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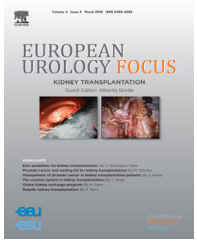

Benign Prostatic Obstruction

Which Drug to Discontinue 3 Months After Combination Therapy of Tadalafil plus Tamsulosin for Men with Lower Urinary Tract Symptom and Erectile Dysfunction? Results of a Prospective Observational Trial

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Abstract

Background: Safety and efficacy of tamsulosin and tadalafil for men with benign prostatic enlargement (BPE) and/or erectile dysfunction (ED) are defined. However, there are only a few pilot studies on combination therapy with these drugs for men with lower urinary tract symptom (LUTS)/BPE and ED. Moreover, preliminary reports are limited to 12 wk, without any information about subsequent therapies.
Objective: To evaluate the impact of discontinuation of tamsulosin versus tadalafil 12 wk after combination therapy.
Design, setting, and participants: Fifty consecutive patients with moderate-to-severe LUTS (International Prostate Symptom Score [IPSS] $>$ 7) and mild-to-severe ED (International Index of Erectile Function-5 [IIEF-5] $<$ 22) were treated with combination therapy (tamsulosin 0.4 mg/d plus tadalafil 5 mg/d) for 12 wk. After 12 wk, 25 patients discontinued tamsulosin (Group TAD), while 25 patients discontinued tadalafil (Group TAM).
Outcome measurements and statistical analysis: Efficacy variables were IPSS (total, voiding, storage) and IIEF-5. Paired samples *t* test and analysis of variance were used.
Results and limitations: Groups TAD and TAM presented similar features (age, BMI, metabolic profile) including symptoms scores at baseline. Similar and significant improvements in IPSS (total, voiding, and storage) and IIEF-5 were recorded in both groups after 12 wk of combination therapy (all $p <$ 0.001). Total IPSS was similar between the two groups at the end of the trial. However, we found between-group significant differences from baseline to 24 wk and from 12 to 24 wk in storage-IPSS (Group TAD: −3.32 vs Group TAM: −1.24, $p =$ 0.002; Group TAD: +0.24 vs Group

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TAM: +1.20, $p = 0.040$, respectively) and in IIEF-5 (Group TAD: +4.64 vs Group TAM: +0.16, $p < 0.001$; Group TAD: –1.64 vs Group TAM: –4.40, $p = 0.003$). No significant treatment-related adverse event was recorded in both groups.

Conclusions: After 12 wk of combination therapy, monotherapy with tadalafil for further 12 wk allows to preserve the improvement of storage IPSS and IIEF-5, in addition to total IPSS.

Patient summary: In this report we evaluated the discontinuation of tamsulosin or tadalafil after 12 wk of combination therapy. We found that tadalafil monotherapy, for a further 12 wk, aids in retaining the improvement of storage symptoms and erectile function.

1. Introduction

Lower urinary tract symptoms (LUTSs) and erectile dysfunction (ED) are significant health concerns that will increase in the next years in relation to the aging of the population. Both conditions have a significant impact on the overall male quality of life (QoL). LUTS, including voiding, storage, and postmicturition symptoms, secondary to benign prostatic hyperplasia (BPH) is frequently reported in middle-aged or older men. They range from mild to severe and could have a major impact on patients' QoL [1,2].

ED, defined as a persistent inability to achieve and maintain an erection sufficient for satisfactory sexual performance, is generally considered the result of para-aging factors and its prevalence has increased from 5% for men in their forties to 15% for those aged 70 yr [3].

Several large-scale epidemiological studies in different population have demonstrated a relationship between LUTS and ED in aging men that is independent of the effects of age or other comorbidities; particularly, men with severe LUTS presented an incidence of ED about three times higher than those without LUTS [1,4].

Today, although the molecular and pathological pathways potentially linking LUTS and ED are not clearly defined, several possible biological mechanisms including an altered nitric oxide/cyclic guanosine monophosphate pathway, an altered RhoA/Rho kinase signaling, systemic inflammation, pelvic ischemia, autonomic adrenergic hyperactivity, or overactivity have been investigated [5–8].

LUTS/BPH medical treatment may also have a significant impact on erectile function (EF). Several randomized controlled trials demonstrated that alpha-blockers (ABs) and 5-alpha reductase inhibitors, the most commonly prescribed drugs for managing patients with LUTS/BPH, can be associated with sexual adverse effects (AEs) such as decreased or loss of libido, ED, and ejaculatory dysfunction [9–11].

Phosphodiesterase type 5 inhibitors (PDE5-Is), the first-line therapy for ED, and particularly tadalafil 5 mg once daily, have been approved and considered an effective and well-tolerated treatment for LUTS [10].

Although the exact mechanism of action of PDE5-Is remains unclear, several preclinical and clinical trials have shown that they can reduce the smooth muscle tone of detrusor, prostate, and urethra together with an increased blood perfusion and oxygenation in the lower urinary tract; besides, its possible effect on chronic inflammation in the prostate and bladder has been proposed [12–15].

Safety and efficacy of PDE5-Is are well defined and combination therapy of PDE5-Is and ABs, particularly tamsulosin, the only AB approved by the Food and Drug Administration in combination with tadalafil, has shown to have an additive favorable effect on International Prostate Symptom Score (IPSS), International Index of Erectile Function-5 (IIEF-5) score, and maximum flow rate (Q_{max}) compared with monotherapy alone [16]. So far, the recent possibility to manage both LUTS and ED by PDE5-i alone or in combination with tamsulosin may open up new management strategies, considering that treatment of one condition may have an impact on the other. However, although a combination therapy is considered a promising and tailored approach seeking a balance between efficacy and tolerability in patients with LUTS, there are no data on when to move from a single-drug management to a combination approach and what are the possible changes in efficacy by switching from one treatment modality to another [17].

The aim of this observational study is to evaluate the impact of discontinuation of tamsulosin (0.4 mg) or tadalafil (5 mg) after 12 wk of combination therapy in patients with LUTS and ED.

2. Material and methods

2.1. Design and participants

A prospective observational trial was designed and performed. Across 12 mo, 50 consecutive patients with ED and LUTS suggestive of benign prostatic obstruction (BPO) were enrolled.

Inclusion criteria were age >40–80 yr, mild to severe ED (IIEF-5 < 22), moderate to severe LUTS (IPSS > 7), and Q_{max} > 5 ml/s (obtained from a uroflowmetry assessment). Exclusion criteria were hypersensitivity to tadalafil or tamsulosin, prostatic cancer or suspected with prostate-specific-antigen > 4.0 ng/ml, bladder lithiasis, previous prostatic surgery, urinary tract infection, neurogenic bladder, finasteride or dutasteride use within 6 mo, and a clinical history of urethral and/or proven bladder neck obstruction.

The study was performed in accordance with applicable laws and regulations, good clinical practices, and ethical principles as described in the Declaration of Helsinki.

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Institutional Review Boards for each site approved the study (Ethics Committee Approval OSS.15.031). All men provided written informed consent before initiating any trial procedure or therapy.

The assessment of patients included age, body mass index, waist circumference, blood pressure, clinical laboratory parameters, digital rectal examination, IPSS [18], IIEF-5 score [19], uroflowmetry, and postvoid residue (PVR) volume (evaluated with abdominal ultrasound immediately after voiding for uroflowmetry). The IPSS storage and voiding subscores, nocturia question, and IPSS-QoL index were also assessed.

After a 4-wk wash-out period from previous therapies for BPO and a 2-wk run-in period with tamsulosin 0.4 mg, patients were treated in two urologic centers with combination therapy of tamsulosin 0.4 mg/d and tadalafil 5 mg/d for 12 wk.

After 12 wk, the tamsulosin therapy was discontinued in one center, leaving 25 patients with tadalafil 5 mg/d alone (Group TAD), whereas tadalafil was discontinued in the other center, leaving 25 patients with tamsulosin 0.4 mg/d only (Group TAM; Fig. 1).

Patients were evaluated at screening time, after 12 wk of combination therapy, and after 12 wk of monotherapy.

Patients were instructed to self-administer the study drugs at the same time every day before sleep, without restrictions of food intake or timing of sexual activity. Patients were considered compliant if at least 90% of the drug amount was taken. Safety was assessed by evaluating patient-reported AEs, orthostatic vital signs, PVR, uroflowmetry, and clinical laboratory parameters. Patients with incomplete data sets were excluded from statistical analysis.

The variables considered for measuring the efficacy of treatment were the changes in IPSS and its subscores (total, voiding, and storage), the modification of IIEF-5 score, and the improving of Q_{max}. All follow-up visits, including uroflowmetry, were performed in the morning (from 8:00 am to 12:00 pm).

2.2. Statistical analysis

Differences between combination therapy and the two groups switched to monotherapy were calculated by an unpaired sample *t* test at baseline, 12 wk, and 24 wk, respectively. Mean changes between baseline and 12 wk and those between 12 and 24 wk were assessed by a paired sample *t* test for each treatment group. Between-group differences in change from baseline to 12 wk and from 12 to 24 wk were measured by one-way analysis of variance (ANOVA). All statistical analyses were performed with SPSS (SPSS Inc., Chicago, IL, USA). A *p* value of 0.05 or less was considered statistically significant.

3. Results

A total of 50 patients were treated with combination therapy of tamsulosin 0.4 mg/d plus tadalafil 5 mg/d for 12 wk [20]. Subsequently, 25 patients continued tadalafil 5 mg/d (Group TAD) and 25 continued tamsulosin 0.4 mg/d (Group TAM) only, for a further 12 wk. A Consolidated Standards of Reporting Trials (CONSORT) flowchart is shown in Fig. 1. All participants completed the study. Compliance with dosing requirements was over 90% in both groups. Both treatment groups were well balanced, without significant differences in metabolic features, age, and BPO-related characteristics (Table 1). The overall improvement from baseline to the first checkpoint after 12 wk of combination therapy (tadalafil plus tamsulosin) was statistically significant for all the items evaluated in

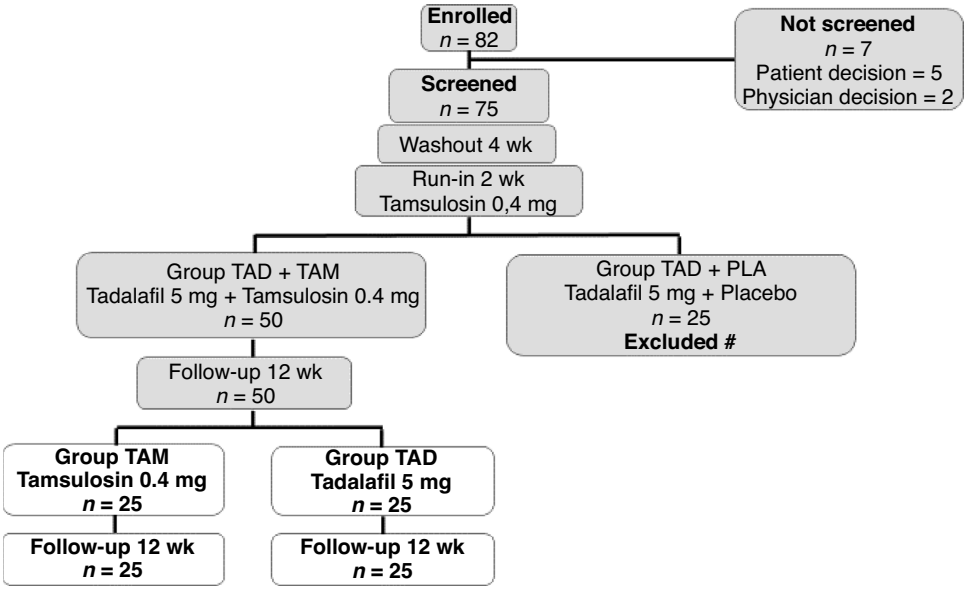

Fig. 1 – Disposition of patients. Patient Consolidated Standards of Reporting Trials (CONSORT) diagram.
PLA = placebo.
[a]Patients who did not perform combination therapy of tadalafil plus tamsulosin for 12 weeks did not continue the study.

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Table 1 – Patients' baseline characteristics.

	Group TAD (n = 25)		Group TAM (n = 25)		
	Mean ± standard deviation	Minimum–Maximum	Mean ± standard deviation	Minimum–Maximum	p value
Age (yr)	64.4 ± 8.3	48–77	67.0 ± 7.8	47–78	0.314
Weight (kg)	77.3 ± 8.2	67–85	75.9 ± 9.5	66–83	0.306
Body mass index (kg/m^2)	27.2 ± 5.3	24–32	25.9 ± 5.7	25–32	0.187
Abdominal obesity: waist circumference (cm)	107.8 ± 6.1	93–133	104.3 ± 4.5	78–128	0.142
Triglycerides (mg/dl)	164.4 ± 6.4	78–268	138.7 ± 6.8	81–203	0.128
HDL cholesterol (mg/dl)	48.7 ± 3.2	28–68	49.2 ± 2.6	31–62	0.275
Glycemia (mg/dl)	123.2 ± 4.5	79–224	107.7 ± 5.7	79–215	0.124
IPSS base	18.1 ± 5.8	8–29	19.6 ± 6.1	11–32	0.369
IPSS voiding base	8.3 ± 4.3	1–16	8.9 ± 3.4	5–20	0.537
IPSS storage base	8.8 ± 3.2	0–14	7.9 ± 3.2	2–13	0.354
IPSS QoL base	3.9 ± 0.9	3–6	3.8 ± 1.2	2–6	0.686
IIEF-5 base	12.3 ± 4.0	6–21	11.8 ± 3.2	6–18	0.587
Q_{max} base (ml/s)	14.0 ± 3.8	8.4–23.0	11.8 ± 4.1	3.4–19.7	0.55

HDL = high-density lipoprotein; IIEF-5 = International Index of Erectile Function-5; IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate; QoL = quality of life.

our population: total, voiding, and storage IPSS; IIEF-5; and Q_{max} (all $p < 0.001$). Between-group ANOVA, comparing Group TAD only versus Group TAM only, did not show significant differences for total IPSS ($p = 0.233$), storage IPSS ($p = 0.235$), voiding IPSS ($p = 0.02$); IIEF-5 ($p = 0.412$); and Q_{max} ($p = 0.908$; Table 2). As shown in Table 3, after 12 wk of monotherapy, a statistically significant difference was found between the two groups for mean IPSS storage score (Group TAD: +0.24 vs Group TAM: +1.2; $p = 0.040$; Fig. 2A), mean IIEF-5 score (Group TAD: −1.64 pts vs Group TAM: −4.4; $p = 0.003$; Fig. 2B), and mean Q_{max} (Group TAD: −2.41 ml/s vs Group TAM: −0.25 ml/s; $p = 0.001$; data not shown). Conversely, total IPSS and voiding IPSS were similar after the switch from combination to monotherapy (Fig. 3A and 3B). The proportion of patients reporting at least one treatment-emergent AE (TEAE) was similar between groups (TAD: 16% vs TAM: 20%; Table 4). TEAEs were mild to moderate in severity, with the most common being headache and back pain. There were no clinically significant changes in laboratory measurements or vital signs. No urinary retention was reported. None of the patients discontinued therapy because of a TEAE.

4. Discussion

Currently, there are four PDE5-Is approved for ED treatment which have been investigated for the treatment of LUTS with or without ED in randomized double-blind clinical trials. In a recent meta-analysis, combination of PDE5-is and ABs improved the IIEF-5 score (+3.6; $p < 0.001$), IPSS (−1.8; $p = 0.05$), and Q_{max} (+1.5 ml; $p < 0.001$) when compared with ABs alone [21].

The authors concluded that, although the cost-effectiveness analysis of this treatment is needed, PDE5-Is are effective and well tolerated either alone or in combination with ABs, particularly in young patients with severe LUTS/BPH. Moreover, a recent prospective urodynamic study evaluating the impact of daily tadalafil 5 mg on storage and voiding function in male BPH patients showed that mean bladder outlet obstruction index significantly decreased from 59.5 at baseline to 45.7 at 3 mo ($p = 0.001$), and to 42.9 at 12 mo ($p < 0.001$) [22].

Thus, tadalafil once daily, alone or in combination with tamsulosin, is increasingly prescribed in clinical practice as an effective therapy for LUTS/BPE and concomitant ED [23,24].

Table 2 – Change from baseline to 12 wk for Group TAD and Group TAM.

	Group TAD (n = 25)	Group TAM (n = 25)	p value*
Mean IPSS 12 wk	10.4	12.6	0.233
Delta3 M (baseline–12 wk)	−7.64	−6.96	
Mean IPSS voiding 12 wk	4.52	5.72	0.200
Delta3 M (baseline–12 wk)	−3.76	−3.24	
Mean IPSS storage 12 wk	5.2	5.48	0.235
Delta3 M (baseline–12 wk)	−3.56	−2.44	
Mean IPSS QoL 12 wk	2.24	2.04	0.461
Delta3 M (baseline–12 wk)	−1.72	−1.8	
Mean IIEF-5 12 wk	18.6	16.88	0.412
Delta3 M (baseline–12 wk)	+6.28	+5.12	
Mean Q_{max} 12 wk	18.28	13.97	0.908
Delta3 M (baseline–12 wk)	+4.27	+2.21	

IPSS = International Prostate Symptom Score; IIEF-5 = International Index of Erectile Function-5; Q_{max} = maximum urinary flow rate; QoL = quality of life.
* Levels of significance are calculated with paired sample t test ($p \leq 0.05$). The p value indicates the level of significance as per analysis of variance.

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Table 3 – Change from 12 wk to 24 wk for TAD and TAM groups.

	Group TAD ($n = 25$)	Group TAM ($n = 25$)	p value*
Mean IPSS 24 wk	12.48	14.32	0.386
Delta6 M (12–24 wk)	+2.08	+1.72	
Mean IPSS voiding 24 wk	6.2	6.36	0.456
Delta6 M (12–24 wk)	+1.68	+0.64	
Mean IPSS storage 24 wk	5.44	6.68	0.040
Delta6 M (12–24 wk)	+0.24	+1.2	
Mean IPSS QoL 24 wk	2.88	2.56	0.628
Delta6 M (12–24 wk)	+0.64	+0.52	
Mean IIEF-5 24 wk	16.96	12.48	0.003
Delta6 M (12–24 wk)	−1.64	−4.4	
Mean Q_{max} 24 wk	15.87	13.72	0.001
Delta6 M (12–24 wk)	−2.41	−0.25	

IPSS = International Prostate Symptom Score; IIEF-5 = International Index of Erectile Function-5; Q_{max} = maximum urinary flow rate; QoL = quality of life.
* Levels of significance are calculated with paired sample t test ($p \leq 0.05$). The p value indicates the level of significance as per analysis of variance.

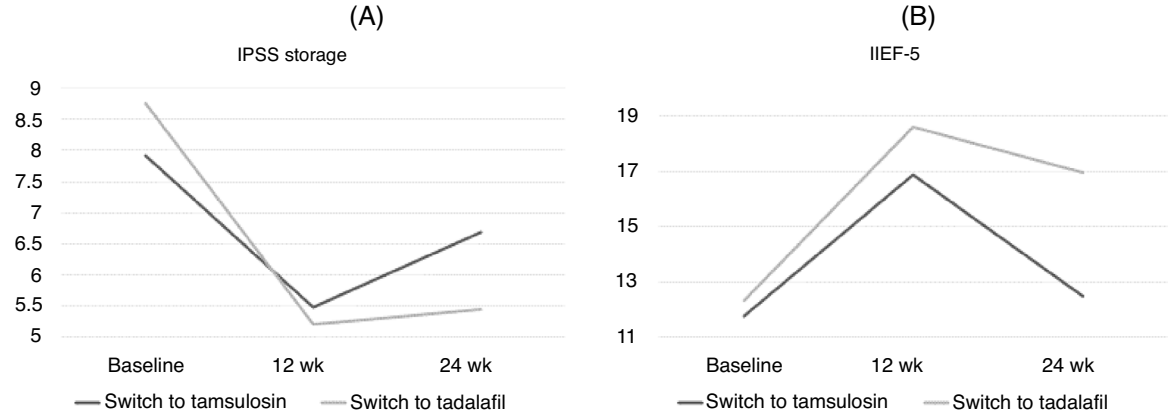

Fig. 2 – Change from baseline to 24 wk for Groups TAD and TAM.
Group TAD = discontinued tamsulosin; Group TAM, discontinued tadalafil; IIEF-5 = International Index of Erectile Function-5; IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate.

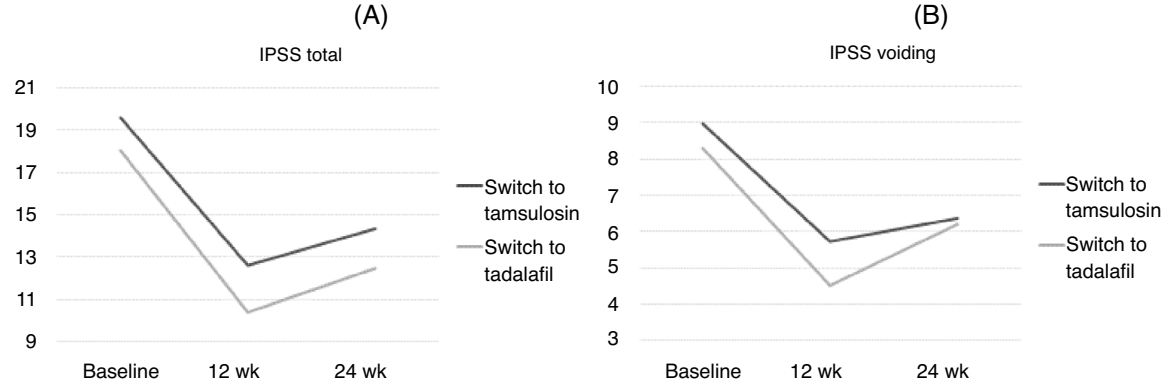

Fig. 3 – Change from baseline to 24 wk for the TAD and TAM groups. IPSS = International Prostate Symptom Score.

As expected, our results confirmed a significant improvement of total IPSS (−7), voiding IPSS (−3.5), storage IPSS (−3), IPSS-QoL (−1.8), IIEF-5 (+5.7), and Q_{max} (+4.2 ml/s; for all, $p < 0.001$) after 12 wk of combination therapy. Indeed, as we previously reported, combination therapy was associated with a better improvement of Q_{max} and voiding IPSS compared with tadalafil alone [20].

Interestingly, at the end of the study, after further 12 wk of monotherapy, patients in both groups shared similar total IPSS, voiding IPSS, and IPSS-QoL scores, all clinically meaningful improvements when compared with baseline. Indeed, Dong et al [25] showed that tadalafil alone seemed to be efficient to improve voiding subscore (−1.47) and IPSS-QoL (−0.35) compared with

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Table 4 – Summary of adverse events reported during the treatment period (24 wk).

	Group TAD (n = 25), n (%)	Group TAM (n = 25), n (%)
Any TEAEs	4 (16)	5 (20)
Serious AEs	0 (0.0)	0 (0.0)
Intensity		
Mild	3 (12)	3 (12)
Moderate	1 (4)	2 (8)
Severe	0 (0.0)	0 (0.0)
Headache	2 (8)	2 (8)
Nasopharyngitis	0 (0.0)	1 (4)
Back pain	1 (4)	1(4)
Dizziness	0 (0.0)	0 (0.0)
Dyspepsia	1 (4)	0 (0.0)
Ejaculatory dysfunction	0 (0.0)	1 (4)

AEs = adverse events; TEAEs = treatment-emergent adverse events.

placebo, although their results were not clinically relevant, because a mean change less than 3 points in IPSS was recorded.

In our study, patients in the TAD group experienced a statistically significant but not clinically relevant (<1-point) change in storage IPSS when compared with patients in the TAM group. However, in both groups we observed a statistically and clinically significant improvement from baseline. Our results confirmed the long-term effect of PDE5-i treatment on LUTS, particularly storage LUTS and that this effect is maintained for at least 12 wk when treatment is suspended.

The urodynamic findings of Matsukawa et al [22] support our results. Indeed, in 49 patients who had detrusor overactivity during cystometry at the baseline assessment, uninhibited detrusor contractions disappeared in 15 (30.6%) after 3 mo ($p = 0.02$), and in 22 (44.9%) after 12 mo ($p < 0.001$) of treatment with tadalafil.

Moreover, tadalafil proved to be an alternative add-on drug for patients with persistent storage LUTS refractory to α_1-adrenoceptor antagonists, even when compared with solifenacin, thus confirming the valuable effect of tadalafil on storage LUTS [26].

Patients in the TAM group retained the improvement of Q_{max} achieved with combination therapy (13.97 at 12 wk vs 13.72 at 24 wk). Conversely, a decrease of Q_{max} was observed in the TAD group (18.28 at 12 wk vs 15.87 at 24 wk); however, an improvement of Q_{max} from baseline was also observed in the TAD group (14.0 vs 15.87 ml/s).

In contrast with our results, the first systematic review by Laydner et al [27] on the use of PDE5-Is for BPE-related LUTS reported that PDE5-Is improved IPSS and IIEF-5 but not Q_{max}.

Moreover, in another meta-analysis, PDE5-Is were more effective in association with ABs, improving IPSS (mean difference –1.8), IIEF-5 score (mean difference +3.6), and Q_{max} (mean difference +1.5 ml/s), when compared with PDE5-Is alone, which improved IPSS and IIEF scores but not Q_{max} [16].

However, Dong et al [25] concluded that even after pooling four doses (2.5, 5, 10, and 20 mg), tadalafil failed to produce a significant outcome in Q_{max}, whereas 5 mg/d tadalafil therapy significantly improved Q_{max} (mean difference = +0.63 ml/s, $p = 0.04$).

As expected, only patients in the TAD group retained the IIEF-5 improvement when compared with the TAM group (16.96 vs 12.48; $p = 0.003$). Interestingly, the impact of tadalafil on IIEF-5 was more pronounced, even if not clinically significant, in combination with tamsulosin (+6.28 vs +4.64), suggesting a possible synergism between these drugs. Indeed, a previous prospective randomized study demonstrated that EF improved with tamsulosin (+39.28% [$p < 0.05$]), tadalafil (+45.96% [$p < 0.05$]), and tamsulosin and tadalafil combination (+60.23% [$p < 0.05$]), with a better improvement seen in combination therapy compared with single agent alone. However, in line with our findings, the impact of combination treatment on EF was significantly greater than tamsulosin alone ($p < 0.05$) but not when compared with tadalafil ($p = 0.125$) [28].

In our study, we described for the first time urinary and sexual outcomes achieved within 12 wk of tamsulosin or tadalafil monotherapy after a previous 12 wk of combination therapy, to achieve a tailored therapy based on patients' predominant symptoms and to reduce drugs' intake.

As previously reported for the combination therapy of tamsulosin and dutasteride, the withdrawal of tamsulosin after 24 wk of combination therapy had no significant effect on urinary outcomes. Indeed, LUTS relief was maintained in the majority of patients after tamsulosin was removed from combination, and the authors concluded that only patients with severe symptoms may benefit from longer-term combination therapy [29].

Even if combination therapy with tamsulosin and tadalafil achieved better urinary and sexual outcomes, after a further 12 wk of monotherapy, both drugs were able to preserve a significant recovery of urinary function from baseline. Nevertheless, only patients treated with tadalafil showed a satisfying sexual function and a better storage IPSS at the end of the trial.

Daily doses of tadalafil 5 mg and tamsulosin 0.4 mg were well tolerated. No patients discontinued the study because of AEs. Headache was the main AE, with a higher incidence in the TAM group (8%) as compared with the TAD group (4%), suggesting that the use of tamsulosin can increase the risk of this AE.

Strengths of the study are the prospective nature of the trial and data collection together with the homogenous population. However, this study may be restricted by some limitations. Because this study was observational, it could be prone to biases. Moreover, prostate size was not considered as inclusion/exclusion criteria or as a potential determinant on the efficacy of therapy. Long-term follow-up is also needed to better evaluate the role of a switching approach versus a continuous treatment in terms of patients' compliance in term of symptoms, EF, urinary flow management and costs.

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5. Conclusion

For men with LUTS and ED, combined treatment with tamsulosin and tadalafil is well tolerated and effective. After 3 mo of combination therapy and consequent discontinuation of tamsulosin, monotherapy with tadalafil was able to further preserve the improvement of LUTS and EF although with a slight decrease of Q_{max}. The possibility to switch from a combination approach to a single-treatment strategy seems a feasible option to improve patients' compliance and to better tailor LUTS treatment.

***Author contributions*:** Mauro Gacci had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Gacci.
Acquisition of data: Frizzi.
Analysis and interpretation of data: Gacci.
Drafting of the manuscript: Sebastianelli, Spatafora.
Critical revision of the manuscript for important intellectual content: De Nunzio, Vignozzi.
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Supervision: Serni, Tubaro, Maggi.
Other: visualization: McVary, Kaplan, Gravas, Chapple.

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