Reviewers report

Title: Finasteride (Proscar) in the treatment of clinical benign prostatic hyperplasia: A systematic review of randomised trials

Authors:

Jayne E Edwards (jayne.edwards@pru.ox.ac.uk)
R Andrew Moore (andrew.moore@pru.ox.ac.uk)

Version: 1 Date: 22 Apr 2002

Reviewer: Dr Timothy Wilt

Level of interest: A paper of considerable general medical or scientific interest

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

The systematic review of RCT evaluating finasteride in the treatment of benign prostatic hyperplasia concludes that this drug has beneficial effects in terms of symptoms, flow rate and prostate volume. While the question is of great importance and the systematic review methods appear to be of high quality there are major concerns with data presentation resulting in "unbalanced" and incomplete conclusions. The primary goal for treatment for BPH in the vast majority of men is to relieve bothersome lower urinary tract symptoms. Outcomes such as urinary flow rates, prostate volume and PSA levels are primarily of theoretic, rather than practical concern. Additionally, the fewer than 5% of men seen in primary care settings who present with bothersome LUTS develop BPH progression resulting in acute urinary retention or requiring urgent surgical intervention. Therefore, the primary outcome of greatest concern to patients and clinicians is...do interventions improve my urinary symptoms, are they safe and available at relatively low cost.

The results of the symptom scores suggest that after 12 months the difference in symptom scores between finasteride and placebo was 1.4 points (-3.7 finasteride; -2.3 placebo). The authors claim this was statistically significant but do not provide S.D. and/or 95% CI to assess potential magnitude of effect. Furthermore, previous work has indicated that changes in symptom scores of 4 points are unlikely to be of clinical significance. Therefore, even if statistically significant the results are of doubtful clinical importance to patients. The Figure 1 is presented on a compressed scale and the magnitude of change is therefore misleading. Furthermore, it is not clear that the reported reductions in SS with finasteride after 12 months are real nor that there was an increase with placebo (no tests of significance are applied and even if P 0.05 they are of doubtful clinical significance). Even results at 24 months only showed a 2.7 point difference in AUA symptom score between finasteride and placebo. Other symptom scale scores do not convincingly demonstrate a clinically significant benefit.

Urinary flow rates are shown in Figure 2 and again are misleading due to the compressed scale. A difference of only 1.2 mL/s are noted with no 95% CI (all of uncertain clinical significance). The outcome of prostate volume is of little clinical importance except mechanistically or unless as a surrogate to future clinical events (like symptom score change or eventual need for surgery etc). The long discussion re: tries to emphasize that there was a benefit regardless of prostate volume. Again the
emphasis is on urinary flow rates rather then on the clinically most relevant outcome (LUTS).

The important PLESS study recruited a select population of men with moderate-severe symptoms and very large prostates. These men do not comprise the vast majority of men presenting to physicians. Again the emphasis is on flow rates. Re: Acute urinary retention and avoidance of BPH related surgery...virtually the entire data at 24 and 48 months are derived from the PLESS study. 12 month data that involved other trials demonstrate markedly lower rates (and much higher NNT). Other placebo controlled trials not evaluating finasteride do not support the high rate of AUR and need for surgery in the control group. Therefore, the patient population enrolled in PLESS is likely to be markedly different then those seen by most physicians and the outcomes different then experienced by most men with LUTS.

The discussion highlights the change in symptom scores from baseline but that is not the appropriate analysis. Rather it should be a comparison to placebo. As noted above this is quite small and previously demonstrated to be not of clinical significance. Emphasis on change in prostate volume and flow rates is of little concern to patients. The NNT for disease progression should include a statement that men also had to have moderate to severe symptoms and large prostates (the minority of men with LUTS).

Additional comments:
Abstract should include data re: aua symptom score change between placebo and finasteride.

Conclusions should be toned down to emphasize small (and questionable clinical benefit) on symptoms.

Little to no information is provided on trials comparing to alpha blockers: VA study is compared to terazosin (not alfuzosin as they mentioned). Recruitment for that study included men with LUTS due to BPH "regardless of prostate size". This is most common way of evaluating and treating men. (rather then statement of "Included men with small prostates). This should no difference vs. placebo and no benefit of finasteride when added to terazosin. This should be emphasized. Additionally, while not yet published in full manuscript, the authors and Merck Pharmaceutical, are well aware of the preliminary results of the PREDICT trial. PREDICT assessed the efficacy and tolerability of doxazosin and finasteride, alone or in combination in treatment of men with LUTS. This 52 week RCT inducted 1095 men with moderate BPH symptoms and enlarged prostates on DRE. Finasteride alone was not statistically significantly different from placebo with respect to flow rates, quality of life or symptoms. Combination therapy with alpha blockers was no better then with alpha blockers alone. Acute urinary retention and need for surgery were rare. There were no differences in rates between finasteride and alpha blockers. While technically excluded from there review because it was not yet published the preliminary results should be mentioned to provide readers with a balanced picture.

The description of NNT can be deleted.

A discussion of the trial of finasteride vs. permixon that showed that permixon was comparable to finasteride and had fewer adverse effects should be discussed. (their explanation for not including them is inadequate and tends to obscure the points that finasteride is unlikely to be the first line treatment for bph).

Costs are not mentioned: generic terazosin or OTC saw palmetto both cost less and have been shown to have superior or comparable efficacy in urinary flow rates.
Conclusion: finasteride may be a useful option for the minority of men with moderate to severe LUTS who do not respond to alpha blockers, have large prostates on DRE and who want to try some prescription medication in hopes of avoiding future acute urinary retention, hematuria or need for surgical or minimally invasive procedures due to disease progression. Their appears to be no role for its use in combination with alpha blockers. Regardless of prostate size alpha blockers appear to provide superior improvement in LUTS at a potentially lower drug cost.

**Competing interests:**

None declared.