Combination Alpha-Blocker and Finasteride Therapy for BPH
RECOMMENDATIONS FOR VA PRIMARY CARE PROVIDERS
September 2004
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

Guidance on Combination Therapy with an Alpha-Blocker and Finasteride for BPH

A. Patients currently receiving monotherapy with an alpha-blocker at maintenance doses (e.g., doxazosin 8 mg qd, prazosin 4 mg BID, terazosin 10 mg qd, tamsulosin 0.4 mg qd or alfuzosin 10mg qd) or at highest tolerated dose if maintenance dose was not achieved, who have a large prostate (typically >40ml, or approximately the size of a golf ball)* and:

- ❑ Clinical progression of BPH symptoms as suggested by either:
  - An increase in the AUA symptom score ≥4 points from baseline
  - A history of acute urinary retention

  OR
- ❑ Persistently bothersome symptoms despite adequate alpha-blocker therapy, as above*

OR

B. Patients who have not tried alpha-blockers but have symptoms of benign prostatic hypertrophy who have a baseline AUA score of ≥12 and who are at high risk for an intervention or urinary retention because of a large prostate volume (typically >40ml, or approximately the size of a golf ball)*

*The risks and benefits of long-term finasteride therapy should be discussed with the patient. At this time finasteride is not recommended for prevention of prostate cancer based on the Prostate Cancer Prevention Trial. Patients should be reevaluated on a regular basis.

1. Introduction

Recently, the results of the four-year Medical Therapy of Prostatic Symptoms (MTOPS) Research Group were published. This study compared monotherapy with an alpha-blocker (doxazosin, titrated to a maximum of 8mg/day), a 5α-reductase inhibitor (finasteride, 5mg/day), or placebo with the combination of doxazosin and finasteride for effects on clinical progression of benign prostatic hyperplasia (BPH) in patients with moderate to severe symptoms (AUA score of ≥8). Clinical progression of BPH was comprised of: ≥4 point increase in the AUA symptom score, acute urinary retention, renal insufficiency, recurrent urinary tract infection, or urinary incontinence.

The study found that clinical progression, mostly symptom progression, occurred in 17% of patients on placebo. Symptom progression occurred in 10% of the doxazosin group, 10% of the finasteride group, and 5% of the combination group. Acute urinary retention events occurred 18 times in the placebo group (cumulative incidence 2%), 9 times in the doxazosin group (cumulative incidence 1%), 6 times in the finasteride group (cumulative incidence <1%), and 4 times in the combination group (cumulative incidence <1%). Similarly, the incidence of invasive surgery was 5% in the placebo group, 3% in the doxazosin group, 2% in the finasteride group, and 1% in the combination group.

On the other hand, a previously unknown hazard risk of long-term finasteride therapy was noted in the Prostate Cancer Prevention Trial that compared finasteride to placebo over 7 years. The finasteride group showed a reduction of 25% in the incidence of prostate cancer over 7 years but higher-grade tumors (Gleason scores 7-10) were more common in the finasteride group (37% of graded tumors or 6.4% of men in the finasteride group versus 22.2% of graded tumors or 5.1% of men in the placebo group).

In balancing the potential benefit (reduced progression to urinary obstruction) with the potential safety issue (increased risk of high grade prostate cancer), PBM believes that it is most prudent to utilize finasteride cautiously, typically when an alpha-blocker does not provide adequate clinical relief of symptoms of moderately enlarged prostates and/or when there is a higher long-term risk of progression. The criteria should be viewed as a guide to utilization of this agent, mostly for primary care physicians who tend to see patients early in their disease. Patients with a higher baseline PSA (>4ng/ml) and larger prostate volumes (>40ml on TRUS) had a higher risk of clinical progression or subsequent intervention. For patients with severe unrelenting symptoms or with very large prostates, or who have smaller prostate mass (e.g., mild enlargement) but a poor response to alpha-blockers, referral to a local expert is strongly advised as these patients may benefit from more focused evaluations or consideration of alternative diagnoses.

Note that finasteride reduces PSA levels and this must be considered when screening for prostate cancer. Typically, once a patient is on finasteride for more than 6 months, PSA levels may be doubled to approximate actual levels (off finasteride)

2. Safety

The most common adverse events due to doxazosin and other non-selective alpha-blockers include dizziness, postural hypotension, and asthenia, which sometimes limit titration. Finasteride can cause erectile dysfunction, decreased libido, or abnormal ejaculation. In the combination group, adverse events were similar, but abnormal ejaculation, peripheral edema, and dyspnea occurred more frequently. Breast cancer was diagnosed in four men receiving finasteride, either as monotherapy or as part of combination therapy.

The concomitant use of alpha-blockers and the PDE5 inhibitors for erectile dysfunction may result in episodes of hypotension. This interaction is variable among the available PDE5 inhibitors and among the available alpha-blockers. Please refer to the chart below.

Concomitant Administration of Alpha-Blockers with PDE5 Inhibitors[a]

PDE5 Inhibitor	Drug Interaction	Recommendations
Sildenafil	Symptomatic hypotension with sildenafil 50mg or 100mg plus an alpha-blocker (doxazosin 4mg); sildenafil 25mg with doxazosin 4mg reduced SBP and DBP 7 mm Hg	Sildenafil 50mg or 100mg should not be taken within 4 hours of an alpha-blocker; 25mg may be taken at any time
Tadalafil	Significant augmentation of BP lowering effect with tadalafil 20mg plus doxazosin 8mg; no clinically significant BP changes with tadalafil 10mg and 20mg plus tamsulosin 0.4mg	Concomitant administration of tadalafil with an alpha-blocker other than tamsulosin 0.4mg is not recommended
Vardenafil	Significant hypotension (standing SBP < 85 mm Hg) with vardenafil 10mg or 20mg simultaneously or 6hrs after terazosin 10mg; also occurred with simultaneous administration of tamsulosin 0.4mg and 6 hrs post dose[b]	Concomitant administration of vardenafil with an alpha-blocker is contraindicated

[a] Unknown if recommendations apply to patients on an alpha-blocker in combination with other antihypertensive medications and a PDE5 inhibitor

[b] Vardenafil 10mg + terazosin 10mg: 6 of 8 patients SBP < 85 mm Hg; vardenafil 20mg + terazosin 10mg: 2 of 9 patients SBP < 85 mm Hg; vardenafil 10mg + terazosin 10mg (post 6 hrs): 7 of 28 patients SBP < 85 mm Hg; vardenafil 10mg + tamsulosin 0.4mg: 2 of 16 patients SBP < 85 mm Hg; vardenafil 20mg + tamsulosin 0.4 (post 6hrs): 1 of 24 patients SBP < 85 mm Hg

References:

1. McConnell JD, Roehrborn CG, Bautista OM, Andriole GL, Dixon CM, Kusek JW, et al. for the Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. NEJM 2003;349:2387-98.
2. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. The influence of finasteride on the development of prostate cancer. NEJM 2003;349:215-224.

3. Andriole GL, Guess HA, Epstein JI. Treatment with finasteride preserves usefulness of prostate-specific antigen in the detection of prostate cancer: results of a randomized, double-blind, placebo-controlled clinical trial. PLESS Study Group. Proscar Long-term Efficacy and Safety Study. Urology. 1998 Aug;52(2):195-201

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AUA SYMPTOM INDEX[1]

AUA Symptom Score (Circle 1 number on each line)						
Questions to be answered	Not at all	Less than 1 time in 9	Less than half the time	About half the time	More than half the time	Almost always
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past month, how often have you had to push and strain to begin urination?	0	1	2	3	4	5
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0 None	1 (1 time)	2 (2 times)	3 (3 times)	4 (4 times)	5 (5 times)
Sum of 7 circled numbers = AUA Symptom Score:_____						

[1] Barry MJ, Fowler FJ, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. J Urol 1992; 148:1549-57.