The MTOPS Study: New Findings, New Insights, and Clinical Implications for the Management of BPH

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1. Introduction

The relationship between benign prostatic hyperplasia (BPH) and age has been clearly established and studies indicate that approximately 50% of men are estimated to have pathologic BPH in their sixth decade of life [1]. Lower urinary tract symptoms (LUTSs) associated with BPH also increase with age and can have a significant effect on a sufferer’s daily life [2]. The progressive nature of the disease has been shown in longitudinal studies including the Olmsted County Study, which was initiated in 1990 and followed a randomly selected cohort of 2115 men aged 40–79 yr over a period of 12 yr [3]. The Olmsted Study revealed that annually, symptom scores (SSs) increased on average by 0.18 points and
peak urinary flow rates decreased by 2% [3,4]. The long-term consequences of BPH progression are acute urinary retention (AUR) and the need for BPH-related surgery [5,6].

Treatment for BPH aims to provide relief of symptoms and improvement in urinary flow rates in the short term, with reduction in the risk of disease progression a long-term goal. The Medical Therapy of Prostatic Symptoms (MTOPS) Study was initiated to establish the efficacy of the selective 5α-reductase inhibitor, finasteride, in combination with a 1-blocker, doxazosin, in delaying or preventing the clinical progression of BPH [7]. However, although the original paper demonstrated that long-term treatment with combination therapy is both safe and the most effective therapy for patients with LUTSs and BPH, it did not elucidate which type of patient would benefit most from combination therapy. This paper addresses this issue.

2. Therapeutic options in the medical management of BPH

Both the European and American Urological Association guidelines on the management of BPH recommend medical or minimally invasive therapy for patients with moderate LUTSs, as defined by an International Prostate Symptom Score (IPSS) of 9–18 [8,9]. For patients with mild LUTSs (IPSS of 0–8), “watchful waiting” is recommended, whereas patients with severe LUTSs (IPSS of 19–35) should be managed either with a transurethral resection of the prostate or with minimally invasive therapy, including medical therapy. The two main medical therapies for BPH are 5α-reductase inhibitors and α1-blockers, both of which have proven efficacy in the treatment of symptomatic BPH [10–13]. The α1-blockers relieve the smooth muscle tension within the prostate and bladder neck by binding to the α1-adrenergic receptors, which leads to an increase in peak urinary flow and a reduction in LUTSs. The effects of α1-blockers are evident approximately 2 wk after their administration. In contrast, 5α-reductase inhibitors work by blocking the action of 5α-reductase, reducing the concentration of dihydrotestosterone, the primary androgen involved in prostate growth. The effect is to reduce prostate size, bringing about a relief in symptom severity and improvement in urinary flow rates at approximately 3 mo after start of treatment. These agents have also been shown to reduce the risk of BPH progression [11,14]. Two isoenzymes of 5α-reductase have been identified: type 1 and type 2. Type 2 5α-reductase is dominant in the prostate and individuals with congenital deficiency of type 2 5α-reductase do not develop BPH or prostatic cancer [15]. The 5α-reductase inhibitors licensed for BPH therapy are finasteride, which selectively targets 5α-reductase type 2, and dutasteride, which targets both the type 1 and 2 isomers. In phase 3 clinical trials for BPH, the additional type 1 isoenzyme inhibition with dutasteride did not translate into additional clinical benefits over those seen with finasteride [16].

The favourable tolerability profiles and differing mechanisms of action of the α1-blockers and 5α-reductase inhibitors make them suitable candidates for combination therapy. Nevertheless, the initial studies on combination therapy involving finasteride combined with terazosin [17] or doxazosin [18] failed to demonstrate a clinical benefit. It should be noted that both studies were 12 mo in duration, which is considered too short a period to evaluate the benefits of medical therapy, given the long-term, chronic nature of BPH. Moreover, both studies focused on changes in symptom score and peak flow rate, rather than overall clinical progression as evidence of success or failure.

3. Key findings from the MTOPS Study

Lasting an average of 4.5 yr and enrolling 3047 patients, the MTOPS Study represents the longest and largest clinical trial conducted in patients with BPH. Sponsored by the United States National Institutes of Health (NIH), the study evaluated whether finasteride (5 mg/d) combined with doxazosin (4 or 8 mg/d) was more effective than placebo or either medication alone in preventing the clinical progression of BPH [11]. The primary outcome measure was clinical progression, assessed according to the following parameters: time to first occurrence of a confirmed >4-point increase in the American Urological Association Symptom Index (AUA-SI), occurrence of AUR, renal insufficiency, incontinence, or recurrent urinary tract infection. Both therapies significantly reduced the risk of progression compared with placebo: doxazosin by 39% (p < 0.001) and finasteride by 34% (p = 0.002). However, the biggest effect was seen with combination therapy, where the risk of progression was reduced by 66% (p < 0.001). Correspondingly, the cumulative incidence of clinical progression was lowest with combination therapy (5%, p < 0.001) compared with doxazosin (10%, p < 0.001), finasteride (10%, p = 0.002), or placebo (17%) (Fig. 1). Although finasteride and doxazosin monotherapies were statistically not different from each other, the effect of combination therapy on
preventing clinical progression was significantly greater than either monotherapy ($p < 0.001$).

The reduction in risk of the occurrence of AUR compared with placebo was also greatest in the combination arm, with an 81% reduction ($p < 0.001$), followed by 68% in the finasteride arm ($p = 0.009$) [11]. In the doxazosin arm, the risk reduction of 35% did not reach statistical significance compared with placebo, suggesting that the overall effect seen in the combination arm may be accounted for by the impact of finasteride therapy (Fig. 2). The greatest reduction in prostate volume measured from baseline was seen in the finasteride ($-16\%, p < 0.001$) and combination ($-13\%, p < 0.001$) arms, whereas both the placebo- and doxazosin-treated patients showed increases in prostate volumes ($+18\%$) from baseline (Fig. 3).

The adverse events (AEs) reported in the MTOPS Study were typical for patients receiving these classes of drugs and patients receiving combination therapy experienced AEs similar to those for each drug alone (Table 1) [11]. None of the AEs occurred with a frequency $> 6$ events per 100 patient-years of follow-up, one that supports the overall safety of long-term combination medical therapy. Although there was a higher incidence of AEs in the combination arm compared with either drug alone, importantly the discontinuation rates were lower with combination therapy (18%) compared with finasteride (24%) and doxazosin (27%) monotherapies.

### 4. Insights into the progression of BPH

Serum prostate-specific antigen (PSA) levels and prostate volume are powerful predictors of AUR and BPH-related invasive intervention. The Olmsted County community study found a median annual growth rate over baseline of 1.9% in 2115 men aged 40–79 yr [19]. In the same study, the 4-yr incidence of AUR was 1.5% in men with prostates $< 30 \text{ ml}$, increasing 3-fold to 4.6% in men with prostate volumes $> 30 \text{ ml}$ ($p = 0.04$) [18]. The risk of AUR also increased with age in men with an AUA-SS $< 7$: men aged 40–49 yr had a risk of AUR of 2.6/1000 patient-years, rising to 9.3/1000 patient-years in men aged 70–79 yr [20]. The increase in the corresponding group of patients with an AUA-SS $> 7$ rose to 3.0/1000 patient-years and 34.7/1000 patient-years, respectively. In the Baltimore Longitudinal Study of Aging, the 10-yr probability of...
BPH-related surgery increased with age and the presence of obstructive symptoms in 1057 men followed prospectively for up to 30 yr [21]. The 20-yr probability of surgery in men aged ≤ 60 yr with prostatic enlargement and obstructive symptoms was 39%.

Similarly, results from the Proscar Long-term Efficacy and Safety Study (PLESS) support the link between increased baseline serum PSA level and prostate volume and an increased risk of AUR and BPH-related surgical intervention [22,23]. A relationship between baseline serum PSA level, prostate volume, and disease progression was also shown in the MTOPS Study. The risk of overall clinical progression, as well as symptom progression and the risk of AUR and invasive surgical treatment, was significantly greater in patients in the placebo arm with a baseline prostate volume ≥ 31 ml compared with a volume of < 31 ml (p < 0.0001) and with a baseline PSA level ≥ 1.6 ng/ml versus < 1.6 ng/ml (p < 0.0009) [24]. This analysis elucidated further information on baseline predictors for clinical progression; a baseline maximum flow rate (Qmax) < 10.6 ml/s, postvoid residual ≥ 39 ml, or age ≥ 62 yr all significantly increased the risk.

5. Targeting patients for combination treatment

Data from the MTOPS Study have been reanalysed according to baseline prostate volume (Table 2) [25]. In men with a total prostate volume < 25 ml, combination therapy led to a similar level of overall improvement versus doxazosin alone and a superior level of overall improvement relative to finasteride alone for decreasing the risk of clinical progression of BPH, the requirement for BPH-related surgery, improvement in AUA-SS, and peak flow rates. However, in patients with prostates sized from 25 to < 40 ml (moderately enlarged size) or > 40 ml (significantly enlarged), combination therapy was superior to both doxazosin and finasteride. It was concluded that combination therapy with doxazosin and finasteride provides benefits over either drug as monotherapy in men with prostates ≥ 25 ml.

6. Duration of therapy

The regimen for an optimal combination therapy of finasteride and doxazosin was also addressed by the MTOPS Study. Differences in mechanisms of action...
may be responsible for the fact that doxazosin only delayed the onset of AUR, whereas finasteride reduced the risk of its occurrence. It has been suggested that this might reflect the possibility that short-term benefits from α1-blockers, namely, the relaxation of the smooth muscle to relieve urinary tension, are negated by continued prostate growth, which itself can be halted and reversed by 5α-reductase inhibition. Two non-placebo-controlled trials studying the discontinuation of the α1-blocker after initial treatment with combination therapy provide additional guidance on the potential phasing of these two treatment modalities. In the study, Symptom Management After Reducing Therapy (SMART-1), 327 patients with BPH were treated with the combination of an α1-blocker (tamsulosin, 0.4 mg/d) plus a 5α-reductase inhibitor (dutasteride, 0.5 mg/d) [26]. One arm of the study received combination therapy for 36 wk, and the other arm combination therapy for 24 wk, after which placebo was substituted for tamsulosin for the remaining 12 wk of the study. Overall, 91% of patients in the arm in which tamsulosin therapy was continued for 36 wk felt the same or better at week 30 as they did at week 24 compared with 77% of patients who had tamsulosin withdrawn at week 24. In patients with moderate symptoms (IPSS < 20), the relative percentages were 93% and 84% and in patients with severe symptoms (IPSS ≥ 20), the percentages were 86% and 58%. These data suggest that tamsulosin can be withdrawn from a tamsulosin-dutasteride combination after 24 wk of therapy, but that men with severe symptoms may need a longer period of combination treatment.

In the second study, 272 consecutive patients with prostates >40 ml and an AUA-SI > 20 were treated with finasteride (5 mg/d) plus doxazosin (2 mg/d) [27]. Of the 240 men who responded to therapy (any reduction in SS and tolerance to therapy), 100 remained on 2 mg doxazosin, whereas 80 had their dose up-titrated to 4 mg, and 60 to 8 mg; finasteride treatment remained at 5 mg. Doxazosin was then discontinued at 3, 6, 9, and 12 mo equally across all doses and patients’ symptoms re-evaluated 1 mo after withdrawal. The results of the study showed that after 9 mo of combination therapy, patients were unlikely to notice withdrawal of doxazosin regardless of dosage. Taken together, the results from the MTOPS Study and these additional combination studies suggest that although treatment with an α1-blocker is warranted in the early stages of the disease to alleviate symptoms of BPH, it could be discontinued once the longer-term effects of a 5α-reductase inhibitor are established.

7. Conclusions

The MTOPS Study has provided clinicians with valuable information on how to optimally treat patients with BPH. Combination therapy with doxazosin and finasteride has been shown to provide fast symptom relief, reduced prostate growth, reduced risk of AUR, and the need for BPH-related surgery. Recent analyses from the MTOPS Study provide important information to help inform clinicians which patients are most appropriate for combination therapy. A prostate volume of ≥25 ml has been identified as the threshold at which patients may benefit from combination therapy. Data analysis from the placebo arm of the MTOPS Study establishes that those men with a baseline prostate volume of ≥31 ml are at a significantly greater risk of clinical progression than those with prostates <31 ml. Given these data, combination therapy will most benefit and is thus indicated in this group of men who are most likely to progress.

References


