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A comparison of the efficacy and tolerability of tamsulosin and finasteride in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia

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In this multicentre, double-blind study, patients with LUTS/BPH were randomised to 26 weeks with finasteride 5 mg once daily ($n = 204$) or tamsulosin 0.4 mg once daily ($n = 199$). Double-blind treatment was continued for another 26 weeks (total treatment duration: 1 y). The primary efficacy parameter was the difference in mean change in total Symptom Problem Index (SPI) from baseline to end point at week-26 in the intention-to-treat (ITT) and per protocol (PP) populations. Tamsulosin induced a greater improvement in total SPI (−5.2 points or −37%) compared to finasteride (−4.5 points or −31%) at week-26 ($P = 0.055$ in ITT and $P = 0.032$ in PP). Tamsulosin improved urinary symptoms (particularly the more bothersome storage symptoms) and flow more quickly than finasteride. The difference was statistically significant for the SPI from week-1 (reduction, respectively, −2.5 *vs* −1.8 points, $P = 0.043$) to week-18 and for Q_{max} from week-1 (increase, respectively, 2.3 *vs* 0.7 ml/s, $P = 0.0007$) to week-12. Both treatments were well tolerated with a comparable incidence of adverse events, including urinary retention.
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Introduction

Many elderly men suffer from lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH). This condition may arise from anatomic obstruction caused by an enlarged prostate (static component), as well as from an increased smooth muscle tone in the prostate, urethra and bladder neck caused by the sympathetic nervous system-mediated stimulation of α_1-adrenoreceptors (ARs) (dynamic component).[1] In addition, other factors such as central nervous system disorders and/or bladder disorders may be involved. Although voiding ('obstructive') symptoms (ie weak stream, hesitancy, intermittency, dribbling, abdominal straining and incomplete bladder emptying) are most prevalent, storage ('irritative') symptoms (ie nocturia, urgency, frequency and urge incontinence) seem to be the most bothersome for the patient.[2] They interfere mostly with daily life activities and not only affect the quality of life (QoL) of patients but also that of their partners.[3] Subjective symptoms (LUTS), bothersomeness and negative impact on QoL are the main reasons for patients to seek treatment for BPH.[4] In case LUTS are due to bladder outflow obstruction, as evidenced by a decreased urinary flow during free flow or during pressure flow studies, an increase in urinary flow is

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another treatment objective from the urologist's point of view. For many years, surgery has been the most important treatment for LUTS/BPH, mainly because of its impressive impact on reducing obstruction. It can, however, be associated with irreversible complications such as impotence, incontinence and retrograde ejaculation, and implies a certain degree of risk associated with surgical stress in aged patients. Since most LUTS/BPH patients seek help for bothersome symptoms and are not very keen to undergo an operation, many patients prefer medical treatment such as a 5α-reductase inhibitor or a α_1-AR antagonist. Finasteride is a 5α-reductase inhibitor and as such reduces the static component (ie an enlarged prostate). There is evidence that finasteride is most effective in patients with a large prostate (>40 ml).[5] Moreover, finasteride has a slow onset of action and needs a relatively long time (at least 6 months) to significantly reduce the prostate volume and, consequently, the obstruction. α_1-AR antagonists block α_1-ARs in the prostate, urethra and bladder neck, thereby decreasing smooth muscle tone and reducing the dynamic component of obstruction. This explains why these agents relieve symptoms effectively and very quickly (within weeks). Of the clinically available α_1-AR antagonists, tamsulosin is the most frequently prescribed and it has a favourable efficacy/tolerability ratio,[6] which is maintained for up to 4 y (Europe)[7] and 6 y (US).[8] Although α_1-AR antagonists have the highest market share among medical treatments for LUTS/BPH, finasteride is also prescribed in many patients, especially in Italy and the UK.[9] Several direct comparative trials have compared the efficacy and tolerability of an α_1-AR antagonist and finasteride.[10–12] Finasteride has been shown to be less effective than alfuzosin, doxazosin and terazosin in relieving LUTS/BPH. So far, tamsulosin has never been directly compared with finasteride in the treatment of LUTS/BPH. The Multicentre Investigation to Characterise the effect of Tamsulosin on Urinary Symptoms (MICTUS) study therefore compared the efficacies and tolerabilities of tamsulosin and finasteride in patients with LUTS/BPH.

Methods

Inclusion/exclusion criteria

The study population consisted of older men between 50 and 80 y with symptomatic LUTS/BPH, as diagnosed by an International Prostate Symptom Score (I-PSS) ≥ 13, a maximum urinary flow rate (Q_{max}) between 4 and 15 ml/s and a total Symptom Problem Index (SPI) score ≥ 7. Patients were included if the postvoid residual volume (PVR: evaluated by ultrasonography) was <400 ml and the prostate-specific antigen (PSA) level was <3 or 3–10 ng/ml (provided that prostate cancer was ruled out by the investigator according to the usual procedure in the centre). Patients with a known history or a diagnosis of urological disturbances, cardiovascular diseases, neurological diseases, hepatic or renal insufficiency were excluded, as were those with clinically significant abnormalities of haematological and biochemical tests. Also excluded were patients taking an α_1-AR antagonist or phytotherapy in the 6 weeks prior to the study or finasteride in the 6 months prior to the study. Patients requiring concomitant medication influencing pharmacodynamic or pharmacokinetic properties of tamsulosin, in particular α_1-AR antagonists, mixed α-β-antagonists, α-agonists and anticholinergics, had to be excluded. All patients gave written informed consent. The study was conducted according to Good Clinical Practice guidelines, and the Ethical Committees approved the protocol.

Study design

This was a 26-week, multicentre, randomised, double-blind, double-dummy and parallel group study with a 2-week, single-blind, placebo run-in period. Double-blind treatment was continued for another 26 weeks. The total treatment duration was therefore 1 y. Patients were randomised to either tamsulosin 0.4 mg once daily or finasteride 5 mg once daily after breakfast. During the 2-week, single-blind, placebo run-in period, patients took one capsule of tamsulosin-matching placebo and one tablet of finasteride-matching placebo once daily. After this period, patients were randomised to one capsule of tamsulosin 0.4 mg and one tablet of finasteride-matching placebo once daily, or one tablet of finasteride 5 mg and one capsule of tamsulosin-matching placebo once daily. Patients were assessed at visit 1 (screening visit) and 2 weeks later (randomisation/baseline visit) during the placebo run-in period. If eligible, the patients started in the double-blind study period where visits took place at weeks 1, 6, 18, 26, 34, 42 and 52.

Assessments

[Efficacy]. The primary efficacy parameter was the SPI, a validated questionnaire measuring the degree to which the patients are bothered by urinary symptoms.[13] This questionnaire consists of seven questions on the same urinary symptoms investigated by the I-PSS questionnaire, but scored from 0 (no problem) to 4 (big problem) (instead of 0–5, as is the case for the I-PSS), with a total score ranging between 0 and 28 (calculated by summing the responses to the individual questions). Secondary efficacy variables were changes from baseline to each assessment time point in total SPI, voiding and storage SPI subscores, total I-PSS score, voiding and storage I-PSS subscores, the I-PSS QoI score, Q_{max}, voided volume and PVR, as obtained during uroflowmetry performed in the centre. In addition, the number of withdrawals due to insufficient efficacy of the study drugs and the number of responders (patients with a $\geq 50\%$ improvement in total SPI and $\geq 50\%$ improvement in total I-PSS) were compared between treatment groups. These assessments were done at each visit throughout the study up to week-52.

[Safety]. The frequency, severity, time to onset and duration of adverse events were compared between treatment groups. Vital signs (blood pressure and heart rate) were documented at each visit during the study. The laboratory assessments (routine biochemistry, haematology, urinalysis and PSA levels) were performed at the screening visit, week-26 and -52, and a physical

examination was done at the screening visit. The sexual activity was measured by means of a questionnaire with six items to be completed by the patient at baseline and at week-26 and -52 of treatment. It included the patient's description of his own libido, the frequency of his sexual activity and his pattern of ejaculation.

The study was supervised by a scientific advisory board including Professor P Rigatti, Dr M Brausi (Modena), Professor RM Scarpa (Orbassano) and Dr D Porru (Pavia). Dr D Porru reviewed the uroflowmetry data.

Statistical methods and sample size

The primary efficacy parameter was the difference in mean change in total SPI from baseline to end point (ie 26 weeks of active treatment) between finasteride and tamsulosin. According to the available literature on the I-PSS, which is comparable to the primary variable but differs by the total range (0–35 for I-PSS *vs* 0–28 for SPI), the extent of total improvement in SPI under finasteride after 26 weeks was expected to be 2.6 score points. The extent of improvement considered of clinical interest with the test medication (tamsulosin) was at least 50% greater, that is, 3.9 score points. The standard deviation of the difference was estimated from the quoted literature as approximately 3.5. Based on these assumptions, according to the protocol, the number of patients required for obtaining a significant test result for the mean change in total SPI at 26 weeks at a two-sided level α of 0.05, with a power of 90%, had to be 154 evaluable patients per group. From the same literature, the dropout rate was estimated to be approximately 10% during the run-in and 20% during the initial 26-week treatment period. The total number of patients to be enrolled was therefore increased to approximately 450 patients.

Descriptive statistical parameters were calculated with missing values being replaced according to the last observation carried forward (LOCF) method; baseline values were not forwarded. Statistical differences between treatments in efficacy parameters (changes from end point to baseline) were analysed by means of a split-plot model for repeated measurements containing factors for treatment, time and their interaction, as well as the respective baseline value as covariate. Treatment least-square means from that model were tested for differences by means of a *t*-test. The primary efficacy analysis (difference in mean change in total SPI from baseline to 26 weeks) was carried out on both the ITT and the PP population, the secondary analyses only on the ITT population. All tests were two-sided, and were carried out at the 5% significance level. The safety variables were analysed by means of descriptive statistics. Sexual activity scores were also analysed individually in terms of shift from baseline to week-26 and -52 by logistic regression, considering age and baseline conditions as covariates. For this analysis, missing data were not imputed. The data in Table 1 and the figures relate to unadjusted means; the *P*-values relate to the adjusted means from the split-plot model described above.

Results

In all, 50 centres in Italy enrolled 441 patients, of whom 403 patients were randomised to finasteride ($n=204$) or tamsulosin ($n=199$); three randomised patients were never treated and therefore excluded from the ITT population. A total of 180 (88%) and 159 (78%) patients in the finasteride group and a total of 165 (84%) and 136 (69%) patients in the tamsulosin group completed 26 and 52 weeks of treatment, respectively.

Baseline characteristics

The mean age in the total safety population was 63 ± 7.1 y. The mean prostate volume (as measured by transrectal or transabdominal ultrasound depending on the procedure used in each centre) was 39 ± 18.9 ml; 68% of patients in the tamsulosin and 75% of patients in the finasteride groups had a prostate volume <50 ml. There were no relevant differences between the treatment groups with regard to baseline characteristics such as age, body weight, duration of disease under study, prostate volume, PSA and efficacy parameters.

Discontinuations

The most common reason for withdrawal was discontinuation due to adverse events in 19 patients in the tamsulosin group (9.7%) and 13 patients in the finasteride group (6.4%). Other reasons for withdrawal in the tamsulosin and finasteride groups were lack of efficacy (four (2.0%) and eight (3.9%) patients, respectively), noncompliance with the study protocol (four (2.0%) and one (0.5%) patients, respectively), loss to follow-up (13 (6.6%) and nine (4.4%) patients, respectively), withdrawal of consent (16 (8.2%) and nine (4.4%) patients, respectively), and other reasons (seven (3.6%) and five (2.5%) patients, respectively).

Efficacy results (Table 1)

Primary. At week-26, tamsulosin induced a greater improvement in total SPI score compared to finasteride ($P=0.055$ for the ITT and $P=0.032$ for the PP populations; Table 1). The difference in score between the two groups was also clinically significant.

Secondary. With tamsulosin, total SPI was improved very quickly (about 50% of the total effect was already achieved after the first assessment after 1 week of treatment) and the maximal improvement in total SPI was reached at week-18 and maintained during long-term treatment up to week-52 (Figure 1). The improvement in total SPI with finasteride was considerably slower and, therefore, there were statistically significant differences ($P<0.05$) between tamsulosin and finasteride at week-1, -6 and -18 (Figure 1).

The analysis of storage SPI (Figure 2) and voiding SPI (Figure 3) showed a similar pattern as the total SPI. However, tamsulosin improved particularly the more bothersome storage symptoms more quickly than finasteride. The difference between both treatments was

Table 1 Effect on primary (ITT and PP) and secondary efficacy variables (ITT population)

Parameter mean (s.d.)	Assessment	Finasteride (n=204)	Tamsulosin (n=196)	P-value
Primary				
Total SPI (points): ITT	N	202	193	
	Baseline	14.0 (4.2)	13.6 (4.4)	
	Change at week-26	−4.5 (5.0)	−5.2 (5.0)	0.055
	% Change at week-26	−31.5%	−37.4%	
Total SPI (points): PP	N	152	130	
	Baseline	14.1 (4.2)	13.6 (4.4)	
	Change at week-26	−4.5 (4.9)	−5.5 (5.0)	0.032
	% change at week-26	−31.5%	−39.6%	
Secondary: ITT				
% SPI responders°	% Patients at week-26	35.1%	43.5%	
SPI-storage (points)	Baseline	6.2 (2.2)	6.1 (2.4)	
	Change at 26 weeks	−1.9 (2.7)	−2.3 (2.5)	0.090
	% Change at week-26	−22.0%	−34.3%	
SPI-voiding (points)	Baseline	7.8 (2.7)	7.5 (3.0)	
	Change at 26 weeks	−2.6 (3.1)	−3.0 (3.2)	0.069
	% Change at week-26	−27.3%	−35.0%	
Total I-PSS (points)	Baseline	16.9 (5.0)	16.3 (5.1)	
	Change at 26 weeks	−5.7 (5.7)	−6.3 (5.5)	0.080
	% Change at week-26	−32.0%	−37.3%	
% I-PSS responders[a]	% Patients at week-26	35.6%	42.5%	
I-PSS Qol (points)	Baseline	3.1 (1.1)	3.2 (1.0)	
	Change at 26 weeks	−1.0 (1.2)	−1.1 (1.2)	0.163
	% Change at week-26	−25.8%	−31.2%	
Q_{max} (ml/s)	Baseline	10.8 (3.4)	10.8 (3.7)	
	Change at 26 weeks	1.9 (5.1)	2.4 (5.9)	0.271
	% change at week-26	21.7%	30.7%	
Voided volume (ml)	Baseline	226.5 (93.1)	239.5 (118.4)	
	Change at 26 weeks	5.2 (141.0)	21.3 (152.4)	0.043
	% Change at week-26	16.4%	29.9%	

s.d.=standard deviation; [a]≥50% improvement from baseline.

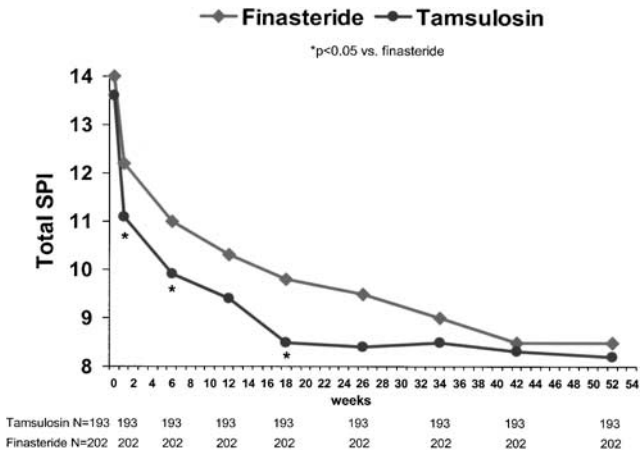

Figure 1 *Evolution of total SPI over time.*

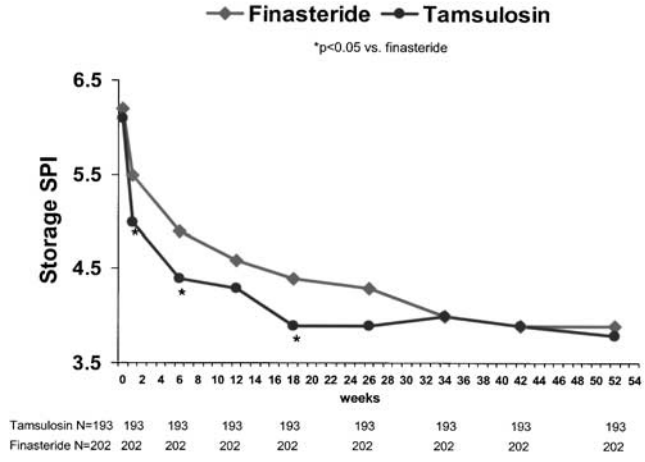

Figure 2 *Evolution of storage SPI over time.*

already statistically significant in favour of tamsulosin at week-1, and also at week-6 and –18 ($P<0.05$) (Figure 2).

The responder rate of patients with ≥50% improvement in total SPI score from baseline was greater with tamsulosin compared to finasteride at week-26 (44 *vs* 35%), a maximum difference being observed at week-1, -6 and -18 (Figure 4).

The results for the total I-PSS over time were in line with the total SPI results over time. Tamsulosin improved the total I-PSS more quickly than finasteride. There was a statistically significant improvement in favour of tamsulosin at week-6 ($P<0.05$) and at week-18 ($P<0.01$). The rate of patients with ≥50% improvement in I-PSS was greater with tamsulosin than with finasteride both at week-26 (43 *vs* 36%) and at week-52 (49 *vs* 43%).

Tamsulosin also improved Q_{max} very quickly with a maximal effect already reached at week-1, which was further maintained throughout the course of the study. The increase in urinary flow was faster than with finasteride with statistically significant differences

compared to finasteride at week-1 ($P<0.001$), week-6 and -12 ($P<0.05$; Figure 5). A *post hoc* subgroup analysis showed that this advantage of tamsulosin over finasteride was mainly apparent for patients with a small prostate (<50 ml) at baseline. The difference in favour of tamsulosin was 1.9 ml/s with $P<0.001$ at week-1, 1.4 ml/s with $P=0.009$ at week-6; 1.2 ml/s with $P<0.05$ at week-12 and 0.5 ml/s with $P=0.343$ at week-26. In patients with a bigger prostate (≥50 ml), the difference between the treatment groups was not statistically significant during the whole treatment period. The voided volume during uroflowmetry also showed a statistically significant change in favour of tamsulosin at week-26 (Table 1), whereas for the PVR no statistically significant changes were seen between the treatments.

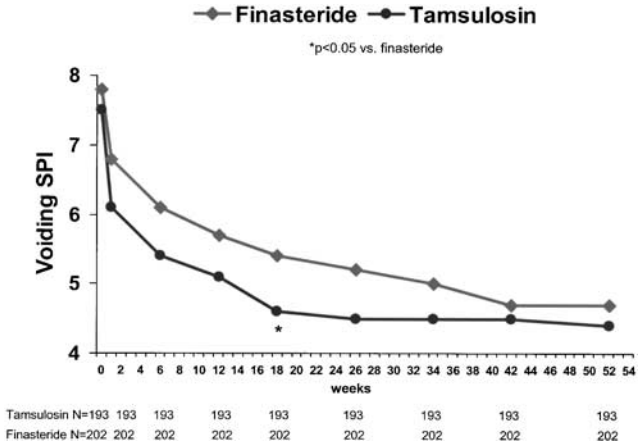

Figure 3 *Evolution of voiding SPI over time.*

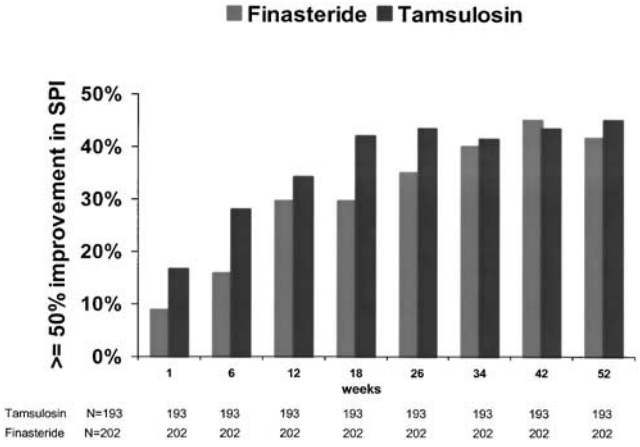

Figure 4 *Evolution of SPI responders over time.*

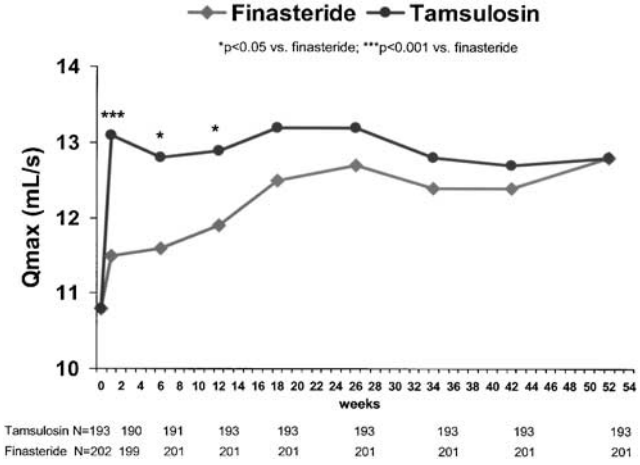

Figure 5 *Evolution of Q_{max} over time.*

Safety results (Table 2)

During the 52 weeks of double-blind treatment, the rate of adverse events was comparable for both treatments: 60 patients (29.4%) in the finasteride group and 63 patients (32.1%) in the tamsulosin group reported 122 and 104 adverse events, respectively. More details are provided in Table 2. Table 2 also displays the most common (>3.0% of patients) adverse events. The occurrence of urinary retention was reported as an adverse event in this study, and was low and comparable for tamsulosin and finasteride (one patient in each group). For the laboratory parameters, no important changes related to the study drugs were seen, except for the serum PSA levels. After 26 weeks of treatment, there was a statistically significant greater mean reduction in PSA levels in the finasteride group compared to the tamsulosin group (−0.78 *vs* −0.13 ng/ml; $P<0.0001$). After 52 weeks, the mean reduction in PSA levels from baseline in the finasteride group was –0.85 ng/ml, whereas in the tamsulosin group there was a slight increase of +0.22 ng/ml ($P<0.0001$). Vital signs revealed no clinically significant changes.

For the questionnaire related to sexual function, the treatment differences are given in terms of odds ratios, together with 95% confidence intervals for each of the six parameters and for the total sum. An odds ratio greater than 1 indicates an advantage of tamsulosin over finasteride, which is statistically significant if the 95% confidence interval is completely lying above 1. The odd ratios after week-26 (Figure 6) showed that, although this study was not powered to evaluate sexual function, for five individual parameters and the total score, there was

Table 2 Number (%) of patients with adverse events

	All adverse events	
n (%)	Finasteride	Tamsulosin
Number of patients treated	204 (100)	196 (100)
Any AE	60 (29.4)	63 (32.1)
Serious AE	15 (7.4)	15 (7.6)
Discontinued due to AE	13 (6.4)	19 (9.7)
Most common AEs[a]		
Influenza-like symptoms	7 (3.4)	12 (6.1)
Impotence	7 (3.4)	6 (3.1)
Abdominal pain	5 (2.5)	6 (3.1)
Ejaculation disorder	2 (1.0)	6 (3.1)

[a]Reported in >3.0% of patients.

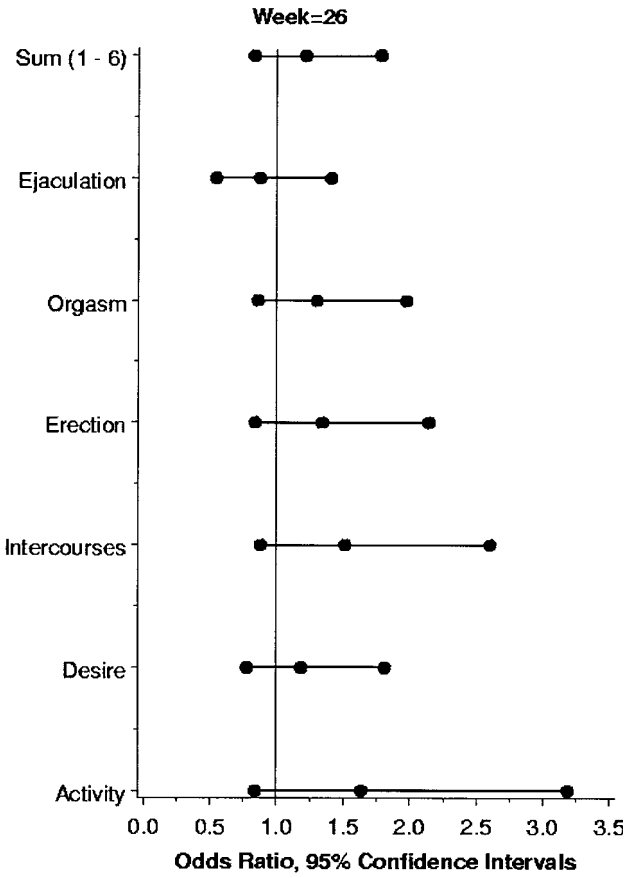

Figure 6 *Effect on sexual function, as assessed by means of a sexual function questionnaire. An odds ratio greater than 1 indicates an advantage of tamsulosin over finasteride, which is statistically significant if the 95% confidence interval is completely lying above 1.*

a tendency for tamsulosin to have a better effect than finasteride. At week-52, the advantage for tamsulosin was statistically significant for the erection-related question.

Discussion

The aim of this study was to have a direct comparison of two medical treatment options commonly prescribed for patients with LUTS/BPH in daily clinical practice, that is, the α_1-AR antagonist tamsulosin and the 5α-reductase inhibitor finasteride, which had never been directly compared. Previous studies with other α_1-AR antagonists, such as the Veterans Affairs (VA), ALFIN and Prospective European Doxazosin and Combination Therapy (PREDICT) trials, failed to demonstrate additional efficacy with the combination of these two classes of drugs.[10–12] Therefore, at variance with the design of the mentioned studies, a combination arm was not included in the MICTUS study. Owing to the low acceptance by European investigators, patients and Ethical Committees of a long-term study with placebo and in line with the European study comparing alfuzosin and finasteride, a placebo group was also not included.

The SPI questionnaire was selected as the primary efficacy parameter because the patient's QoL and his interference with daily life activities are more affected by the extent to which he is bothered by his urinary symptoms, than solely by the frequency of these symptoms. Furthermore, at the time of developing the protocol for this study, there was only limited information available on the bother associated with urinary symptoms and how this was affected by different (medical) therapies. As the SPI captures information on the bother associated with the seven questions included in the I-PSS questionnaire, which is generally accepted for obtaining data on the frequency of urinary symptoms, this questionnaire was selected for measuring the bothersomeness associated with urinary symptoms.

The primary end point of the difference in mean change in total SPI was set in the protocol at week-26 (in line with the ALFIN study). This is because this period is minimally required for finasteride to achieve its full efficacy. Furthermore, as it concerned a phase IV study and the investigators were aware of the fact that both involved treatments should have been able to provide their optimum response by 26 weeks, it was feared that investigators might, in particular, withdraw patients with insufficient response from the study after 26 weeks, which could have a negative impact on the efficacy of the involved treatments. Therefore, the analysis of the data related to the primary efficacy end point was planned at the end of the minimum required period (26 weeks). It was, however, felt that it was also important to collect longer term data on the efficacy and, in particular, the safety/tolerability of both agents. Therefore, it was decided to continue the study for another 26 weeks, providing a total treatment duration of 1 y. The double-blind design was continued to assure a higher quality of the collected long-term data.

The primary evaluation of the difference in efficacy between the two compounds was based on the change in total SPI from baseline to week-26 in both the ITT and PP population. The greater reduction in total SPI with tamsulosin (0.4 mg once daily) over finasteride (5 mg once daily) approached statistical significance in the ITT ($P = 0.055$), and was statistically significant in the PP ($P = 0.032$). It can, therefore, be concluded that tamsulosin is superior to finasteride in this respect. After week-26, both treatments reduced total SPI to the same extent. The major conclusion from this study is that tamsulosin improves urinary symptoms, its associated bother and flow more quickly than finasteride with statistically significant differences between the treatments noticed up to 12 or 18 weeks of therapy, dependent on the efficacy variable. Compared to finasteride, tamsulosin has, particularly, a faster onset of action with respect to storage symptoms, which are regarded as the most bothersome to the patient.[2] The results are especially remarkable for Q_{max}, as this improves to nearly the maximal extent at the first assessment after only 1 week of tamsulosin treatment. The faster improvement in Q_{max} with tamsulosin over finasteride seems to be most apparent in patients with a small prostate (<50 ml) at baseline. This seems not surprising because finasteride is mainly effective in patients with a large prostate,[5,11] whereas α_1-AR antagonists work in patients with a small or large prostate.[11]

The results of the present study may relate to the fact that finasteride targets the prostate by reducing prostate size, and therefore slowly reduces obstruction and related voiding and storage symptoms. Tamsulosin, by blocking the prostatic α_{1A}-ARs, in contrast, very quickly reduces obstruction and related voiding symptoms. The fast relief of the bothersome storage symptoms with tamsulosin could be related to the fact that it may reduce not only bladder overactivity due to a reduction of bladder wall hypertrophy secondary to improving obstruction (which is a longer term process), but also bladder overactivity due to direct blockade of (upregulated) α_{1D}-ARs in the bladder and/or in its innervating structures such as the spinal cord (which is a more immediate process).[14–16]

The results of this trial are in line with other data in the literature. Other α_1-AR antagonists appear to have similar efficacy in improving symptoms and urinary flow.[6] The total symptom score generally improves by 30–40% — which is consistent with the 37% improvement in total I-PSS found with tamsulosin in the present study — and Q_{max} by 16–25% — for which an improvement of 31% is obtained in this study. Also, the results related to finasteride are consistent with the literature. Among the α_1-AR antagonist-finasteride head-to-head comparative studies, the ALFIN study (a 6-month, double-blind trial with alfuzosin, finasteride or the combination of both drugs[10]) is most comparable to the present MICTUS study concerning time to end point (26 weeks) and lack of a placebo arm. In the ALFIN study, the results obtained with finasteride were very similar to those recorded in the present trial. The improvement in total I-PSS was 5.2 *vs* 5.7 points in this study; the responder rate (total I-PSS improvement of $\geq$50%) was 33% of patients *vs* 36% in this study and the increase in Q_{max} was 18 *vs* 22% in this study. The better performance of finasteride in the MICTUS and the ALFIN study as compared to the VA trial can be explained at least in part by the lower mean prostate volume at baseline in the latter study. Not only finasteride, but also the two α_1-AR antagonists show a similar performance in the MICTUS and the ALFIN study. Total I-PSS was reduced by 6.3 points for both treatments; the percentage of patients with $\geq$50% improvement in total I-PSS was in both cases 43%, and the Q_{max} improved by 1.8 ml/s with alfuzosin and by 1.9 ml/s with tamsulosin. The results of the two studies are, in general, superior in terms of efficacy for all treatments compared to the VA study. Apart from the above-mentioned consideration on the relation between the efficacy of finasteride and baseline prostate volume, this could be due to the lack of a placebo arm, which usually results in a reduced effect of active treatment when symptom scores are used. In this respect, it is noteworthy that in the present trial the time course of an objective assessment such as the Q_{max} shows a more pronounced difference between treatments than that of the total I-PSS or SPI.

No important differences were observed between the tolerability profiles of tamsulosin and finasteride, which also confirms the data reported in the literature. The incidence of discontinuations due to adverse events for tamsulosin over 52 weeks of treatment was 9.7%, which is similar to the rates reported in a meta-analysis of studies with α_1-AR antagonists (4–10%) with, however, shorter treatment durations.[6] The withdrawal rate with finasteride was lower than that reported in the large trial mentioned before (6.4 *vs* 11%) with a treatment duration of only 6 months instead of 1 y in this study.[10] The urinary retention episodes, the incidence of which can be reduced with finasteride, as previously shown,[17] occurred in a comparable and low rate with finasteride and tamsulosin in the present study. The PSA level was significantly decreased after 26 and 52 weeks of treatment with finasteride, whereas tamsulosin had no clinically significant effect on PSA. These results are also is in line with previous results with finasteride[18] and tamsulosin.[19]

At the time of performing the study, the Sexual Function Inventory was not yet available. Therefore, an alternative nonvalidated questionnaire was used to assess sexual function. There is a tendency for tamsulosin to have less impact on most domains of sexual function than finasteride. This is in line with the fact that finasteride can induce decreased libido, ejaculation disorders (primarily decreased ejaculation volume) and impotence.[18] As a sexual adverse event, patients on tamsulosin may report abnormal ejaculation related to the α_1-blockade in the bladder neck, vas deferens and seminal vesicles, but impotence or decreased libido has not been associated with tamsulosin.[20] Abnormal ejaculation is furthermore, in general, a very well-tolerated adverse event, as only few patients stop tamsulosin treatments for this reason.[20]

As already indicated, our study did not include a combination arm of tamsulosin and finasteride as the VA, ALFIN and PREDICT study did not show an advantage of this treatment over monotherapy with an α_1-AR antagonist after up to 1 y of treatment.[10–12] Recently, the results of the landmark Medical Therapy Of Prostatic Symptoms (MTOPS) trial, a placebo-controlled study comparing the α_1-AR antagonist doxazosin, finasteride and their combination in 3047 LUTS/BPH patients with a mean follow-up of 5 y, became available.[21,22] These results indicate that, in the long term, combination therapy is statistically significantly more effective than both monotherapies, in improving urinary symptoms (total I-PSS) and reducing clinical progression. It seems that, in particular, high-risk patients (those with a large prostate volume/high PSA) may benefit from combination therapy. It was also shown that, in the long run (after 4 y), α_1-AR antagonists reduce total I-PSS to a slightly greater extent than finasteride (median reduction 6.0 and 5.0 points, respectively). Therefore, it seems appropriate to start treatment for LUTS/BPH with an α_1-AR antagonist such as tamsulosin, and add finasteride in patients with a large prostate volume/high PSA.

Conclusions

Tamsulosin provides greater improvement of the bothersomeness associated with urinary symptoms (total SPI) than finasteride. In addition, tamsulosin has a faster onset of action compared to finasteride with regard to improvement of urinary symptoms (total I-PSS), its associated bothersomeness (total SPI) and Q_{max}. Both drugs are very well tolerated during long-term treatment. They have a comparable rate of adverse events,

including urinary retention. Although not statistically significant for most sexual function-related items, there is a tendency for tamsulosin to have a better effect on sexual function compared to finasteride, in particular with regard to erection.

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Appendix 1 Investigators of the MICTUS study group:

Table 3

Investigator	City	Investigator	City
Anselmo G	Treviso	Marcelli G	Rho
Beleggia E	Taranto	Martini G	Pescara
Belgrano E	Trieste	Martorana G	Bologna
Bercovich E	Sassari	Masala A	Napoli
Boccafoschi C	Alessandria	Motta M	Catania
Campo B	Melegano	Paola Q	Sciacca
Carini M	Antella	Pellegrino A	Foggia
Cicalese V	Avellino	Perego S	Crema
Comeri G	Como	Porena M	Perugia
Cortellini PG	Parma	Potenzoni D	Fidenza
Cozzupoli P	Reggio Calabria	Rigatti P	Milano
De Grande G	Siracusa	Rizzo M	Firenze
Di Santo V	Acquaviva Delle Fonti	Robles A	Frosinone
Ferrari P	Modena	Roggia A	Gallarate
Fiaccavento G	Portogruaro	Scalfari A	Catanzaro
Fontana D	Orbassano	Selvaggi F	Bari
Fontana G	Savigliano	Siragusa A	Caltagirone
Francesca F	Pisa	Tenaglia R	Chieti
Frea B	Novara	Testa G	Napoli
Garbeglio A	Pordenone	Tizzani A	Torino
Grassetti F	Roma	Usai E	Cagliari
Jacobellis U	Bari	Vassallo F	Potenza
Lavelli D	Camposampiero	Vicini D	Voghera
Leoni S	Reggio Emilia	Zanollo A	Magenta
Manganelli A	Siena	Zattoni F	Udine