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A Risk-Benefit Assessment of Treatment with Finasteride in Benign Prostatic Hyperplasia

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Summary

As an androgen target organ, the prostate gland has the almost unique characteristic of being less sensitive to testosterone than to its metabolite 5α-dihydrotestosterone (5α-DHT). The conversion of testosterone to 5α-DHT is induced by the enzyme 5α-reductase. By blocking the activity of 5α-reductase, the androgenic stimulation of the prostate gland can be significantly reduced. The first drug with such capacity to be introduced on the market was finasteride. Following the administration of this drug to men, serum 5α-DHT levels were reduced by approximately 80%.

Large phase III trials have demonstrated the efficacy of finasteride in treating benign prostatic hyperplasia (BPH). While in some patients the drug was poorly effective, other patients showed significant improvements. The mean reduction in size of the prostate gland was 20 to 25% after 6 months of therapy, and this effect was maintained as long as the patient was on the drug, at least up to the end of a 6-year follow-up period. Prostatic symptom scores were improved by a mean of 30%, while urinary flow was only improved by a mean of 1.5 ml/sec (15%).

In a recent double-blind, placebo-controlled study comparing the α-blocker terazosin with finasteride, significant improvement was demonstrated for the α-blocker, while finasteride produced little improvement overall and was not significantly more effective than placebo in treating moderately symptomatic

BPH. However, a subanalysis of this study showed that while finasteride was poorly effective in patients with small prostate glands, a significant improvement was apparent in those with glands larger than 40ml.

There is some evidence that early intervention with finasteride can reduce the number of surgical procedures that are required, at least over a 2-year period.

Finasteride is very well tolerated. However, since 5α-DHT potentiates erectile capacity, a 3 to 4% incidence of impotence has been reported, as well as a decreased ejaculatory volume. Gynaecomastia has been noted in a few patients (0.4%).

In conclusion, finasteride appears to be a very well tolerated drug to treat outflow obstruction in patients with moderately symptomatic BPH caused by large prostate glands.

Even though the hormone dependency of the prostate gland has been known for over a century, and hormonal manipulations have been used in an attempt to deal with prostate cancer as well as benign prostatic hyperplasia (BPH), the pioneering studies by Charles Huggins and associates in the 1940s represent a landmark in the understanding of how endocrine manipulations can be used against prostatic disorders.[1] However, while becoming a standard for the treatment of symptomatic, advanced prostate cancer, the efficacy of this method in patients with BPH has been less impressive; estrogen therapy actually appeared to enlarge the gland.[2] Hormonal manipulations against BPH were used in a number of small studies between the 1960s and the mid-1980s, but never became a routine part of clinical practice.[3-5]

Another landmark in the understanding of prostate biophysiology was the observation that the active androgen in the prostate was *not* testosterone, but instead its metabolite 5α-dihydrotestosterone (5α-DHT); this sensitivity is an almost unique property of the prostate gland among androgen-dependent organs.[6] The only other structures dependent on this metabolite are the hair follicles, a phenomenon that probably contributes to male-pattern baldness.

Since neither BPH, nor prostate cancer, develops in men who were castrated at younger ages[7] it seemed likely that, if the process to convert testosterone to 5α-DHT could be stopped, a highly specific remedy against the evolution of BPH, and possibly also against prostate cancer, could be developed.

A third important observation was made in the 1970s by Imperato-McGinley and collaborators, who studied a genetic defect in a small population in the Dominican Republic.[8] The affected men had a genetic Δ^4 steroid 5α-reductase deficiency, which made it impossible for them to convert testosterone to 5α-DHT. This resulted in a form of male pseudohermaphroditism, since 5α-DHT is important for the normal fetal development of the sexual organs. The affected men, who had a normal chromosomal pattern, were born with marked ambiguity of the external genitalia. They had bilateral testes presenting as labial masses, a blind vaginal pouch and a clitoris-like phallus. At puberty, however, they showed normal male development – increase in muscle mass and no breast enlargement, while the phallus enlarged to become a functional penis.[8] They were referred to by the local people as 'penis at 12'. However, it was interesting to note that the prostate remained small. Also, these men had hardly any beard growth, and they retained a female hair line.

1. Finasteride

1.1 Pharmacology

Finasteride (MK906) is a 4-aza steroid that selectively and competitively inhibits the activity of 5α-reductase.[9] This reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent enzyme is necessary for converting testosterone to 5α-DHT. The drug specifically inhibits the type II isoenzyme of 5α-reductase, the predominant form in prostatic tissue. Dose-dependent inhibition of

5α-reductase results in significant reductions in prostatic and circulating 5α-DHT levels (by 90 and 80%, respectively).

1.2 Early Clinical Studies

Finasteride was introduced as the first drug that obviously fulfilled the criteria of interfering with the metabolism of testosterone to 5α-DHT.[9-10] In phase I and II trials,[9,10] the drug seemed to be fairly nontoxic. Dosages up to 100 mg/day were tried without any significant negative adverse effects, although headache was reported by a few patients. It was found that a dosage as low as 1 mg/day should be sufficient for adequate effect. However, because of a slight therapeutic advantage, 5 mg/day was chosen as the final dosage.[10]

Since the prostate is the major source of circulating 5α-DHT, treatment with finasteride reduces serum levels of circulating 5α-DHT by about 80%. Moreover, the size of the gland has been shown to be reduced by about 25% in volunteers taking the drug for 3 to 6 months.[9]

The efficacy of finasteride has now been assessed in placebo-controlled trials (of up to 4 years in duration), and in over 4000 patients recruited for open-labelled extensions (for up to 6 years). Controlled trials have also been conducted[10-15] comparing finasteride with terazosin, or the combination of finasteride plus terazosin. In all of these trials, patients had mild to moderate, uncomplicated symptomatic BPH. However, other entry criteria differed slightly between studies: maximal urinary flow rate was between 5 to 15 ml/sec; postvoiding residual urine ranged from <150 to <350ml; prostate volume was >25 to >30ml; serum prostate specific antigen (PSA) levels at entry were ≤10 μg/L.

Most patients received finasteride 5 mg/day, although some trials included an arm with 1 mg/day.[10] Most trials included a placebo group and involved a large number of patients. The efficacy of treatment was measured first by a modified

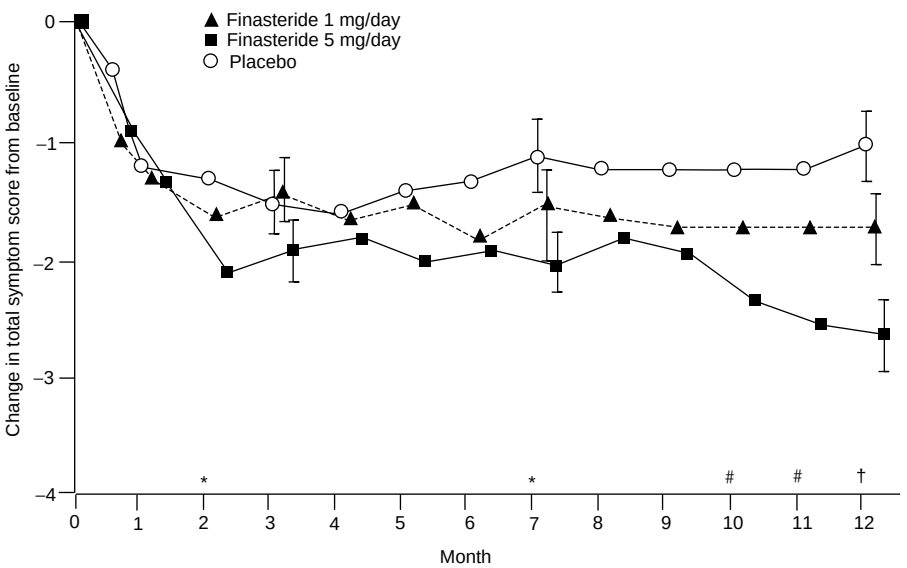

Fig. 1. Mean change in total symptom score (modified Boyarsky symptom scores) in men with benign prostatic hyperplasia during treatment with placebo, or finasteride 1 or 5 mg/day. Bars indicate standard error of the mean (reproduced from Gormley et al.,[10] with permission). *Symbols:* * = $p < 0.05$ between finasteride-treated groups and the placebo group ; # = $p < 0.01$ between finasteride-treated groups and the placebo group; † = $p < 0.001$ between finasteride-treated groups and the placebo group.

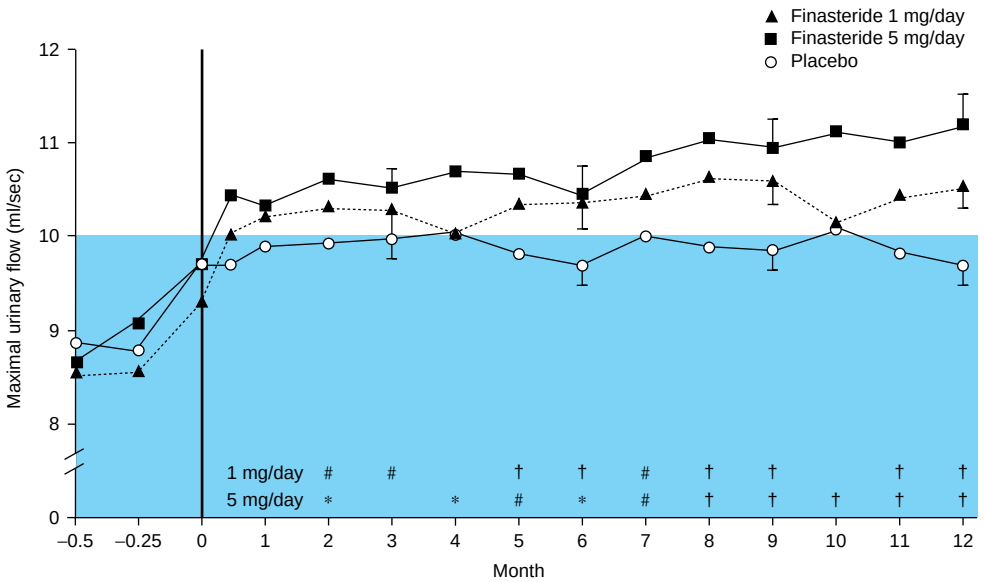

Fig. 2. Mean maximal urinary flow rates in men with benign prostatic hyperplasia during treatment with placebo, or finasteride 1 or 5 mg/day. Bars indicate standard error of the mean. The shaded area indicates the range in which urinary flow was considered to be obstructed. Month 0 represents the baseline. Values before month 0 were obtained during the 2-week placebo run-in period (reproduced from Gormley et al.,[10] with permission). *Symbols:* * = $p < 0.05$ between finasteride-treated groups and the placebo group ; # = $p < 0.01$ between finasteride-treated groups and the placebo group; † = $p < 0.001$ between finasteride-treated groups and the placebo group.

Boyarsky score, and later by the International Prostate Symptom (IPS) score. Changes in prostate volume were measured by transrectal ultrasound or magnetic resonance imaging; peak urinary flow was measured as well as mean urinary flow.

In placebo-controlled trials of 1 or 2 years in duration, finasteride 5 mg/day had significantly superior efficacy to that of placebo, according to total modified Boyarsky symptom scores (–13 to –23% *vs* –14 to +1.5%) [fig. 1], maximal urinary flow (+12.5 to +22% *vs* –3 to +8%) [fig. 2], and prostate volume (–15 to –47% *vs* –5 to +27.5%) [fig. 3] in patients with mild to moderate symptomatic BPH.[10-14] The maximum efficacy was noted within 6 months of treatment, while some studies registered further improvement beyond 1 year, and even 3 years in open extensions of these studies.[11-14]

1.3 Urodynamics

Symptoms of prostatic hyperplasia are classified either as storing dysfunction (irritative) – comprising urgency, frequency and nocturia – or emptying dysfunction (obstructive) – comprising slow flow, hesitancy, dribbling and incomplete voiding. The standard treatment for relieving BPH, transurethral resection of the prostate (TUR-P), primarily relieves obstructive symptoms. It was therefore of interest to study, using urodynamic techniques, whether or not finasteride could improve signs of obstruction in affected patients.

Urodynamic evaluation, apart from uroflow, was not carried out on a routine basis. A small substudy of one of the controlled trials, outside the main protocol, was carried out in northern Finland by Tammela and associates,[15] and only included patients with severe outflow obstruction. Most patients showed urodynamic improvement from the obstructed to the equivocal zone when the data were plotted on an Abrams-Griffiths nomogram. The uroflow was improved by 3 to 3.5 ml/sec, but most importantly, bladder opening pressure was reduced from 115 to 75cm H_2O within 6 months of

the start of treatment, and to 45 cm H_2O over the following 4 years of continued treatment.[16] Further studies confirming these results are still awaited.

1.4 Long Term Controlled Studies

Since it was felt that 1 year was too short a time to reveal the natural course of BPH, a 2-year study was initiated in the Scandinavian countries in 1992. The Scandinavian Reduction of the Prostate Gland (SCARP) study[14] was a double-blind study comparing the efficacy of finasteride with that of placebo in 707 patients enrolled at 59 centres in 5 Nordic countries. Following enrolment and a 4 week single-blind, placebo run-in period, patients were randomised to received finasteride 5mg (n = 353) or placebo (n = 354) once daily for 24 months. Urinary symptoms, urinary flow rate, prostate volume, post-voiding residual urine volume and serum PSA levels were measured at entry, and at 12 and 24 months.

The study results are shown in table I and figure 4. As an additional end-point, it was found that 15 patients in the placebo group had to seek medical advice for urinary retention, compared with only 4 in the finasteride group. Nine patients in the placebo group required a TUR-P during the 2-year study period, whereas no patient in the finasteride group did so. Adverse effects were similar to those reported in previous studies (see section 3), mainly sexual dysfunction; 9% of the patients in the finasteride group experienced erectile dysfunction, compared with 6% of those in the placebo group; these differences were significant.[14]

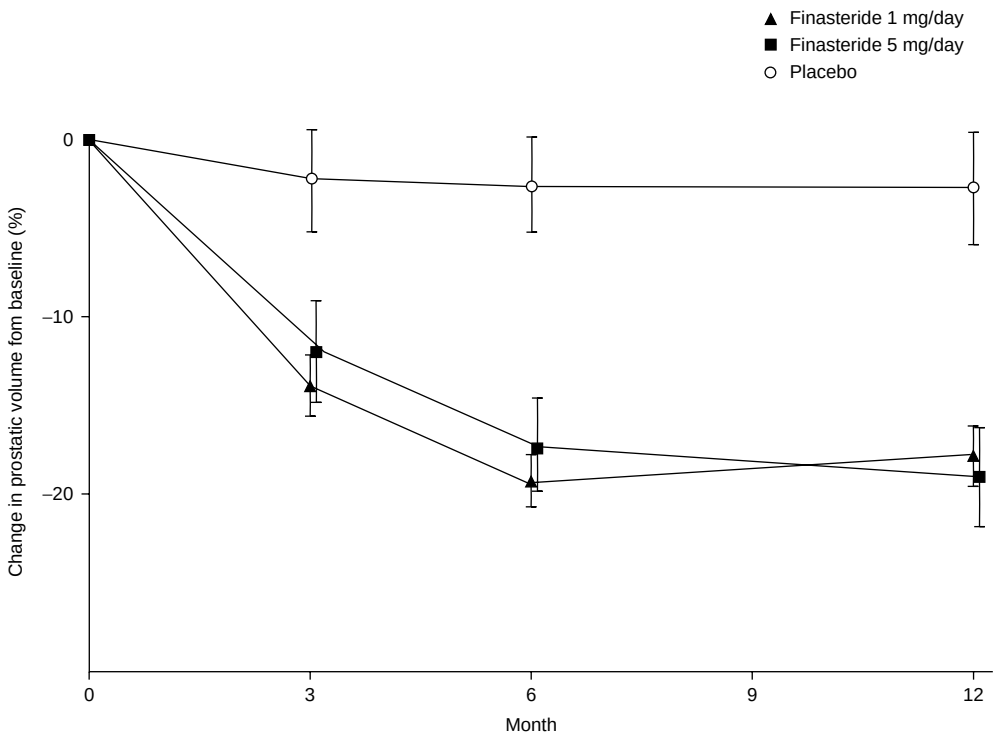

Fig. 3. Median change in prostatic volume in men with benign prostatic hyperplasia during treatment with placebo, or finasteride 1 or 5 mg/day. Bars indicate 95% confidence interval (reproduced from Gormley et al.,[10] with permission).

Similar results were found in a 2-year double-blind parallel-group, placebo-controlled, multicentre, prospective, randomised trial, which recruited 613 men from 28 centres across Canada (the 'Prospect' study) [table I].[17] Again, impotence was the most common adverse effect, reported by 15.8% of patients in the finasteride group, compared with 6.3% of those in the placebo group ($p < 0.01$).[17]

2. Comparison with α-Blockers

2.1 Results of Trials with α-Blockers

An alternative way to relieve outflow obstruction by drug therapy is to relax the smooth muscle that forms a major component of the prostate gland and bladder neck. This region is dominated by α-adrenergic receptors, and the use of α-blocking agents can produce relief of lower urinary tract symptoms. In several double-blind, placebo-controlled studies,[18-21] α-blockers have proven to be effective remedies when treating outflow obstruction caused by BPH. Moreover, the effect of α-blockers is more immediate compared with that of finasteride; improvement with α-blockers usually occurs within weeks of the start of treatment, compared with 3 to 6 months after initiating treatment with 5α-reductase inhibitors.

Numerous α-blockers have been marketed (e.g. terazosin, alfuzosin, doxazosin, tamsulosin). The results from shorter and longer term trials are similar. For instance, in the Hytrin Community Assessment Trial (HYCAT) a total of 2084 men were recruited from 141 private urology practices.[21] Inclusion criteria were an American Urological Association symptom score of ≥13 points, a peak urinary flow rate <15 ml/sec and a voided volume ≥150ml. AUA symptom score improved by 38% in the terazosin group, compared with 18% in the placebo group, while peak urinary flow improved by 2.2 and 0.7 ml/sec, respectively. The major adverse effects were dizziness (12% with terazosin *vs* 6% with placebo) and asthenia (7.5 *vs* 2.9%).

A long term (42 months), open-label multicentre study of terazosin has also been completed.[22] 494 patients with symptomatic BPH were recruited. Of note, only 47 patients remained in the study at 42 months. After 2 months of treatment, urinary flow had improved by a mean of 1.4 ml/sec, and by 42 months the improvement was 2.8 ml/sec. Total symptom score, as measured by the Boyarsky index, was improved by 5 points at 1 year, but was improved by only 4 points at 42 months. In this study, dizziness was reported in 6.7% of patients and asthenia in 3.8%.[22]

2.2 Finasteride versus α-Blockers

Terazosin monotherapy and terazosin plus finasteride therapy reduced AUA symptom scores and improved maximal urinary flow to a significantly greater extent than either finasteride monotherapy or placebo[23] at all follow-up visits during a 1-year US Veterans' Affairs study of patients with lower urinary tract symptoms. There were no significant differences between the effects of terazosin monotherapy and the combination of the 2 drugs, nor was there any difference between finasteride monotherapy and placebo on the measured parameters, except prostate volume.

Table I. Results of the Scandinavian Reduction of the Prostate Gland (SCARP) study[14] and the Prospect study,[17] which compared finasteride 5 mg/day with placebo over 2 years in men with benign prostatic hyperplasia. All the differences between finasteride and placebo are significant

End-point (24 months)	SCARP study		Prospect study	
	finasteride	placebo	finasteride	placebo
Improvement in total symptom score[a]	–15%	+2%	–2 points	–0.8 points
Urinary flow rate (ml/sec)	+1.5	–0.3	+1.3	+0.3
Prostate volume	–19.2%	+11%	–21%	+7%
Serum prostate specific antigen level	–50%	+5%	NR	NR

a As measured using the International Prostate Symptom score. A reduction in score indicates an improvement in symptoms.

Abbreviation: NR = not reported.

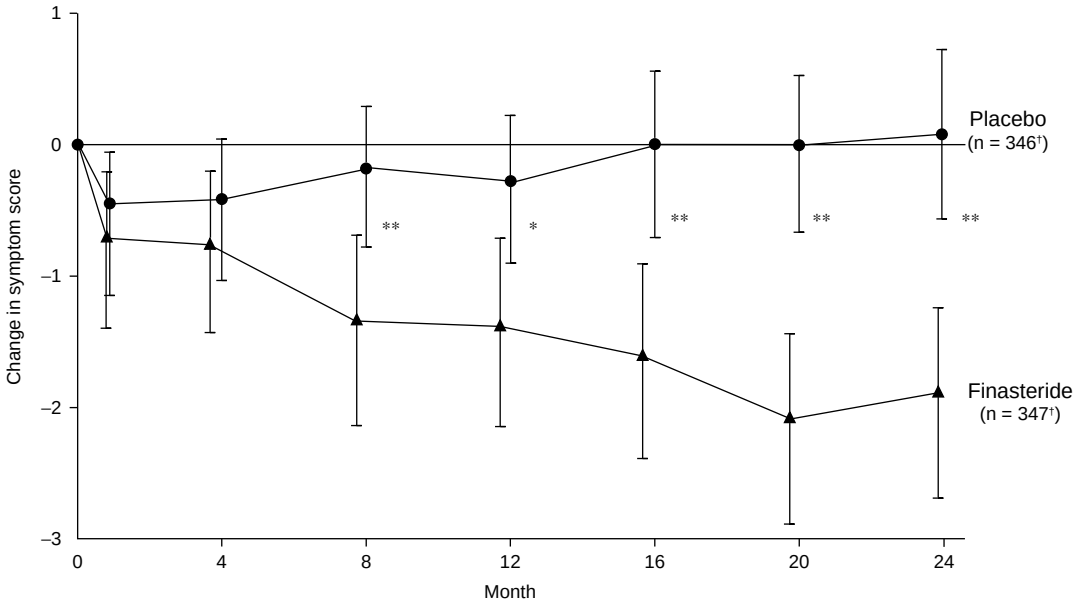

Fig. 4. Mean (± 95% confidence interval) changes in total symptom score from baseline in the intention-to-treat analysis of patients enrolled in the Scandinavian Reduction of the Prostate Gland (SCARP) study (reproduced from Andersen et al.,[14] with permission). *Symbols:* * = $p \leq 0.05$; ** = $p \leq 0.01$; † = at 24 months.

Prostate volume was approximately 37ml in all groups at baseline, and decreased by 17% in the finasteride monotherapy and combination arms, but increased by 1.5% in the terazosin monotherapy and placebo arms. Urinary flow was improved by 3.2 ml/sec in the finasteride plus terazosin arm, compared with 2.7 ml/sec in the terazosin monotherapy arm which were both statistically superior to placebo. In the finasteride monotherapy arm, the increase in urinary flow was only 1.6 ml/sec, an increase that was not significantly different from placebo. Improvement in symptom IPS score was 6.2 points in the combination therapy group, 6.1 points in the terazosin monotherapy group and 3.2 points in the finasteride monotherapy group; again, the result achieved in the finasteride-only group was not statistically significantly different from that achieved with placebo, whereas both groups containing terazosin were significantly improved relative to placebo.[23]

It was concluded from this study[23] that treatment with finasteride was no better than placebo alone. However, the study has been criticised[24] for including patients with small prostates, and for including patients with lower urinary tract symptoms without considering whether or not they were caused by an enlarged prostate.[23]

In the short term, α-blockers seem to be more effective than 5α-reductase inhibitors. However, in the long term, some advantage could be expected from drugs that can reverse or at least halt the natural history of BPH, such as 5α-reductase inhibitors.[14] While these drugs seem to be able to stop the natural process of the disease, I believe that it is possible that the efficacy of α-blockers could diminish with time.

2.3 Influence of Prostate Size

To further explore the controversy regarding the efficacy of finasteride and terazosin, the size of the prostate gland has been given special consideration. In agreement with preliminary observations, it was noted that 5α-reductase inhibitors were more effective in patients with large prostates. A

more recent, detailed analysis of the results confirmed that these agents were of little value over placebo when administered to patients with prostate glands smaller than 40ml, while in those with larger prostate glands, finasteride seemed to be as effective as α-blockers.[24]

In a recent study summarising follow-up data from an open-label extension study with finasteride, the long term efficacy of finasteride was documented. After 6 years of follow-up, 54.5% of the patients remained in the study. An attempt was made to differentiate between the characteristics of 'responders' and 'drop-outs'. There was no significant difference between these 2 patient groups with regard to reduction in size of the gland at 6 months, or improvement of symptom score. The only difference was that 'responders' had a mean improvement in urinary flow of 2.4 ml/sec at 6 months, compared with 1.1 ml/sec in 'drop-outs'.[25]

3. Risk-Benefit Assessment

While TUR-P has long been regarded as the 'gold standard' for treatment of urinary obstruction caused by BPH, the last 5 to 10 years have seen a marked increase in the level of interest in alternative therapeutic modalities. This is partly the result of an overwhelming commercial input, but also because of a desire to reduce the risks associated with surgery. Apart from the surgical trauma, as such, excess bleeding and the risk of TUR syndrome (potentially fatal hypervolaemia and hyponatraemia) long term adverse effects include stricture formation and sexual dysfunction; retrograde ejaculation occurs in approximately 70% of patients who have undergone TUR-P. The question of whether TUR-P may cause impotence has been much discussed.[26]

The main aim of this article is to address risk-benefit when using finasteride in the treatment of BPH. The drug has virtually no adverse effects, except an approximately 3 to 5% risk of impotence.[10] Considering the age of patients who usually experience BPH, reduced erectile function could be seen as an acceptable problem. Outside randomised protocols, gynaecomastia has been reported in 0.4% of patients; this usually resolved when therapy with the drug was stopped.[27] No relationship between finasteride treatment and breast cancer has been found, the incidence being equal to that in the untreated male population.[27]

Finasteride and α-blockers seem to be well-tolerated drugs during long term use. The dominating adverse effect with finasteride is the risk of impotence (3 to 5%); with α-blockers, the common adverse effect is dizziness (5 to 15%). Long term tolerability with finasteride seems to be better than with terazosin.[22,25]

The ability of finasteride to prevent the development of prostate cancer has been widely discussed. A large randomised trial recruiting 18 000 men is presently under way in the US. The follow-up period is planned to extend over 8 years, and the results are awaited. However, a recent study of finasteride treatment versus placebo in patients with premalignant differentiation in the prostate disclosed that the evolution to clinical cancer was slightly higher in the finasteride group.[28]

There is also concern that prostate cancer might be obscured by the use of finasteride, since serum PSA levels are lowered by, on average, 50% during finasteride treatment. This issue has been extensively studied,[29] the results indicating that patients who are receiving finasteride should have their PSA values doubled. Hence, a PSA value over 2 μg/L should raise the suspicion of a coexisting prostate cancer. Since finasteride mainly influences levels of free PSA, it has even been suggested that the treatment could be advantageous. The lowering of PSA in patients with prostate cancer is less marked than in those with BPH. Hence, a doubling of the PSA value in such a patient may suggest the presence of prostate cancer, even if his pretreatment value was below 4 μg/L.[30] This issue requires further study.

4. Cost-Benefit Analysis

A major argument when introducing alternatives to TUR-P for BPH therapy has been the considerable cost to society associated with TUR-P. However, comparisons of various treatment mo-

dalities are not easy to make. Introducing new treatment alternatives that are less traumatic is attractive to a large number of patients who previously refrained from therapy because of fear of surgical complications. Hence, a dramatic increase in patients seeking medical advice for lower urinary tract symptoms caused by BPH is to be expected, which could considerably increase the total cost to society associated with this disease.

Attempts have been made to estimate how many years of medical treatment are comparable to the cost of TUR-P. Such estimates are difficult to make for several reasons. The cost of TUR-P is a 'one-off' cost, while the cost of drug therapy is cumulative. It has been argued that the interest gained from the sum that would have been spent on a TUR-P procedure should offset the cost of purchasing the drug; a Canadian study indicated that in patients with moderate symptoms, the cost of a TUR-P procedure equalled 15 years of finasteride therapy.[31] However, such comparisons are not applicable worldwide; the cost of a TUR-P procedure in the US is estimated at $US7000,[31] while the same procedure in Turkey is estimated at $US700.

Whether or not long term treatment with finasteride reduces the requirement for TUR-P in patients experiencing lower urinary tract symptoms caused by BPH remains to be proven. This question has been approached in a meta-analysis of 4222 patients who received placebo or finasteride.[32] The authors of that analysis found that 89 surgical interventions were required in the finasteride group, compared with 138 in the placebo group, and concluded that finasteride treatment reduced the need for surgery by 34%.[32] However, in this pooled analysis[32] the cost of 49 TUR-P procedures, even when using the US figures, would amount to $US343 000, whereas treating 2111 patients with finasteride for 2 years would cost over $US1.5 million. It is likely that in extended studies, this discrepancy would be even more pronounced.

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