic vascular resistance, and the parent compound doxazosin is primarily responsible for the antihypertensive activity. It is easily absorbed from the alimentary tract. Peak blood plasma concentration is reached on average after 2 h of drug intake. Protein binding is 98%, and biological half-life is 22 h (5).

Terazosin chemically known as 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-((tetrahydro-2-furanyl)carbonyl)piperazine is a selective α1-AR antagonist. Inhibition of α1-ARs in the vasculature and prostate results in muscle relaxation, decreased blood pressure, and improved urinary outflow in symptomatic BPH. As there are relatively few α1-ARs in the body of the bladder, terazosin decreases obstruction syndromes without any impact on contraction of the whole urinary bladder. Obstruction of α1-ARs leads to decreased blood pressure following a decrease in peripheral vascular resistance. This drug causes a decreased systolic and diastolic pressure in both standing and sitting positions, but a stronger drug activity on diastolic pressure has been reported. It is easily absorbed from the alimentary tract. Bioavailability is 90% (5).

Tamsulosin known chemically as 5-[2-[2-(2-ethoxyphenoxy)ethylamino]propyl]-2-methoxy-benzenesulfonamide is a selective α1-AR antagonist. Tamsulosin acts by inhibiting postsynaptic α1-ARs in vascular smooth muscles. This drug decreases symptoms in irritation syndromes and in obstruction, in which contraction of smooth muscles in the lower urinary tract plays a significant role. Tamsulosin increases maximum flow rate following smooth muscle relaxation in the prostate gland and urethra. Tamsulosin is rapidly absorbed from the intestine and is almost completely bioavailable (6).

The aim of this study was to evaluate α1-adrenolytics in combination therapy with finasteride in patients diagnosed with BPH.

METHODS

The clinical trial was conducted in 2 stages: Stage I from October 2008 to November 2009, and Stage II from November 2009 to November 2010. A total of 10 066 patients, n1 = 4315 and n2 = 5751, respectively, for each stage were enrolled in 50 urological centers in Poland participating in the clinical trial. This clinical trial was organized by Moneo Pharma Group. The researchers who conducted the trial were urologists from different regions of Poland. The clinical trial involved 6 follow-up visits – the time interval between every visit was 2 months.

The most frequently reported discomforts were as follows: frequent urination in 77.5% (n = 7804) of the patients, nocturia in 78.13% (n = 7865), decreased size and strength of the urinary stream in 67.33% (n = 6778), and compelling urge to urinate (urgency) in 62.43% (n = 6285). The detailed data are presented in Fig. 2.

The following data on co-morbidities were collected: hypertension, diabetes, elevated cholesterol...
and lipid levels, erectile dysfunctions, and neurological diseases (Fig. 3).

The data, including those self-reported by the patients, were stored in a database available to urologists to facilitate the selection of a suitable pharmacotherapy.

The pharmacotherapy selected was applied to all patients. The patients were prescribed finasteride at a dose of 5 mg/day because of BPH and urinary dysfunctions. In addition, the combination therapy of finasteride and α1-adrenolytics consisting of the following: alfuzosin (10 mg/day), doxazosin (4 or 6 mg/day), tamsulosin (0.4 mg/day), and terazosin (10 mg/day).

Patients were included in the study if they met the following inclusion criteria: LUTSs, age > 40 years, BPH, and finasteride use for at least 2 weeks. The mean age of the patients was 67 years (range, 45–93 years; median, 67.00; SD, 8.304). The clinical trial involved 6 follow-up visits and lasted 25 months. On the first visit, a self-reported evaluation and physical examination, including a digital rectal examination (DRE), were performed. The data pertaining to LUTSs were evaluated using IPSS (International Prostate Symptoms Score) with regard to the intensification or attenuation of the urinary system symptoms. Moreover, the patients underwent additional examinations, including serum concentrations of prostate-specific antigen (PSA), urinary tract ultrasonography (USG) with evaluation of total prostate volume (TPV), and uroflowmetry with evaluation of residual urine volume. These all examinations were repeated on the sixth visit, after 12 months of treatment.

On the succeeding visits, the data pertaining to LUTSs were evaluated using IPSS with regard to the intensification or attenuation of the urinary system symptoms. Furthermore, whether the treatment was continued or modified after the first visit was recorded; in addition, the possible adverse effects of the pharmacotherapy were also documented. On the second and on the third visit, uroflowmetry with evaluation of residual urine volume was again performed.

Based on the results of the physical examination, BPH occurred to be concomitant with other diseases such as hypertension in 51.50% of patients (n = 5184), diabetes in 20.01% (n = 2216), hypercholesterolemia and hyperlipidemia in 16.03% (n = 1614), erectile dysfunctions in 16.77% (n = 1689), neurological diseases (Parkinson’s disease and multiple sclerosis) in 3.92% (n = 395), and other comorbidities in 4.10% (n = 413; Fig. 2).

On the second visit, in addition to the administration of finasteride at a dose of 5 mg/day in 10,066 patients, the combination of drug therapy consisting of finasteride + an α1-adrenolytic was administered to 63.65% of the patients (n = 6408/10,066), including 52.30% (n = 3352), 34.14% (n = 2189), 7.59% (n = 487), and 5.93% (n = 380) of the patients receiving tamsulosin, doxazosin, alfuzosin, and terazosin, respectively (Fig. 4).

This combination of drug therapy was caused by a low efficiency of monotherapy applied earlier.

RESULTS

The analyzed group, in which the combination of drug therapy was prescribed on the second visit, included 6408/10,066 (63.05%) patients. On the third visit following the administration of an α1-adrenolytic, attenuation of BPH symptoms was observed in 3882/6408 (60.58%) patients. The improvement was most common within the spectrum of the following symptoms: residual urine after miction (62.3%), frequent urination (61.7%), decreased size and strength of the urinary stream (61.5%), and nocturia (60.2%).

Adverse effects were observed in 2306 patients (36%) after combination of drug therapy. The most common side effects were reported in patients using doxazosin (n = 897; 14%) and included palpitations...
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(434 patients; 6.77%), arrhythmia (n = 351; 5.47%), tachycardia (n = 142; 2.21%), chest pain (n = 353; 5.50%), orthostatic hypotension (n = 601; 9.37%), paresthesia (n = 67; 1.04%), apathy (n = 101; 1.57%), and drowsiness (n = 112; 1.74%). In the group of patients using alfuzosin, the following adverse effects were observed (n = 450; 7%): orthostatic hypotension (n = 347; 5.41%), stomachache (n = 311; 4.85%), tachycardia (n = 201; 3.13%), palpitations (n = 86; 1.34%), rash (n = 68; 1.06%), and pruritus (n = 58; 0.90%). In the group of patients using terazosin, the following adverse effects were observed (n = 449; 7%): orthostatic hypotension (n = 257; 4.01%), palpitations (n = 172; 2.68%), tachycardia (n = 36; 0.56%), chest pain (n = 42; 0.65%), irritability (n = 28; 0.43%), anxiety (n = 31; 0.48%), weakness (n = 18; 0.28%), and drowsiness (n = 23; 0.35%). The least number of side effects were observed in patients using tamsulosin (n = 255; 4%) and included retrograde ejaculation (n = 83; 1.29%), decreased ejaculation (n = 124; 1.93%), orthostatic hypotension (n = 46; 0.71%), intraoperative floppy iris syndrome (n = 1; 0.01%) (Fig. 5).

The results of the following were analyzed: PSA levels, urinary tract USG with evaluation of TPV, and uroflowmetry with the evaluation of residual urine volume and maximal flow rate.

$\alpha_1$-Adrenolytics showed high efficiency in decreasing dysuric discomforts, improving objective parameters, increasing maximum flow rate, and decreasing residual urine after miction. The most efficient $\alpha_1$-adrenolytics were doxazosin and tamsulosin, which contributed to significant improve-

Table 1. Analysis of finasteride (F), alfuzosin (A), doxazosin (D), tamsulosin (Ta), and terazosin (Te) with mean values of $Q_{\text{max}}$, T flow, and Rv.

<table>
<thead>
<tr>
<th>II. Visit</th>
<th>III. Visit</th>
<th>VI. Visit</th>
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<tr>
<td></td>
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<tr>
<td>F</td>
<td>A</td>
<td>D</td>
</tr>
<tr>
<td>$Q_{\text{max}}$</td>
<td>9 mL/s</td>
<td>11 mL/s</td>
</tr>
<tr>
<td>T flow</td>
<td>47 s</td>
<td>40 s</td>
</tr>
<tr>
<td>Rv</td>
<td>90 mL</td>
<td>80 mL</td>
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Figure 5. Side effects after using $\alpha_1$-adrenolytics in "n" patients.
ment of maximum flow rate (Q_{max}) and time of micturition (T flow), and decreased residual urine after micturition R_{v} (Table 1).

From the abovementioned drugs, it is important to emphasize the uroselective activity of tamsulosin as it had the lowest influence on arterial blood pressure. Furthermore, finasteride confirmed its overall efficiency by the significant decrease in TPV by 35% and in PSA level by 30% observed even after 12 months of treatment (on the sixth visit).

In this clinical trial, on the second to the sixth visits, progressive improvement in the spectrum of LUTSs was observed as self-reported by patients (Table 2).

The McNemar’s test showed a significant difference in improvement of the spectrum of LUTSs between the second and sixth visits (p < 0.001). The prevalence of adverse effects after pharmacotherapy was also evaluated. ANOVA test was applied to elaborate the significance of difference between various parameters. The level of significance was set at 0.05. ANOVA test showed a significant difference in the total amount of adverse effects reported by patients between the second and sixth visits (p < 0.03).

The clinical trial was completed after the sixth visit, and the data on urological symptoms were analyzed at the last visit. Figure 5 shows the noticeable decrease of LUTSs owing to the efficiency of the combination therapy. In 376/6408 (5.86%) patients, the efficiency of combination of drug therapy with finasteride and an α-1-adrenolytic was low and patients qualified for surgical treatment.

**DISCUSSION**

The aim of this study was to evaluate the efficacy of α-1-adrenolytics in combination therapy with finasteride in patients with diagnosed BPH based on the clinical trial PLESS (Proscar Long-term, Efficacy and Safety Study) (6). The different pharmacological activities of the 2 drug groups, α-1-adrenolytics and 5-α-reductase blockers, probably influenced the long-term effects of BPH treatment in combination drug therapy. The combination therapy was more effective than placebo, α-1-adrenolytic monotherapy, or finasteride monotherapy in the suppression of BPH progression (6).

Until date of this study, few randomized studies have been conducted evaluating the long-term efficiency of BPH treatment with α-1-adrenolytics. The results of previous studies on combination therapy consisting of terazosin, alfuzosin, tamsulosin, and doxazosin after approximately 4 years demonstrated a long-lasting improvement in the degree of symptoms and uroflow rate (7). The α-1-adrenolytic doxazosin was demonstrated to suppress the duration of BPH. However, it did not contribute to the slowing down progression of the disease. α-1-A drenolytics were also prescribed to patients with hypertension and BPH. In these patients, combination therapy normalized arterial blood pressure and eliminated LUTSs. In the present study, doxazosin showed the highest number of side effects, such as palpitation, arrhythmia, tachycardia, and orthostatic hypotonia. However, according to Kirby (7), patients receiving doxazosin or terazosin with accurate arterial blood pressure data available did not report any discomforts, which is of clinical importance.

Furthermore, in both studies doxazosin showed a positive effect on lipid profiles by reducing LDL-cholesterol and triglyceride levels, and increasing HDL-cholesterol levels. Hence, doxazosin provides a peculiar health protection from cardiac infarction.
Clinical evaluation of α-1-adrenolytics in patients diagnosed with lower urinary tract symptoms (LUTS) or stroke. It is important to emphasize the uroselective activity of tamsulosin, since it had the lowest influence on arterial blood pressure compared to the other agents (8). However, it should be underlined that BPH can occur as full-blown LUTSs without prostate gland enlargement or as independent symptoms of benign prostatic obstruction. Therefore, tamsulosin is recommended for full-blown LUTSs, in which LUTSs are dominant. When symptoms of benign prostatic obstruction intensify, doxazosin is recommended (8). However, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial does not recommend pharmacotherapy with α-1-adrenolytic drugs to patients with hypertension and congestive heart failure (7). In the present study, tamsulosin was the safest and the most efficient α-1-adrenolytic but it should not be prescribed in sexually active patients because it may cause ejaculation disorders, such as decreased ejaculate or retrograde ejaculation. α-1-Adrenolytics are very efficient because they decrease dysuric discomforts, improve objective parameters, increase maximum flow rate, and decrease residual urine (9).

The Medical Treatment of Prostatic Symptoms (MTOPS) study reported a decrease in TPV by 25% in comparison with the placebo group, in patients administered only finasteride or finasteride + doxazosin. The decrease in TPV in the MTOPS study was comparable with that in our study, wherein patients underwent pharmacotherapy with finasteride at a baseline TPV of 40 mL or higher. Furthermore, compared to that in the placebo group, the estimated decrease in TPV by 25% in patients treated with finasteride and with a baseline prostate volume of 25 mL < TPV > 40 mL contributed to the beneficial value of the combination therapy with doxazosin in the clinical improvement of BPH. A decrease in TPV by 20% was observed in patients with a baseline prostate volume of 25 mL < TPV > 40 mL, who only took doxazosin as monotherapy and placebo (10).

The Veteran’s Administration Cooperative Study conducted a contrastive analysis between the activity of terazosin and that of finasteride and the combination of both with placebo (8). The study showed that α-1-adrenolytic drugs were more effective than finasteride after 1 year of pharmacotherapy. However, they were associated with more adverse drug reactions such as dizziness (9).

This medical trial conducted in Poland (n = 10 066) in 2 stages – Stage I from October 2008 to November 2009 and Stage II from November 2009 to November 2010 – demonstrated that in the 4806 patients (75%) who were receiving both α-1-adrenolytic drugs and finasteride, disease progression and LUTSs were suppressed, and micturition improved significantly within Qmax, T flow, and Rv and TPV decreased by 35%.

The data from the present medical trial confirmed the high efficiency of α-1-adrenolytics in combination therapy with finasteride administered to patients with extensive LUTSs related to BPH. The α-1-Adrenolytics evaluated in the study demonstrated high efficiency in improving dysuric discomforts, Qmax, T flow, and Rv. Furthermore, finasteride confirmed its overall efficiency by the significant decrease in TPV (35%) observed even after 12 months of treatment. It was also found to contribute to the attenuation of LUTSs, improvement in maximum flow rate, decrease in nocturia, and improvement in quality of life.

There is no conflict of interest. There is absence of any interest to disclose.

REFERENCES


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