Correspondence:
Sabina Cauci, Dipartimento di Scienze Mediche e Biologiche, Università di Udine, Piazzale Kolbe 4, 33100 Udine, Italy.
E-mail: sabina.cauci@uniud.it

Keywords:
5-alpha-reductase inhibitor, AGA, benign prostatic hyperplasia, erectile dysfunction, finasteride safety, finasteride side effects, follicle stimulating hormone, free testosterone, loss of libido, luteinizing hormone, male pattern hair loss, PFS, Post-finasteride syndrome, sexual dysfunction, testosterone

Accepted: 15-Nov-2015

An observational retrospective evaluation of 79 young men with long-term adverse effects after use of finasteride against androgenetic alopecia

[1]G. Chiriacò, [2]S. Cauci, [1]G. Mazzon and [1]C. Trombetta

[1]Urological Hospital Department, Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy, and [2]Department of Medical and Biological Sciences, School of Medicine, University of Udine, Udine, Italy

SUMMARY

Concern regarding adverse effects of finasteride is increasing. We aimed to determine the type and frequency of symptoms in men having long-term sexual and non-sexual side effects after finasteride treatment (a condition recently called post-finasteride syndrome, PFS) against androgenetic alopecia (AGA). Subjects were recruited at the Urology Unit of the Trieste University-Hospital, and from a dedicated website. Out of 79 participants, 34% were white Italians, mean age was 33.4 ± 7.60 years, mean duration of finasteride use was 27.3 ± 33.21 months; mean time from finasteride discontinuation was 44.1 ± 34.20 months. Symptoms were investigated by an ad hoc 100 questions' questionnaire, and by validated Arizona Sexual Experience Scale (ASEX) and Aging Male Symptom Scale (AMS) questionnaires. By ASEX questionnaire, 40.5% of participants declared getting and keeping erection very difficult, and 3.8% never achieved; reaching orgasm was declared very difficult by 16.5%, and never achieved by 2.5%. By the ad hoc questionnaire, the most frequent sexual symptoms referred were loss of penis sensitivity (87.3%), decreased ejaculatory force (82.3%), and low penile temperature (78.5%). The most frequent non-sexual symptoms were reduced feeling of life pleasure or emotions (anhedonia) (75.9%); lack of mental concentration (72.2%), and loss of muscle tone/mass (51.9%). We contributed to inform about symptoms of PFS patients; unexpectedly loss of penis sensitivity was more frequent than severe erectile dysfunction and loss of muscle tone/mass was affecting half of the subjects. Further studies are necessary to investigate the pathophysiological and biochemical pathways leading to the post-finasteride syndrome.

INTRODUCTION

Finasteride is a 4-azasteroid that was selected among a vast array of chemically synthesized steroid analogs for its special ability to inhibit 5-α-reductase (5-α-R), the enzyme responsible for reduction in several steroid substrates to their dihydro-forms, mainly the conversion of testosterone (T) into dihydrotestosterone (DHT) (Traish *et al.*, 2014a). Finasteride as a drug was approved by the US Food and Drug Administration (FDA) in 1992 against benign prostate hyperplasia (BPH) (5 mg/day), and in 1997 against androgenetic alopecia (AGA, also called male pattern hair loss) (Nickel, 1998; Lowe *et al.*, 2003; Aggarwal *et al.*, 2010). Since its discovery, several evidence documented that finasteride inhibits 5-α-R type 2 much more strongly than type 1 (Aggarwal *et al.*, 2010). More recently, it was demonstrated that finasteride is also able to strongly inhibit human 5-α-R of type 3 (Yamana *et al.*, 2010). Type 2 enzyme is located mainly in the prostate, muscle, liver, and kidney, whereas type 3 is found mainly in the brain, mammary glands, frontal cortex, total skin, epidermis, pancreas, spleen, kidney, heart, testicle, stomach, dermis, small intestine and the liver (Yamana *et al.*, 2010). Consequently, only recently it was evidenced that inhibition of 5-α-R by finasteride can potentially affect several different human tissues (Yamana *et al.*, 2010; Irwig, 2014; Traish *et al.*, 2014b).

From early human studies it has emerged that finasteride had several side effects, including erectile dysfunction, loss of libido, and reduced ejaculatory volume (Mella *et al.*, 2010). Less

common side effects include anxiety, depression, gynecomastia, and breast cancer in men (Traish *et al.*, 2015b). In 1996, the PROSPECT study (Nickel *et al.*, 1996), which investigated finasteride (5 mg/day) safety for BPH, showed significant differences between patients and controls in ejaculation disorders (7.7% vs. 1.7%), erectile dysfunction (15.8% vs. 6.3%); and loss of libido (10.0% vs. 6.3%) (Nickel *et al.*, 1996).

Starting from 2011, independent studies (Irwig & Kolukula, 2011; Traish *et al.*, 2011) described severe sexual side effects in young men who used finasteride against AGA as persistent several months or even years after finasteride discontinuation (Irwig & Kolukula, 2011; Traish *et al.*, 2011, 2015b; La Marra *et al.*, 2012; Cecchin *et al.*, 2014; Di Loreto *et al.*, 2014; Ali *et al.*, 2015; Ganzer *et al.*, 2015; Irwig, 2015). A very recent review assessing safety reporting of clinical trials regarding finasteride used for AGA found that none of 34 clinical trials had adequate safety reporting, 19 were partially adequate, 12 were inadequate, and 3 reported no adverse events (Belknap *et al.*, 2015). Belknap *et al.* claimed that available toxicity information from clinical trials is very limited, of poor quality, and seems to be systematically biased. Indeed in April 2012, the FDA expanded the list of persistent sexual adverse events indicated in the labels for Propecia. Of interest, a recent work (Di Loreto *et al.*, 2014) examining eight patients with the so-called post-finasteride syndrome (PFS) (Cecchin *et al.*, 2014; Ganzer *et al.*, 2015) found increased levels of androgen receptor (AR) in epithelial and stromal cells from foreskin of men with PFS compared with healthy men (Di Loreto *et al.*, 2014). However, the pathophysiology of PFS is still unknown and a detailed clinical definition of PFS is still poor (Traish *et al.*, 2015b). Currently, concern about side effects of 5-α-R inhibitors is increasing (Traish *et al.*, 2014b, 2015b; Belknap *et al.*, 2015; Irwig, 2015).

In this study, we explored by three different questionnaires the clinical symptoms of 79 men who took finasteride to treat AGA, and who experienced sexual and non-sexual side effects over 6 months after finasteride discontinuation.

PATIENTS AND METHODS

Subjects

Enrollment and medical visits (when done) of patients were performed at the Urological Unit of Trieste University-Hospital. The Institutional Ethical Committee of each participating institution approved the study protocol (according to the Declaration of Helsinki), and all the subjects signed a written informed consent.

This was an observational-retrospective study. We enrolled 79 males (>18 and <50 years old) who used finasteride for AGA (Norwood, 1975), and developed persistent side effects for at least 6 months after drug discontinuation, that induced the subject to consult a physician at least once for assessment of his status, including at least one blood examination. Patients were recruited from our clinical practice (n = 17) and from Propecia-help.com (n = 62), an Internet forum for subjects suffering from PFS; 66 of them were previously enrolled in our previous studies (Cecchin *et al.*, 2014; Di Loreto *et al.*, 2014). Each participant was asked to provide every available medical record attesting his health status before, during, and after finasteride use. Exclusion criteria were any documented sexual dysfunction and/or mental disease before finasteride treatment, obesity (body mass index, BMI, >30 kg/m^2), any acute or chronic disease like diabetes mellitus, cardiovascular diseases, liver or thyroid diseases, autoimmune pathologies and malignancies, and no history of drugs capable of altering hormonal status before finasteride use. We excluded participants involved in any class action or other legal suits regarding side effects of finasteride use at time of study entry. BMI was calculated by self-reported weight (kg) and height (m).

Assessment of symptoms

Three different questionnaires were administered to participants to evaluate the development and severity of persistent side effects. An ad hoc questionnaire was elaborated by the study authors to interview subjects about demographic and clinical characteristics, lifestyle habits, finasteride dosage, period of drug use, onset, type, and duration of side effects (Di Loreto *et al.*, 2014). Such ad hoc questionnaire was based on clinical expertise of our research group including also evidence based on collection of spontaneous declarations by PFS patients. Our questionnaire comprised 100 items (time required to fill about 1 h), and for several questions it gave the opportunity to the participant to do also spontaneous declarations. The duration of the finasteride therapy was calculated in days (months) of use. In particular, we asked patients to report in detail every persistent symptom started during and/or soon after taking finasteride and never experienced before finasteride use.

Additionally, participants filled twice the Arizona Sexual Experience Scale (ASEX) questionnaire (McGahuey *et al.*, 2000), a validated instrument to assess sexual function at the time of study enrollment (post-ASEX) and retrospectively before finasteride use (pre-ASEX). The ASEX questionnaire comprises five-item rating scales graded from 1 to 6 that quantify sex drive, arousal, penile erection, ability to reach orgasm, and satisfaction from orgasm. Total ASEX score ranges 5–30 points, with the higher scores indicating more severe sexual dysfunction.

The ASEX questionnaire was preferred for PFS patients (Di Loreto *et al.*, 2014) more than other questionnaires like the largely used International Index of Erectile Function Questionnaire five Items (IIEF-5) because IIEF-5 applied only to symptoms related to sexual intercourse over the previous 6 months, and, thus, it is not suitable to subjects not practicing sexual intercourse.

Further, participants filled another validated structured questionnaire the Aging Male Symptom Scale questionnaire (AMS) one of the most accepted to measure androgenic dysfunction (Heinemann *et al.*, 2003, 2006). The AMS is composed of three subscales, measuring respectively: psychological, somatic and sexual symptoms, for a total of 17 items. Each item is graded from 1 (absent) to 5 (very severe), leading to a total AMS score of 17–85 points defining the androgen deficiency level as absent (17–26), slight (27–36), moderate (37–49) or severe (≥50 points).

Present study inclusion criteria were an ASEX total score corresponding to sexual dysfunction (total ASEX score ≥19 points or if any one item is ≥5 or if any three items are ≥4 points) or AMS total score indicating androgenic deficiency (≥27 points).

Finasteride dosage was 1 mg/day, 1.25 mg/day (obtained by breaking in 4 parts 5 mg finasteride pills (Di Loreto *et al.*, 2014), or 0.5 mg/day.

Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD). Mann–Whitney *U*-test was used to compare results from continuous variables. Chi square or Fisher's test was used to compare results from categorical variables, as appropriate. Two-sided p values <0.05 were considered significant, $p < 0.10$ a tendency. Statistical analyses were performed by SPSS (Statistical Package for Social Sciences) software for Windows, SPSS Inc., NY, USA.

RESULTS

Demographic characteristics and results from our ad-hoc and AMS questionnaires are summarized in Table 1. Participants were 22–50 years old (33.4 ± 7.60 years). The majority were Caucasians, 34.2% were white Italians. Most were single and had college and/or university level education.

Patients started finasteride use in the age range of 18–48 years (27.5 ± 7.34 years). Finasteride was assumed in a range of 1–120 months, (27 ± 33.2 months, i.e. approximately 2 years). Patients were enrolled 180–5057 days after drug discontinuation (44.1 ± 34.2 months, i.e. almost 4 years). In all subjects adverse side effects persisted for over 6 months after finasteride discontinuation and were still affecting the patients at the time of the study enrolment. Seventy-two percent assumed finasteride at dosage of 1 mg/day, 22.8% had 1.25 mg/day, and 5.1% had 0.5 mg/day. In 89.9% of participants onset of symptoms occurred during finasteride use, and the trend of symptoms worsened in 62%. By our ad-hoc questionnaire, the most frequent sexual symptom was loss of penis sensitivity (87.3%); among mental disorders was reduced feeling of life pleasure or emotions (anhedonia) (75.9%); among somatic symptoms was loss of muscle tone/mass (51.9%).

Total AMS score was ranging 29–75 (52.3 ± 10.47) points, data were available for 78 patients of which 4 subjects (5.1%) had AMS <37 points attesting a slight androgen deficiency, 27 subjects (34.6%) had AMS ≥37 to ≤49 points indicating a moderate deficiency, and 47 subjects (60.3%) had AMS ≥50 points indicating severe deficiency. By considering the AMS somato-vegetative, psychological and sexual subscales the item with higher mean value was physical exhaustion (3.3 ± 1.08), the depressive mood (3.1 ± 1.15), and the disturbed libido (4.4 ± 0.88), respectively.

Table 2 showed the detailed scoring of the five items of the ASEX score. Patients had post-ASEX ranging 13–30 (21.0 ± 2.67) points, 78.5% had ASEX ≥19 points indicating sexual dysfunction. Pre-ASEX score was much lower ($p < 0.001$) ranging 5–15 (7.7 ± 2.52) points, indicating no overt sexual dysfunction. Specifically, in pre-ASEX the majority of subjects indicated his condition by score 1, conversely, in post-ASEX only one or no patient referred score 1 of each item. The scores 5 and 6 of each item were never referred by any subject in pre-ASEX. In post-ASEX, regarding sex drive the score 5 (very weak) plus 6 (absent) was indicated by 69.6% of subjects; sexual arousal score 5 (very difficult) plus 6 (absent) was referred by 13.9% of subjects; getting and keeping erection score 5 (very difficult) plus 6 (never) was referred by 44.3% of subjects; easiness of reaching orgasm score 5 (very difficult) plus 6 (never) was referred by 19.0% of subjects; finally regarding orgasm satisfaction score 5 (extremely unsatisfying) plus 6 (never achieved orgasm) was referred by

Table 1 Demographic characteristics, sexual and non-sexual symptoms referred as reported in our ad-hoc questionnaire by 79 PFS patients, and in AMS questionnaire by 78 PFS patients

Characteristic or symptom	Patients, $N = 79$ Mean ± SD or n (%) or (range)
Age, years	33.4 ± 7.60
Height, cm	180.4 ± 6.53
Weight, kg	78.8 ± 10.52
BMI, kg/m^2	24.2 ± 3.30
Ethnicity	
Caucasian	69 (87.3)
Asian	5 (6.3)
White Hispanic	5 (6.3)
Citizenship	
Italy	27 (34.2)
Canada	16 (20.2)
USA	16 (20.2)
UK	10 (12.7)
Other countries	10 (12.7)
Scholarity	
Primary	1 (1.3)
High School	16 (20.3)
College and/or University	62 (78.5)
Marital status	
Single	63 (79.7)
Married	13 (16.5)
Divorced	3 (3.8)
Age at starting finasteride assumption, years	27.5 ± 7.34
Duration of finasteride use	
Days	820 ± 996.3
Months	27.3 ± 33.21
Discontinuation of finasteride	
Days	1324 ± 1025.3
Months	44.1 ± 34.2
Dosage used	
1 mg/day	57 (72.2)
1.25 mg/day	18 (22.8)
0.5 mg/day	4 (5.1)
Onset of symptoms	
During finasteride use	71 (89.9)
After finasteride use	8 (10.1)
Within 1 month after discontinuation	6 (7.6)
More than 1 month after discontinuation	2 (2.5)
Trend of symptoms after finasteride discontinuation	
Worsening	49 (62.0)
Unchanged	19 (24.1)
Improved	11 (13.9)
Sexual symptoms	
Loss of penis sensitivity	69 (87.3)
Decreased ejaculatory force	65 (82.3)
Decreased penile temperature	62 (78.5)
Reduced ejaculate volume	58 (73.4)
Penile flaccidity/wrinkling	54 (68.4)
Loss of scrotum fullness	54 (68.4)
Reduction in penile dimension	52 (65.8)
Loss of scrotum sensitivity	49 (62.0)
Perineal tightness	36 (45.6)
Premature ejaculation	25 (31.6)
Mental disorders	
Reduced feeling of life pleasure or emotions (anhedonia)	60 (75.9)
Lack of mental concentration	57 (72.2)
Involuntary muscle spasms	30 (38.0)
Anxiety	20 (25.3)
Somatic symptoms	
Loss of muscle tone/mass	41 (51.9)
Increased body weight (>2 kg difference)	38 (48.1)
More rigidity in physical movements	30 (38.0)
Gynecomastia	8 (10.1)
AMS total score, points	52.3 ± 10.47
AMS (item *n.*) Somato-vegetative subscale, points	
(1) Well-being, impaired	3.2 ± 1.06 (1–5)

(continued)

Table 1 (continued)

Characteristic or symptom	Patients, *N* = 79 Mean ± SD or *n* (%) or (range)
(2) Joint complaints, more	2.3 ± 0.98 (1–5)
(3) Sweating, increased	1.8 ± 0.96 (1–5)
(4) Sleep, disturbances	3.0 ± 1.28 (1–5)
(5) Sleep, need for more	3.2 ± 1.17 (1–5)
(9) Physical exhaustion	3.3 ± 1.08 (1–5)
(10) Muscular weakness	2.8 ± 1.13 (1–5)
AMS (item *n.*) Psychological subscale, points	
(6) Irritability, increased	3.0 ± 1.20 (1–5)
(7) Nervousness, more	2.9 ± 1.20 (1–5)
(8) Anxious, more	2.7 ± 1.26 (1–5)
(11) Depressive mood	3.1 ± 1.15 (1–5)
(13) Burned out	3.0 ± 1.22 (1–5)
AMS (item n.) Sexual subscale, points	
(12) Passed peak	3.5 ± 1.14 (1–5)
(14) Decreased beard growth	1.8 ± 1.09 (1–5)
(15) Sexual potency, impaired	4.3 ± 0.79 (1–5)
(16) Morning erections, less	4.3 ± 0.79 (1–5)
(17) Libido, disturbed	4.4 ± 0.88 (1–5)

20.3% of subjects. By comparing the mean values of each item or total points of pre-ASEX vs. post-ASEX all differences were highly significant ($p < 0.001$).

DISCUSSION

Treatment of young men with oral finasteride is of increasing concern due to emerging evidence that even low dose (1 mg) daily use of finasteride has several severe adverse effects (Mella *et al.*, 2010; Irwig & Kolukula, 2011; Traish *et al.*, 2011; La Marra *et al.*, 2012; Di Loreto *et al.*, 2014). According to recent literature, by far, insufficient information is available to establish the safety profile for finasteride in the treatment of AGA (Irwig, 2014, 2015; Belknap *et al.*, 2015; Traish *et al.*, 2015b).

We performed a detailed assessment of the type of symptoms experienced by PFS patients. Although previous investigations reported major sexual adverse side effects in these kind of patients, mainly by use of conventional questionnaires like ASEX (Irwig & Kolukula, 2011), by use of our 100 questions' ad-hoc questionnaire, we found that the majority of patients are suffering from loss of penis sensitivity, decreased ejaculatory force, decreased penile temperature, reduced feeling of life pleasure/emotions (anhedonia), and lack of mental concentration. Roughly half of patients had muscle symptoms in term of loss of muscle tone/mass, 38% declared more rigidity in physical movements, and 10% had gynecomastia. This array of symptoms appears to span tissues were 5-α-R of type 3 is expressed including testicle, brain, frontal cortex, mammary gland in addition to tissues like prostate and muscle were 5-α-R of type 2 is mainly present. Moreover, 5-α-R of type 1 is expressed in the brain and other tissues and can contribute to elicit finasteride side effects. Symptoms reported by our PFS patients are suggestive of androgens deficiency in several different tissues where 5-α-R is expressed. The intriguing finding is that this occurred long after finasteride discontinuation (on average 44 months; i.e., almost 4 years), thus, this phenomenon seems to indicate that some (till unknown) permanent changes occurred and spread in human body. Our present data do not permit to identify which kind of molecular impairment occurred. The only molecular pathway so far described in former finasteride users with PFS was the significant upregulation of AR in epithelial and stromal cells of the foreskin dermis of eight subjects with persistent loss of penis sensitivity and loss of pleasurable response to touch (Di Loreto *et al.*, 2014). An interesting observation of our previous study was that the ratio of AR positive stromal cells (%) to serum TT and FT was twofold higher in PFS patients than controls, such a finding could indicate the presence in PFS patients of an augmented regulatory feedback loop or could derive from local low levels of androgens' effects (Di Loreto *et al.*, 2014).

In the present study, we carefully examined medical records of PFS patients, no concurrent pathologies were evidenced after finasteride discontinuation.

Androgens and, particularly, testosterone are clearly involved in sexual and erectile function, but are also implicated in muscle and brain functions (Traish, 2009; Zhang *et al.*, 2012; Isidori *et al.*, 2014). Finasteride consequences on circulating androgens levels include both increasing and decreasing effects that are consistent with the finasteride inhibition of testosterone conversion into DHT (which is the most potent androgen). An early study (Gormley *et al.*, 1990) performed in normal male volunteers showed that finasteride daily administration at 1.0 mg dose for 14 days significantly reduced DHT, and increased testosterone only during the first 8 days of treatment. The T/DHT ratio increased and returned to baseline when drug was discontinued. Moreover, DHT levels returned to pretreatment values within 14 days of discontinuing treatment (Gormley *et al.*, 1990). Further, the effects of finasteride were assessed in patients with

Table 2 Detailed results of ASEX score pre- and post-finasteride use in 79 PFS patients, values ranging from 1 to 6 points for each of the 5 items are reported

	Pre-finasteride ASEX points for each item *N* = 79 (%)						Post-finasteride ASEX points for each item *N* = 79 (%)						Pre-finasteride use points Mean ± SD	Post-finasteride use points Mean ± SD	
	1	2	3	4	5	6	1	2	3	4	5	6			*p* value
Sex drive	43 (54.4)	28 (35.4)	7 (8.9)	1 (1.3)	0 (0)	0 (0)	0 (0)	1 (1.3)	8 (10.1)	15 (19.0)	40 (50.6)	15 (19.0)	1.6 ± 0.71	4.8 ± 0.92	$p < 0.001$
Sexual arousal	44 (55.7)	31 (39.2)	4 (5.1)	0 (0)	0 (0)	0 (0)	1 (1.3)	11 (13.9)	30 (38.0)	31 (39.2)	5 (6.3)	6 (7.6)	1.5 ± 0.60	4.4 ± 0.87	$p < 0.001$
Getting/keeping erection	51 (64.6)	22 (27.8)	6 (7.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (11.4)	35 (44.3)	32 (40.5)	3 (3.8)	1.4 ± 0.63	4.4 ± 0.74	$p < 0.001$
Reaching orgasm	33 (41.8)	38 (48.1)	6 (7.6)	2 (2.5)	0 (0)	0 (0)	1 (1.3)	5 (6.3)	23 (29.1)	35 (44.3)	13 (16.5)	2 (2.5)	1.7 ± 0.72	3.8 ± 0.94	$p < 0.001$
Orgasm satisfaction	47 (59.5)	28 (35.4)	4 (5.1)	0 (0)	0 (0)	0 (0)	1 (1.3)	4 (5.1)	31 (39.2)	27 (34.2)	13 (16.5)	3 (3.8)	1.5 ± 0.59	3.7 ± 0.98	$p < 0.001$
Total ASEX													7.7 ± 2.52	21.0 ± 2.67	$p < 0.001$

BPH randomized to finasteride, 1 or 5 mg, or placebo, daily for 12 months (Gormley *et al.*, 1992). By 1 mg treatment, the mean serum DHT decreased significantly over 60% during the first 2 weeks of treatment and did not change thereafter, on the opposite serum testosterone concentrations (452 ± 148 ng/dL) increased approximately by 10% after 2 weeks of treatment (492 ± 161 ng/dL) and remained increased thereafter (489 ± 161 ng/dL at 12 months treatment). A recent study (Stanczyk *et al.*, 2013) also observed significant increases from baseline in testosterone levels at 1, 3, 6 and 12 months in 5 mg finasteride daily treated patients having elevated serum PSA (>4.0 ng/mL). However, a very recent study investigating the long-term adverse effects of finasteride treatment in men with BPH found reduction in TT levels, apparently contributing to a state of hypogonadism (Traish *et al.*, 2015a). It is to note that studies performed in BPH patients were not designed to investigate hormonal levels after discontinuation of the drug. A study by Irwig (Irwig, 2014) in former users of finasteride with persistent sexual adverse effects found low T levels in 3 out of 20 patients (15%), and low DHT in 3 out of 18 patients (17%) examined. Moreover, it was demonstrated the neurosteroids levels in the cerebral spinal fluid were reduced in males with long-term finasteride side effects (Melcangi *et al.*, 2013). Further studies are needed to assess these complex issues.

A major limitation of our investigation was the retrospective nature of the study implying absence of baseline information before finasteride use. The design of our study included patients that were personally phone recalled following their participation in a dedicated site, thus, we cannot exclude several biases, including incomplete clinical assessment by provided medical records, missing or not spontaneous information given by participants and lack of objective testing to measure penile sensitivity.

A further limitation was the relatively small number of subjects enrolled, which is derived in part by the strict selection of patients. Strength of our study is that we documented in detail several severe sexual and non-sexual side effects in PFS patients.

CONCLUSION

This study adds information on an array of sexual, somatic, and psychological symptoms of young men with long-term side effects after finasteride use against AGA. The novelty of our findings included the elevated frequencies of penis sensitivity loss (87.3%), decreased ejaculatory force (82.3%), and decreased penile temperature (78.5%) perceived by PFS patients (evaluated by the ad hoc questionnaire) that were all higher than frequencies of severe reduction of sex drive (69.6%) and sexual arousal (13.9%), severe incapability of getting/keeping erection (44.3%) and reaching orgasm (19.0%), and very poor or no orgasm satisfaction (20.3%) (evaluated by ASEX questionnaire). Frequency and type of symptoms we described could help clinicians to better diagnose the newly described PFS. In the context of personalized medicine approach, when confirmed in enlarged studies, our findings suggest that the ASEX score should be carefully evaluated before and after finasteride prescription to young men with AGA.

ACKNOWLEDGEMENT

We gratefully thank all volunteers who accepted to participate in the study, and Francesco La Marra, MD, for help in patient enrollment. Funding was obtained by the University of Udine and the University of Trieste grants 2012–2014.

DISCLOSURES

Authors have no conflict of interest.

AUTHORS' CONTRIBUTION

CG, MG, and CS performed the research, CS and CG analyzed the data and wrote the paper, CS and TC designed the research study, and TC critically revised the manuscript. All authors had full access to all data in the study, take responsibility for the integrity and accuracy of the data analysis, and approved the submitted version.

REFERENCES

Aggarwal S, Thareja S, Verma A, Bhardwaj TR & Kumar M. (2010) An overview on 5alpha-reductase inhibitors. *Steroids* 75, 109–153.

Ali AK, Heran BS & Etminan M. (2015) Persistent sexual dysfunction and suicidal ideation in young men treated with low-dose finasteride: a pharmacovigilance study. *Pharmacotherapy* 35, 687–695.

Belknap SM, Aslam I, Kiguradze T, Temps WH, Yarnold PR, Cashy J, Brannigan RE, Micali G, Nardone B & West DP. (2015) Adverse event reporting in clinical trials of finasteride for androgenic alopecia: a meta-analysis. *JAMA Dermatol* 151, 600–606.

Cecchin E, De Mattia E, Mazzon G, Cauci S, Trombetta C & Toffoli G. (2014) A pharmacogenetic survey of androgen receptor (CAG)n and (GGN)n polymorphisms in patients experiencing long-term side effects after finasteride discontinuation. *Int J Biol Markers* 29, e310–e316.

Di Loreto C, La Marra F, Mazzon G, Belgrano E, Trombetta C & Cauci S. (2014) Immunohistochemical evaluation of androgen receptor and nerve structure density in human prepuce from patients with persistent sexual side effects after finasteride use for androgenetic alopecia. *PLoS ONE* 9, e100237.

Ganzer CA, Jacobs AR & Iqbal F. (2015) Persistent sexual, emotional, and cognitive impairment post-finasteride: a survey of men reporting symptoms. *Am J Mens Health* 9, 222–228.

Gormley GJ, Stoner E, Rittmaster RS, Gregg H, Thompson DL, Lasseter KC, Vlasses PH & Stein EA. (1990) Effects of finasteride (MK-906), a 5 alpha-reductase inhibitor, on circulating androgens in male volunteers. *J Clin Endocrinol Metab* 70, 1136–1141.

Gormley GJ, Stoner E, Bruskewitz RC, Imperato-McGinley J, Walsh PC, McConnell JD, Andriole GL, Geller J, Bracken BR, Tenover JS, Vaughan ED, Pappas F, Taylor A, Binkowitz B & Ng J; For the Finasteride Study Group (1992) The effect of Finasteride in men with benign prostatic hyperplasia. *N Engl J Med* 327, 1185–1191.

Heinemann LA, Saad F, Zimmermann T, Novak A, Myon E, Badia X, Potthoff P, T'Sjoen G, Pollanen P, Goncharow NP, Kim S & Giroudet C. (2003) The Aging Males' Symptoms (AMS) scale: update and compilation of international versions. *Health Qual Life Outcomes* 1, 15.

Heinemann LA, Moore C, Dinger JC & Stoehr D. (2006) Sensitivity as outcome measure of androgen replacement: the AMS scale. *Health Qual Life Outcomes* 4, 23.

Irwig MS. (2014) Androgen levels and semen parameters among former users of finasteride with persistent sexual adverse effects. *JAMA Dermatol* 150, 1361–1363.

Irwig MS. (2015) Safety concerns regarding 5alpha reductase inhibitors for the treatment of androgenetic alopecia. *Curr Opin Endocrinol Diabetes Obes* 22, 248–253.

Irwig MS & Kolukula S. (2011) Persistent sexual side effects of finasteride for male pattern hair loss. *J Sex Med* 8, 1747–1753.

Isidori AM, Buvat J, Corona G, Goldstein I, Jannini EA, Lenzi A, Porst H, Salonia A, Traish AM & Maggi M. (2014) A critical analysis of the role

of testosterone in erectile function: from pathophysiology to treatment – a systematic review. *Eur Urol* 65, 99–112.

La Marra F, Di Loreto C, Mazzon G, Chiriacò G, Trombetta C & Cauci S. (2012) Preliminary evidence of a peculiar hormonal profile in men with adverse effects after use of finasteride against androgenetic alopecia. *Am J Pathol* 181, S8.

Lowe FC, McConnell JD, Hudson PB, Romas NA, Boake R, Lieber M, Elhilali M, Geller J, Imperto-McGinely J, Andriole GL, Bruskewitz RC, Walsh PC, Bartsch G, Nacey JN, Shah S, Pappas F, Ko A, Cook T, Stoner E & Waldstreicher J. (2003) Long-term 6-year experience with finasteride in patients with benign prostatic hyperplasia. *Urology* 61, 791–796.

McGahuey CA, Gelenberg AJ, Laukes CA, Moreno FA, Delgado PL, McKnight KM & Manber R. (2000) The Arizona Sexual Experience Scale (ASEX): reliability and validity. *J Sex Marital Ther* 26, 25–40.

Melcangi RC, Caruso D, Abbiati F, Giatti S, Calabrese D, Piazza F & Cavaletti G. (2013) Neuroactive steroid levels are modified in cerebrospinal fluid and plasma of post-finasteride patients showing persistent sexual side effects and anxious/depressive symptomatology. *J Sex Med* 10, 2598–2603.

Mella JM, Perret MC, Manzotti M, Catalano HN & Guyatt G. (2010) Efficacy and safety of finasteride therapy for androgenetic alopecia: a systematic review. *Arch Dermatol* 146, 1141–1150.

Nickel JC. (1998) Placebo therapy of benign prostatic hyperplasia: a 25-month study. Canadian PROSPECT Study Group. *Br J Urol* 81, 383–387.

Nickel JC, Fradet Y, Boake RC, Pommerville PJ, Perreault JP, Afridi SK & Elhilali MM. (1996) Efficacy and safety of finasteride therapy for benign prostatic hyperplasia: results of a 2-year randomized controlled trial (the PROSPECT study). PROSCAR Safety Plus Efficacy Canadian Two Year Study. *CMAJ* 155, 1251–1259.

Norwood OT. (1975) Male pattern baldness: classification and incidence. *South Med J* 68, 1359–1365.

Stanczyk FZ, Azen CG & Pike MC. (2013) Effect of finasteride on serum levels of androstenedione, testosterone and their 5α-reduced metabolites in men at risk for prostate cancer. *J Steroid Biochem Mol Biol* 138, 10–16.

Traish AM. (2009) Androgens play a pivotal role in maintaining penile tissue architecture and erection: a review. *J Androl* 30, 363–369.

Traish AM, Hassani J, Guay AT, Zitzmann M & Hansen ML. (2011) Adverse side effects of 5alpha-reductase inhibitors therapy: persistent diminished libido and erectile dysfunction and depression in a subset of patients. *J Sex Med* 8, 872–884.

Traish AM, Guay AT & Zitzmann M. (2014a) 5alpha-Reductase inhibitors alter steroid metabolism and may contribute to insulin resistance, diabetes, metabolic syndrome and vascular disease: a medical hypothesis. *Horm Mol Biol Clin Investig* 20, 73–80.

Traish AM, Mulgaonkar A & Giordano N. (2014b) The dark side of 5alpha-reductase inhibitors' therapy: sexual dysfunction, high Gleason grade prostate cancer and depression. *Korean J Urol* 55, 367–379.

Traish AM, Haider KS, Doros G & Haider A. (2015a) Finasteride, not tamsulosin, increases severity of erectile dysfunction and decreases testosterone levels in men with benign prostatic hyperplasia. *Horm Mol Biol Clin Investig* 23, 85–96.

Traish AM, Melcangi RC, Bortolato M, Garcia-Segura LM & Zitzmann M (2015b) Adverse effects of 5alpha-reductase inhibitors: what do we know, don't know, and need to know? *Rev Endocr Metab Disord* 2015, 1–22.

Yamana K, Labrie F & Luu-The V. (2010) Human type 3 5alpha-reductase is expressed in peripheral tissues at higher levels than types 1 and 2 and its activity is potently inhibited by finasteride and dutasteride. *Horm Mol Biol Clin Investig* 2, 293–299.

Zhang MG, Wu W, Zhang CM, Wang XJ, Gao PJ, Lu YL & Shen ZJ. (2012) Effects of oral finasteride on erectile function in a rat model. *J Sex Med* 9, 1328–1336.