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Finasteride, not tamsulosin, increases severity of erectile dysfunction and decreases testosterone levels in men with benign prostatic hyperplasia

DOI 10.1515/hmbci-2015-0015
Received April 2, 2015; accepted May 6, 2015

Abstract

Background: 5α-reductase inhibitors (5α-RIs) (finasteride and dutasteride) have been proven useful in treatment of lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH). However, these inhibitors exert undesirable sexual side effects and, in some cases, these effects are persistent. There is considerable disagreement with regard to whether the adverse side effects resolve with continuous treatment.
Aim: To investigate the long-term adverse effects of finasteride treatment in men with BPH on erectile function and to compare these adverse effects in men treated with the α_1-adrenergic receptor blocker, tamsolusin.
Methods: In this retrospective registry study, a cohort of 470 men aged between 47 and 68 years (mean 57.78±4.81) were treated with finasteride (5 mg/day). A second cohort of 230 men aged between 52 and 72 years (mean 62.62±4.65) were treated with tamsulosin (0.4 mg). All men were followed up for 45 months. At intervals of 3 months and at each visit, plasma testosterone (T) levels and the international index of erectile function (IIEF-EF) questionnaire scores were determined.
Results: Long-term treatment with finasteride therapy is associated with worsening of erectile dysfunction (ED) as shown by the significant decrease in the IIEF-EF scores in men treated with finasteride. No worsening of ED was observed in men treated with tamsulosin. The increase in ED due to finasteride did not resolve with continued treatment with finasteride. Most importantly, long-term finasteride therapy resulted in reduction in total T levels, contributing to a state of hypogonadism. On the contrary, no changes in T levels were noted in men treated with tamsolusin.
Conclusion: Our findings suggest that in men with BPH, long-term finasteride therapy but not tamsulosin results in worsening of ED and reduces total T concentrations. Clinicians are urged to discuss the impact of 5α-RIs therapy on sexual function with their patients before commencing this therapy.

Keywords: dutasteride; erectile dysfunction; finasteride; sexual adverse effects; testosterone.

Introduction

5α-Reductase inhibitors (5α-RIs) therapy with finasteride or dutasteride and α_1-adrenergic receptor blockers such as tamsulosin are widely used for treatment of lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) [1, 2]. 5α-RIs therapy with finasteride is also widely used for treatment of male pattern hair loss (MPHL), commonly known as androgenetic alopecia (AGA) [3, 4]. However, one of the main concerns with 5α-RIs therapy is the serious adverse effects on sexual function [1, 5–16].

Considerable controversy exists regarding the severity and persistence of the adverse effects of 5α-RIs therapy. Many investigators believe that the adverse effects on sexual function affects only a small proportion of treated patients and such adverse effects are thought to resolve with continuing treatment [1, 16–37]. Unfortunately, this notion is inaccurate and a significant number of patients complain of erectile dysfunction (ED) which does not resolve with continued treatment as claimed previously [6–15, 33, 36]. This discrepancy in reporting may be attributed, in part, to the often quoted studies on 5α-RIs therapy, which used crude methods for assessing erectile function [e.g. patient self-report of binary outcomes, lower power to detect changes in erectile function and use of

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phosphodiesterase type 5 inhibitors (PDE 5i) and patient population with low rate of sexual activity].

It is well accepted that androgens play an important role in sexual function, including libido, erectile function, orgasm, and have central as well as peripheral physiological effects on male sexuality. More importantly, erectile physiology in animal model studies and in humans depends on the integrity of the androgen milieu. Furthermore, because 5α-reductases (5α-Rs) play a central role in androgens metabolism [38, 39], these enzymes are likely to modulate sexual function [6–8]. Thus, it is conceivable that inhibition of 5α-Rs may result in serious sexual adverse effects during the treatment and even after cessation of the treatment due to the complex mechanism of these enzyme reactions [6–8]. Pre-clinical studies provided biochemical and physiological evidence for a role for 5α-dihydrotestosterone (5α-DHT) in erectile physiology [40–42]. A number of studies demonstrated that the effects of androgens on erectile physiology were likely mediated by the 5α-reduced metabolite, 5α-DHT [43–50]. Testosterone (T) treatment of castrated animals restored erectile function [51, 52]. T treatment together with finasteride did not restore erectile function in castrated animals, indicating that 5α-DHT is a required hormone in erectile physiology. Administration of 5α-DHT together with finasteride in castrated animals restored nitric oxide synthase expression and activity in the penile corpus cavernosum and also restored the erectile response to electric field stimulation [51, 52].

Treatment of mature male animals with dutasteride produced significant reductions in the intracavernosal pressure (ICP) [40, 41]. Electrical field stimulation (EFS) or acetylcholine-induced smooth muscle relaxation was significantly attenuated in corpus cavernousm tissues from dutasteride-treated animals [40, 41]. Dutasteride treatment also increased deposition of connective tissue with concomitant reduction in the trabecular smooth muscle content of the cavernosal tissue [40, 41]. Neuronal nitric oxide synthase (nNOS) expression was significantly attenuated by dutasteride, concomitant with increased expression of inducible NOS (iNOS) [40, 41]. Similarly, treatment of male mature animals for 16 weeks with a daily oral dose of 4.5 mg/kg finasteride produced marked decrease in penile erectile response to electrical field stimulation of the cavernous nerve [42]. Significant decrease in trabecular smooth muscle content and increased connective tissue deposition was also noted. Endothelial nitric oxide synthase (eNOS) expression was markedly and significantly reduced in response to finasteride treatment [42]. Thus the findings from preclinical studies clearly suggest that 5α-RIs treatment produces significant sexual adverse effects. Clinical studies demonstrated that 5α-RIs therapy in men with BPH resulted in diminished libido, erectile, and ejaculatory functions [1, 16–37].

The data provided by the manufacturer in the package insert for finasteride, showed that loss or reduction in libido was approximately 10% for finasteride and 12% for combination therapy with alpha blockers [53]. Similarly, ED was increased by approximately 18% in the finasteride and 22% in the combination therapy. Abnormal ejaculation was reported as 7% in the finasteride and 14% in the combination therapy. These findings represent significant adverse effects and raise the concern that such therapy does bring about changes in sexual function. The suggestion that the adverse events, such as libido, erection or ejaculation, appear early in the first 6 months and then return back to normal is, at best, inaccurate and is not supported by evidence-based medicine [1, 16–37]. In this study, we report on the adverse effects of finasteride on the erectile function domain in patients with BPH and compare these findings with the effects of tamsulosin in a long-term study with a follow-up of 45 months in order to evaluate the effects of finasteride on erectile function and to assess if these adverse effects resolve or worsen over time [16, 24, 54–58].

Methods

All subjects had sought urological consultation in a single urologist's office for LUTS due to BPH. A cohort of 470 men between age 57 and 68 years (mean age 57.78±4.81 years), with total plasma T levels at baseline between 310 and 740 ng/dL (mean 517±100.25 ng/dL) were treated with finasteride (5 mg/day). A 2nd cohort of 230 men between age 53 and 72 years (mean age 62.62±4.65 years), with total plasma T levels at baseline between 310 and 740 ng/dL (mean 533±123 ng/dL) were assigned to tamsulosin (0.4 mg) treatment. There were 183 men with diabetes, 120 of them were in the finasteride group (25.5%) and 63 men with diabetes were in the tamsulosin group (27.4%). Only four men were on PDE 5i. All four patients using PDE 5i were in the finasteride group and none in the tamsulosin group. The choice of treatment drug was based on patient's preference after discussion with their urologist. In all men, baseline prostatic specific antigen (PSA) levels were determined (ng/mL). They were followed up for 45 months at intervals of 3 months. At each visit, blood was sampled between 8.00 and 11.00 h after overnight fasting. Prostate volumes (PV) were measured using Sonoace SA 8000 SE with ultrasound probes (Samsung Electronics GmbH, 65824 Schwalbach/Taunus, Germany). The International Prostate Symptoms Score (IPSS) was assessed at each visit (3 months), men completed the Aging Males' symptoms scale (AMS), and international index of erectile function (IIEF-EF) questionnaire, maximum score 30 [59]. Prostate size was assessed by ultrasonography. Blood samples drawn at each visit and total T levels were measured by standard laboratory measurement as described previously [60]. PSA was also determined as described

previously [60]. Liver function test was also carried out as described previously [60]. All subjects on finasteride and tamsulosin were followed up for at least 45 months. The declining number of patients reflects duration of treatment but not dropout rates. Adherence to treatment was excellent and none of the patients dropped out. All patients gave their informed consent to be included in this study, and in accordance to the rules of the German Medical Association for evaluation of patient data from patients receiving standard therapy.

Statistical analyses

For continuous variables, the mean, median, standard deviation, range, minimum, maximum, and sample size for the overall sample and various groups were reported at each time point. For categorical variables, the frequency distribution was reported. We tested the hypotheses regarding change in outcome scores across the study period and between the two groups by fitting a linear mixed effects model to the data. Time (to indicate follow-up interviews) groups and interaction between groups were included as fixed effects in the model. A random effect was included in the model for the intercept. Estimation and test of change across time and differences between groups at each time point were determined by computing the differences in least square means at baseline vs. the score at each follow-up interview. In all figures, the time point when the two curves separate with statistical significance from each other is indicated by an arrow.

Results

The data in Table 1 provide baseline characteristics of 700 patients included in this study. All men were treated for LUTS in men with BPH in one single clinical center. Choice of the medication was based on patients' preference after consultation with their urologist. Four hundred seventy men were treated with finasteride and 230 men were treated with tamsulosin. The two groups were similar in most parameters. However, we wish to point out that at baseline, patients in the tamsulosin group were slightly older, had larger waist circumference, and higher AMS score at baseline than those in the finasteride group.

One of the most notable adverse side effects of 5α-RIs therapy is diminished sexual function, and more specifically increased ED. In this study, we assessed the effects of long-term therapy by finasteride and tamsulosin on ED. As shown in Figure 1, finasteride treatment in men with BPH resulted in a marked and significant gradual decrease in erectile function, as assessed by the IIEF-EF score. The decrease was progressive and was sustained over the 45 months of follow-up. The IIEF-EF score was reduced by more than 6–8 points, which is deemed clinically meaningful [61]. It is important to note that treatment with the α_1-adrenergic receptor blocker, tamsulosin, did not produce significant reductions in the IIEF-EF domain (Figure 1), suggesting that tamsulosin does not exert similar adverse effects on erectile function as those produced by finasteride.

Most surprisingly, we noted that patients receiving finasteride but not tamsulosin therapy had significant and progressive decline in total T levels (Figure 2A,B). The reasons for this reduction in T levels remain unclear.

As shown in Figure 3 the AMS score increased in men treated with finasteride but not with tamsulosin. This increase in the AMS score with finasteride suggests increased adverse events, which impacts the overall quality of life in patients treated with finasteride but not with tamsulosin. Our findings are consistent with those of Fwu et al. [36, 89] who reported that quality of life was improved significantly during 4 years in men assigned to doxazosin therapy group but not in the group assigned to the finasteride arm only.

An intriguing observation in this study is the increased activity of liver aspartate transaminase (AST) and alanine aminotransferase (ALT) in response to finasteride but not to tamsulosin (Figure 4A,B). This finding suggests that inhibition of 5α-Rs in liver brings about biochemical changes in liver function and may represent alterations in liver metabolism [90–92]. In addition, finasteride inhibits not only type 2 but also type 1 5α-reductase, albeit at a slower rate, suggesting that this drug may alter liver function via inhibition of 5α-reductases types 1 and 2 [93–94].

In this study we have also observed marked reduction in prostate volume with finasteride but increased prostate volume with tamsulosin (Figure 5) consistent with previous studies [36]. The International Prostate Symptom Score (IPSS) was reduced by tamsulosin, and finasteride therapy, with tamsuloisn showing stronger effect (Figure 6). As expected, PSA levels were reduced in response to finasteride but not with tamsulosin (Figure 7), again confirming previous observations.

Discussion

This retrospective observational registry study showed that 5α-RIs therapy adversely affected erectile function in BPH patients treated with finasteride. The continued worsening of erectile function, as determined by the IIEF-EF score, over time, was markedly significant in patients treated with 5α-RIs therapy over a period of 45 months. This is not the case in patients treated with tamsulosin. This observation is consistent with recent data reported over 4 years period by Fwu et al. [36], which

Table 1: Baseline characteristics of patients in the registry treated for long term with finasteride or tamsulosin.

Characteristic	Overall (n=700)	Finasteride (n=470)	Tamsulosin (n=230)	p-Value
Age, years				
Mean±SD	59.37±5.27	57.78±4.81	62.62±4.65	p<0.001
Median and range	59.15 (47.4–72.3)	57.7 (47.4–68.7)	62.65 (53.5–72.3)	
Waist circumference, cm				
Mean±SD	103.07±6.46	101.95±5.57	105.36±7.5	p<0.001
Median and range	102 (86–123)	101 (86–123)	105 (93–122)	
Weight, kg				
Mean±SD	89.48±9.52	89.37±9.4	89.73±9.77	0.638532
Median and range	89 (71–112)	89 (71–112)	89 (72–110)	
Prostate volume, mL				
Mean±SD	46.56±8.32	46.63±8.17	46.42±8.63	0.751302
Median and range	47 (32–60)	47 (32–60)	46 (32–60)	
IPSS				
Mean±SD	9.05±1.42	9±1.42	9.17±1.42	0.1487
Median and range	9 (7–11)	9 (7–11)	9 (7–11)	
AMS				
Mean±SD	19.12±2.44	18.41±2.03	20.56±2.58	p<0.001
Median and range	18 (17–30)	18 (17–27)	21 (17–30)	
IIEF (EF)				
Mean±SD	22.06±2.38	23.03±1.9	20.07±2	1.92E-65
Median and range	22 (17–27)	23 (17–27)	20 (17–23)	
Hemactocrit, %				
Mean±SD	45.91±1.41	45.95±1.41	45.83±1.41	0.297956
Median and range	46 (43–49)	46 (43–49)	46 (43–49)	
Leukocytes, g/L				
Mean±SD	6.94±1.04	6.94±1.01	6.95±1.09	0.861534
Median and range	6.9 (5.2–8.8)	6.9 (5.2–8.8)	7 (5.2–8.8)	
Creatinine, mg/dL				
Mean±SD	1±0.12	1±0.12	0.99±0.12	0.447374
Median and range	1 (0.8–1.2)	1 (0.8–1.2)	1 (0.8–1.2)	
Glucose, mg/dL				
Mean±SD	100.48±6.07	100.41±6.16	100.62±5.88	0.669231
Median and range	99 (92–118)	99 (92–118)	100 (92–118)	
AST, U/L				
Mean±SD	24.09±2.94	24.04±3	24.19±2.82	0.530419
Median and range e	24 (19–29)	24 (19–29)	24 (19–29)	
ALT, U/L				
Mean±SD	28.08±3.14	28±3.18	28.25±3.06	0.314922
Median and range	28 (21–35)	28 (21–35)	28 (22–35)	
CRP, ng/mL				
Mean±SD	1.14±1.17	1.2±1.26	1.02±0.97	0.062924
Median and range	0.8 (0.1–7.8)	0.8 (0.1–7.8)	0.8 (0.1–4.6)	
PSA, ng/mL				
Mean±SD	2.22±1.2	2.19±1.2	2.27±1.21	0.399382
Median and range	2.3 (0.2–4.2)	2.25 (0.2–4.2)	2.3 (0.2–4.2)	
Testosterone, ng/mL				
Mean±SD	5.22±1.24	5.17±1.25	5.33±1.23	0.09914
Median and range	5.2 (3.1–7.4)	5.1 (3.1–7.4)	5.5 (3.1–7.4)	

Table 1 (continued)

Characteristic	Overall (n=700)	Finasteride (n=470)	Tamsulosin (n=230)	p-Value
Diastolic BP, mm Hg				
Mean±SD	72.6±20.81	72.77±21.1	72.26±20.23	0.7573
Median and range	68 (40–140)	68 (40–140)	69 (40–135)	
Pulse				
Mean±SD	86.84±19.97	86.27±19.57	87.99±20.76	0.286936
Median and range	84 (54–143)	84 (54–143)	85 (55–141)	
Diabetes				
Non-diabetic	517 (73.9%)	350 (74.5%)	167 (72.6%)	0.598993
Diabetic	183 (26.1%)	120 (25.5%)	63 (27.4%)	
PDE-5 inhibitors				
Nonusers	696 (99.4%)	470 (100%)	226 (98.3%)	0.004141
Users	4 (0.6%)	0 (0.0%)	4 (1.7%)	

IPSS, International Prostate Symptom Score; AMS scale, Aging Male Symptom Scale; IIEF-EF, International Index of Erectile Function-Erectile Function Domain; AST, Aspartate aminotransferase; ALT, Alanine Aminotransferase; CRP, C-Reactive Protein; PSA, Prostate Specific Antigen; BP, Blood Pressure; PDE-5, Phosphodiesterase type 5.

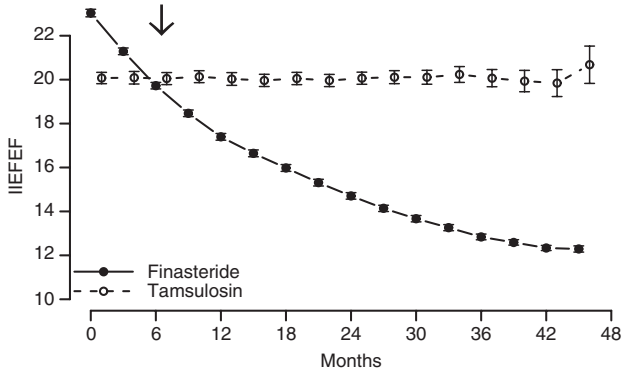

Figure 1: Effects of long-term treatment with finasteride or tamsulosin on erectile function as assessed by the International Index of Erectile Function (IIEF-EF) domain.

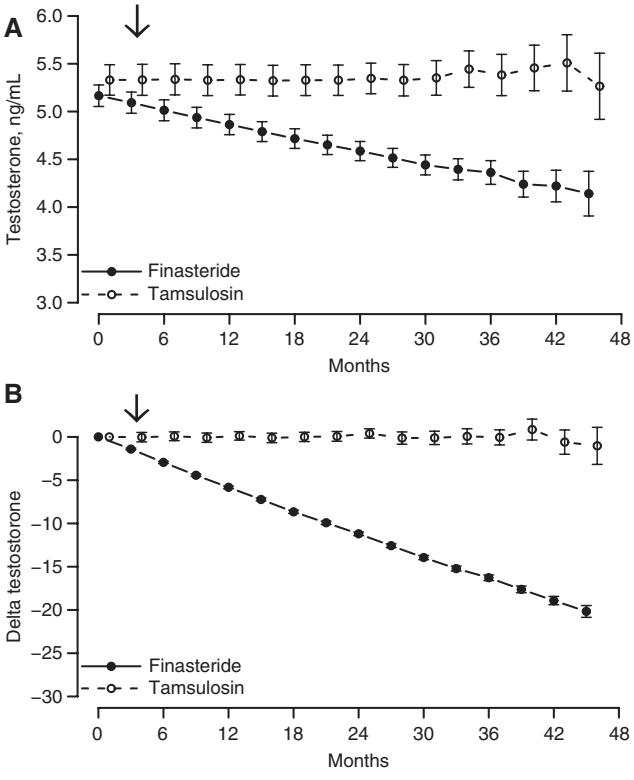

Figure 2: Effects of long-term therapy with finasteride or tamsulosin on total circulating testosterone levels (A, upper panel). Percent reduction in the total testosterone levels in response to long-term therapy with finasteride or tamsulosin treatment (B, lower panel).

showed progressive worsening of erectile dysfunction. The data presented in Figure 1 contradicts previously reported studies [16, 24, 54–58] suggesting that the adverse effects of 5α-RIs therapy on erectile function resolve with continued treatment. The finasteride-induced adverse side effects on erectile function did not resolve with continued therapy, as was suggested previously [16, 24, 55–58]. Thus, our findings are inconsistent with previous claims that the adverse effects resolve within the 1st year of treatment [16, 24, 55–58]. Our findings are also inconsistent with that of Debruyne et al. [56], who suggested that long-term use of dutasteride showed no safety issues over 4 years of treatment and therefore this therapy is deemed safe and effective. Debruyne et al. [56] concluded that the onset of drug-related adverse events were reported most frequently at the start of therapy and declined over time in patients receiving dutasteride. Roehrborn et al. [16] suggested that the majority of the adverse events reported were not drug related in the judgment of the investigators. The authors further stated that the drug-related events were of

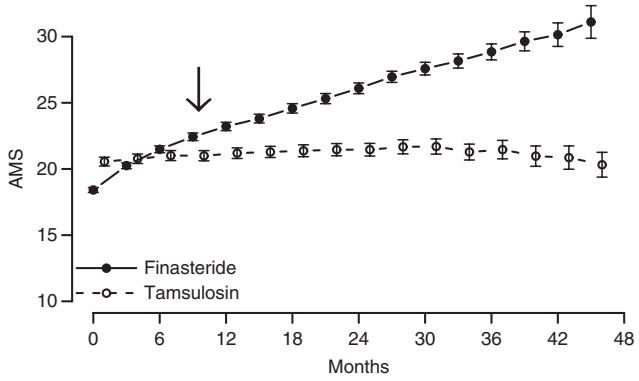

Figure 3: Effects of long-term therapy with finasteride or tamsulosin on the Aging Male Symptoms Score (AMS).

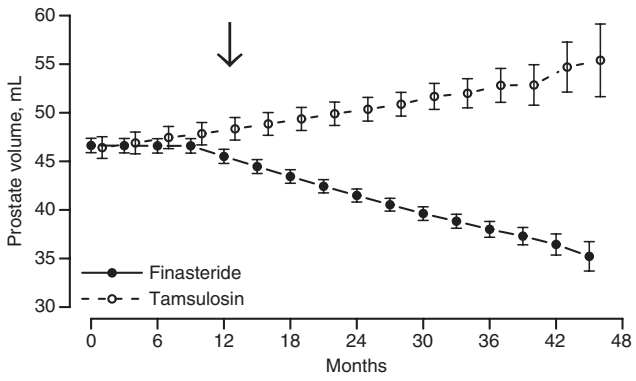

Figure 5: Effects of long-term therapy with finasteride or tamsulosin on prostate volume.

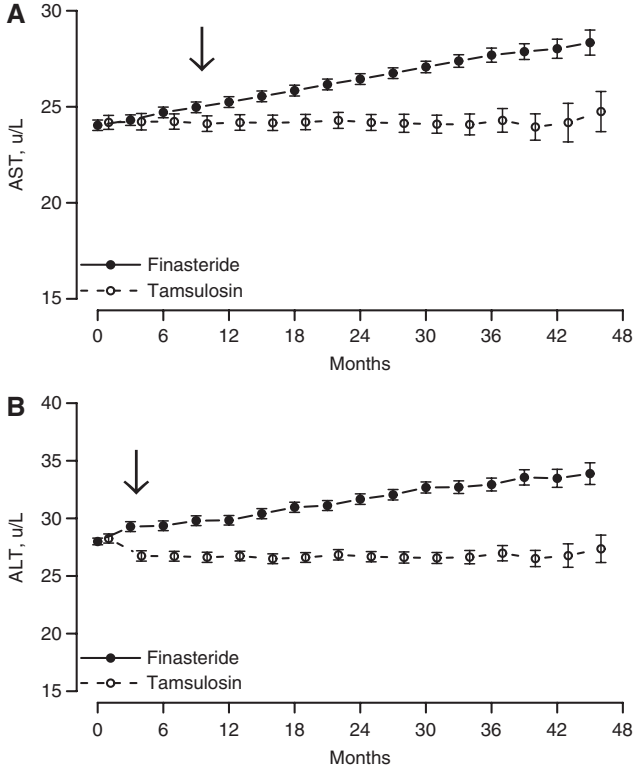

Figure 4: (A, B) Effects of long-term therapy with finasteride or tamsulosin on liver function enzymes (AST and ALT).

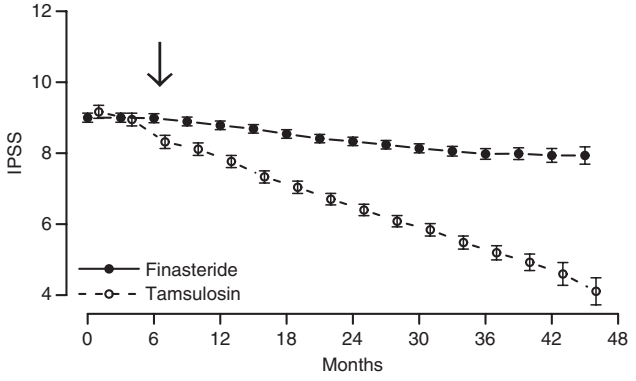

Figure 6: Effects of long-term therapy with finasteride or tamsulosin on the International Prostate Symptom Score (IPSS).

sexual nature and were the most common and included impotence, decreased libido, ejaculation disorders, and gynecomastia in the course of the 24-month study. More importantly, the authors claimed that most of these effects were transient, and the incidence of new occurrences of each event decreased in the 2nd year. Our findings strongly support previous reports [6–8, 36] suggesting that, unlike tamsulosin, finasteride treatment worsened ED and may increase the severity of ED in BPH patients treated with 5α-RIs. It should be noted that there was no resolution of the side effects by continued treatment, as suggested previously by others.

Most recently, Glina et al. [58] reported that the IIEF EF declined with finasteride treatment but returned to

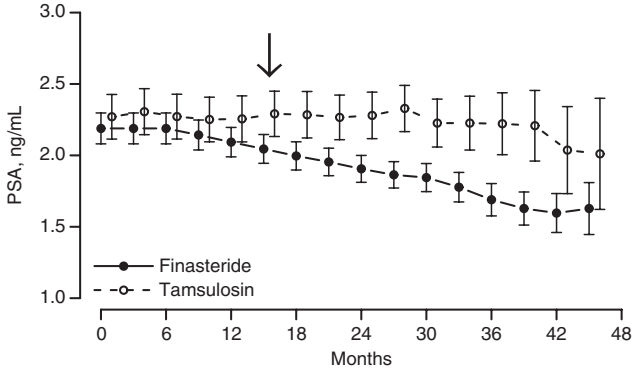

Figure 7: Effects of long-term therapy with finasteride or tamsulosin on levels of prostate specific antigen (PSA).

baseline after 26 weeks of treatment. These data are incongruent with other reports. Chi and Kim [33] showed that after 1 month of treatment, dutasteride therapy resulted in a significant reduction in all investigated sexual function domains. The authors noted that partial recovery in sexual function was noted at 3 months, and orgasmic function and sexual desire were restored to baseline levels at 6 months. However, erectile function was still significantly reduced even at 12 months. Thus, these findings are inconsistent to the claims made by Glina et al. [58]

The findings in our study are further supported by the data from the MTOPS study, which showed similar worsening of the erectile function domain over 4-year period, when compared with placebo [36]. Of note, we did not observe worsening of erectile function with the α-adrenergic receptor blocker, tamsulosin. This finding is similar to that reported by Fwu et al. [36] with doxazosin, an α-adrenergic receptor blocker. Our findings are also supported by the study of Zlotta et al. [95] in which the authors evaluated 354 patients treated with tamsulosin and 545 on finasteride using a validated MSF-4 questionnaire, including four items that explored the patient's interest in sex, quality of erection, achievement of orgasm, and ejaculation. The authors presented data showing that at 6 months, as compared to pretreatment, there was greater increase in sexual disorders in the finasteride-treated group when compared to pretreatment or tamsulosin-treated patients. Our findings are also consistent with those reported by Fwu et al. [36] in which they examined the change in sexual function in 2783 men and reported that sexual function diminished over time with finasteride and with finasteride in combination with doxazosin therapy. Most importantly, there was no significant difference in changes in any inventory domains in men treated with doxazosin alone compared to placebo. It should be pointed out that the symptoms of ED did not resolve over time during the 4-year study period. This is inconsistent with previous claims [16, 24, 55–58]. Recently, Ganzer et al. [15] reported that persistent sexual side effects of 5α-RIs therapy were prevalent in a large number of subjects. These observations support prior findings on the sexual adverse effects of finasteride [9–13, 37]. Our data confirm prior suspicions that 5α-RIs therapy is indeed associated with sexual adverse effects, and such adverse effects do not resolve with continuation of therapy, as previously claimed [16, 24, 55–58]. The worsening of the sexual adverse events cannot be attributed to aging as men treated with tamsulosin did not show worsening of the erectile function domain over time, as compared with patients treated with finasteride. Furthermore, our findings are contrary to previous claims suggesting that 5α-RIs had minimal adverse effects on erectile function and these adverse events resolve with continued treatment [16, 23, 24, 31, 33, 55–58, 96].

Andriole et al. [25, 31] suggested that dutasteride showed adverse effects of sexual dysfunction in men with BPH during a 4-year period in a prostate cancer prevention clinical trial. Kaplan et al. [34] performed a retrospective analysis of 378 consecutive men treated with 5α-reductase inhibitor monotherapy (197 on finasteride and 211 on dutasteride) in a single clinic and reported that the incidences of erectile dysfunction, ejaculatory dysfunction, and decreased libido resulting in discontinuation from therapy was significantly ($p<0.01$) higher in the dutasteride compared with the finasteride group. Furthermore, the data from consecutive patients treated with dutasteride or finasteride resulted in significantly more sexual adverse effects than noted with placebo. Similarly, Park and Choi [97] performed a systematic review and meta-analysis and demonstrated that pooled data indicated adverse events and drug-related adverse events were significantly more common in patients treated with dutasteride compared with placebo. Sexual adverse events, including ED, diminished and/or loss of libido, and gynecomastia were more frequently reported. Interestingly, Wessells et al. [24] suggested that the sexual adverse events were resolved in patients continuing therapy. The authors further suggested that in men who discontinued the drug due to sexual adverse events, more than 50% experienced resolution of their sexual adverse effects. The authors however did not address what happened to the other 50% in whom adverse effects were not resolved. Furthermore, Wessells et al. [24] concluded that "compared with placebo, men treated with finasteride experienced new drug-related sexual AEs with an increased incidence only during the first year of therapy". It should be noted that the authors did not account for drop-outs and no follow-up data were provided. Also, this study did not employ the IIEF scale, as the sexual function assessment scale and therefore such findings may not reflect objective assessment of the adverse sexual adverse effects.

Whether the findings from previous studies suggesting resolution of the sexual adverse events are attributed to use of different, and in some cases, un-validated scales or questionnaires for evaluation of sexual dysfunction, remains to be determined. Most importantly long-term treatment with doxazosin alone had minimal, if any, negative impact on sexual function [36]. Men treated with finasteride or finasteride together with doxazosin experienced worsening of several sexual function domains compared to those on placebo [36], thus, supporting data from several previous RCTs [17, 23, 98]. When the effects

of finasteride on sexual function in the same trial were assessed by the Sexual Activity Scale, the adverse events were found to be minimal [99], suggesting that the use of various scales for sexual function assessment may have contributed to the discrepancies in the various reports.

Recently Belknap and colleagues [100] have reported that considerable bias and inaccuracy exists in reporting of adverse effects from 34 clinical trials with 5aRIs in management of hair loss or restoration. Thus, it is not surprising that similar potential bias and inaccuracies may have occurred in reporting of adverse effects from previous trials on use of 5aRIs in treatment of BPH. An editorial following the report by Belknap et al., [100] has highlighted the need to re-think the safety of these drugs [101].

One of the arguments advanced in favor of 5α-RIs therapy in men is that the adverse sexual adverse effects do resolve with time. However, no long-term clinical evidence was provided to support this argument, especially as many of the studies have used non-validated questionnaires or a "yes" or "no" question regarding sexual dysfunction. On the contrary, the recent analysis by Fwu et al. [36] showed the sexual adverse effects worsen with treatment over time and do not resolve as suggested previously.

In this study, we also report that finasteride treatment resulted in a significant reduction in T levels over the 45 months period of treatment. However, there was no reduction in T levels with tamsulosin treatment in this study. This finding is inconsistent with some prior reports in which T levels were shown either to remain unchanged subsequent to 5α-RI therapy [62–77] or relative increase in T levels were reported with 5α-RI therapy [56, 78–87]. Kacker et al. [88] did not find any changes in T levels in men receiving dutasteride treatment; however, there was a clear tendency for a decline in T which did not reach statistical significance.

Several studies have shown that treatment with 5α-RIs resulted in either no significant changes in T levels [62–77] or in increased T levels [78–87]. It should be noted that Hong et al. [83] and Roehrborn et al. [82] noted marked increase in T levels in patients with low baseline T and reduced increase in T levels in patients with high baseline T levels. Thus, it remains to be determined why T levels are inconsistent among the various studies utilizing 5α-RI therapy [62–87]. The discrepancies among the various studies may be attributed to: (i) short therapy durations, (ii) small number of patients studied, (iii) age of patients, (iv) baseline T levels, or (v) SHBG levels prior to therapy [83, 88]. Thus, it remains to be determined why T levels are inconsistent among the various studies utilizing 5α-RIs therapy. In addition, these observations are consistent with the findings in Figures 1 and 2, whereby finasteride but not tamsulosin resulted in reduction in the EF domain of the IIEF scale and reduced total T levels, reflecting potential new hypogonadal state. This observation suggests that 5α-RIs therapy produces significant adverse effects as assessed by patients' responses on the AMS questionnaire. This is not surprising since one of the most noted adverse effects is ED. This, coupled with reduced T levels, which represent an induced form of hypogonadism, may contribute to the observed increase in the AMS score in the finasteride group. Clearly, this is an important observation and merits further study. We are not aware of any studies that demonstrated a decrease in T levels subsequent to finasteride or dutasteride therapy. The noted discrepancies among the various studies cannot be easily attributed to one specific factor.

We also report an increase in the AMS scale suggesting that patients treated with finasteride have poor quality of life relative to those treated with tamsulosin, which may be attributed either to the sexual adverse effects of the drug or to the induced hypogonadal state due to reduced T levels. Further, the observed increase in liver enzymes suggests that finasteride alters liver function. As it was recently shown that 5α-RI therapy increases insulin resistance and reduces glucose disposal in humans and animals, it is possible that 5α-RI therapy alters liver function and may be responsible for the reduced levels of circulating testosterone through increased metabolism and clearance.

The data on prostate volume, IPSS score, and PSA levels are consistent with previous studies reported using 5α-RI therapy or alpha blockers in men with BPH. We did not observe changes in PSA with tamsulosin but we noted an improved IPSS score. Tamsulosin did not result in changes in AMS or liver function enzymes. This latter observation is of critical importance to management of BPH patients taking into account the potential adverse effects of 5α-RI therapy in light of similar improvements with the alpha adrenergic blocker tamsulosin. In summary, our study shows that 5α-RI therapy exerts worsening of ED and the adverse effects on this domain do not resolve by continued treatment. The limitation of this study is its retrospective nature. The strengths of this study are the large number of patients in each cohort and the long-term follow-up of 45 months.

Summary

This study showed that long-term 5α-RIs therapy but not tamsulosin in men with BPH is associated with continued worsening of ED, which does not resolve with continued

treatment, contrary to previous claims. Most importantly, it appears that 5α-RIs therapy but not tamsulosin results in reduction of T levels and increased AMS score as well as AST and ALT in liver. These findings raise a safety concern regarding 5α-RI therapy for the long-term. Clinicians are urged to discuss the impact of 5α-RIs therapy with their patients before commencing this therapy.

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