



Indian Health Service
IHS National Pharmacy and Therapeutics Committee
5-Alpha Reductase Inhibitors
March 2011



Background:

In March 2011, the IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed the agents used for the treatment of benign prostatic hyperplasia (BPH). The NPTC voted to add finasteride to the NCF.

Clinical Review:

5-Alpha reductase inhibitors (5-ARI) inhibit the enzyme that converts testosterone into dihydrotestosterone (DHT). DHT is necessary for normal growth and development of the prostate gland. 5-ARIs reduce DHT concentrations, reduce the size of the prostate gland, and improve urinary flow rates through effects on increasing apoptosis of prostatic epithelial and stromal tissue and decreases in bladder detrusor muscle pressures. These agents are most effective in men with enlarged prostate glands (> 40 ml volume). There are two agents in this class: finasteride and dutasteride.

Efficacy:

No direct head-to-head trials comparing the two agents in this class have been conducted.

Finasteride: The results of trials in the Finasteride Study Group were published in 1992. This was a randomized double-blinded, placebo-controlled trial (DBPCT) involving 895 men, ages 40-83 with symptoms of urinary obstruction, and enlarged prostate on DRE, and maximal urinary flow rates (Q_{max}) < 15 ml/sec treated with either finasteride or placebo for 12 months. Those in the treatment group showed a 70% reduction in DHT, a 23% reduction in American Urological Association (AUA) Urinary Symptom Scores, a 1.6ml/sec increase in Q_{max} , and a 19% reduction in mean prostate volume.¹ The Finasteride Long-Term Efficacy and Safety Study Group trial was published in 1998. This was a similar study involving treatment of 3040 men over a 4 year time period. It showed a 51% reduction in the need for surgery or catheterization for acute urinary retention, symptom score reductions by 3.3 points, increases in Q_{max} by 1.9 ml/sec, and an 18% reduction in mean prostate volume. Most positive effects were seen within 4 months of starting therapy.²

Dutasteride: A DBPCT looking at the efficacy of dutasteride was published in 2002. It involved 4325 men with AUA symptom scores ≥ 12 , prostate volumes ≥ 30 ml, and Q_{max} < 15 ml/sec treated with dutasteride or placebo for 24 months. Serum DHT was reduced 90.2%, symptom scores reduced 4.5 points, Q_{max} increased 2.2 ml/sec, mean prostate volume reduced 25.7%, urinary retention risk was reduced 57%, and need for surgery reduced 48%.³

Clinical trials of combined treatment with an α_1 adrenergic antagonist and a 5-alpha reductase inhibitor have shown greater reductions in risk for clinical progression, acute urinary retention, symptom scores, and improved quality of life measures in those treated with combination therapy versus monotherapy with either class of agent when used in men with clinically enlarged prostate glands with moderate to severe LUTS.⁴⁻⁶

After careful review of the clinical data on this class, the NPTC felt that finasteride and dutasteride were clinically equivalent in efficacy.

Side Effects:

Decreased libido, ejaculatory problems or erectile dysfunction were seen in 4-6% of men in the Finasteride Study Group.¹ Similar issues were seen in 2.2-7.3% of men treated with dutasteride in clinical trials.³

Decreased PSA levels are a common effect seen in patients treated with 5-ARI. The Proscar Long-Term Efficacy and Safety Study (PLESS) looked at the effect of finasteride on PSA and any effect this might have on utilizing PSA as a screening measure for prostate cancer in men treated with 5-ARIs. This trial showed that doubling the measured PSA in men treated with finasteride for 6 months or more and using a reference range applicable to untreated men has predictive properties similar to those of PSA in untreated men with BPH.⁷

The use of 5-alpha reductase inhibitors in **prostate cancer prevention** has been studied in two major trials with some controversial results. The Prostate Cancer Prevention Trial involved 18,882 men 55 years or older and who had a normal-sized prostate on DRE and a PSA \leq 3 ng/ml. These men were randomized to receive finasteride 5mg or placebo and followed over 7 years. The men received a prostate biopsy if the DRE was felt to be abnormal or the PSA was $>$ 4.0 ng/ml. Prostate cancer was detected in 18.4% of those treated with finasteride vs. 24.4% in the placebo group. However, of those in the finasteride group who developed prostate cancer, 37% were of Gleason grade 7-10 vs. only 22.2% in the placebo group (overall higher grade tumors occurred in 6.4% of those on finasteride vs. 5.1% on placebo).⁸ Follow-up studies have suggested multiple explanations for this finding, including grading bias, tumor induction due to low intracellular DHT levels, selective inhibition of lower grade tumors, or facilitated diagnosis due to the reduction in size of the prostate.

The REDUCE trial evaluated dutasteride's utility in prostate cancer prevention. It involved 6,729 men aged 50-75 who were at high risk for prostate cancer based on age, an elevated PSA level, and having had a prostate biopsy within 6 months prior to beginning the study. They were treated with dutasteride 0.5 mg or placebo and followed for 4 years. They were followed with symptom scores, PSA levels, prostatic ultrasounds and biopsies. Prostate cancer was detected in 19.9% of the men taking dutasteride vs. 25.1% in the placebo group. Tumors with a Gleason score of 7-10 were no more common in the treatment vs. the placebo group (6.7% in those on dutasteride vs. 6.8% of those on placebo).⁹

It should be noted that these were two very different study groups. If a clinician should choose to use one of these agents, the absolute risk reduction in prostate cancer among those treated with 5-alpha reductase inhibitors must be balanced against the potential absolute increased risk in developing higher grade prostate tumors.

If you have any questions regarding this document, please contact the NPTC at nptc1@ihs.gov.

References:

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