How Do New Data from Clinical Trials Allow Us to Optimise the Assessment and Treatment of Patients with Benign Prostatic Hyperplasia?

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1. Introduction

Within the last few years, both the European Association of Urology (EAU) and the American Urological Association (AUA) have compiled evidence-based guidelines for the assessment, management, and follow-up of men with benign prostatic hyperplasia (BPH) [1,2]. These guidelines offer broadly similar advice for the initial assessment of men presenting with lower urinary tract symptoms (LUTS) suggestive of BPH. Whilst the guidelines offer clear guidance on the use of surgical
approaches in men with absolute indications (such as obstructive uropathy), less advice is offered on how to determine the optimal use of surgical versus minimally invasive versus medical therapies for remaining patients. Although symptom severity and patient preference are suggested as methods for assisting decision-making, little further guidance is offered to assist in making the decision between medical and surgical approaches, and among the choices of pharmacotherapy, little advice is offered beyond the observation that 5α-reductase (5-AR) inhibitors are suitable only for men with prostatic enlargement. In this review, the evidence for the risk–benefit profiles of surgical, minimally invasive, and medical therapies in men with symptomatic BPH are reviewed, and an examination is made of alternative approaches to determining the optimal therapy choice for individual patients based on their differing needs and wishes.

2. Surgical and minimally invasive therapies

Minimally invasive therapies (MITs) and alternative surgical techniques have been gaining ground as alternatives to both surgical and medical therapies. They are the result of research and development aimed at finding simpler and less morbid alternatives to transurethral resection of the prostate (TURP). The term MIT covers a wide range of alternatives including transurethral microwave therapy (TUMT), laser coagulation, electrovaporisation, water-induced thermotherapy, high-intensity focused ultrasound, and transurethral needle ablation (TUNA). Most MIT methods use heat energy to cause thermoablation/necrosis – the necrotic tissue is then absorbed or turned into scar. All MITs are less invasive than surgery (open and transurethral) and require minimal anaesthesia – most procedures can be carried out in the physician’s office and patients can return to their normal activities within a few days afterwards.

The majority of data on MITs are from studies using TUMT, which some consider to be the gold standard for MIT [3]. A meta-analysis of published data performed by the AUA showed that TUMT reduces AUA Symptom Index (AUA-SI) score by approximately 9–11 points, a benefit that appears durable to >16 mo (Fig. 1) [1]. In the average patient, TUMT is more effective than medical therapy but less effective than surgery in relieving symptoms. In comparison, TUNA therapy has on average a numerically lower benefit on symptom scores [1]. Improvements in symptoms for both TUMT and TUNA are above the 5- to 6-point improvement seen with sham treatment and are in excess of the benefits seen with medical therapy. They are, however, significantly below the 14- to 15-point improvement seen with TURP. TUNA is associated with a significantly higher need for secondary procedures compared with TURP (23% vs. 5%), and there is a numerically greater need compared with TUMT [1]. There is also generally a greater requirement for analgesia, sedation, and anaesthesia with TUNA compared with TUMT. The newer MITs, such as laser coagulation and electrovaporisation, are not currently widely used in clinical practice; however, the AUA meta-analysis indicates that symptom benefit appears to be equivalent to TURP, although long-term and comparative data studies are lacking [1].

Intraoperative complications associated with MIT occur at a similar rate (≤3%) compared with TURP. Rates for significant haematuria appear to be similar between the MITs and TURP, although data are limited. Postvoiding irritative symptoms occur more commonly with MITs than TURP, and acute urinary retention (AUR) is significantly higher with TUMT and TUNA compared with TURP, with rates up to 20% [4]. However, long-term complications following MIT are generally low. Urinary incontinence rates of 1–2% are generally observed, whereas bladder-neck contractures and urethral strictures are uncommon (2–4%). In terms of sexual side effects, erectile dysfunction is lower with MIT than with TURP (2–3%), whereas ejaculatory dysfunction is considerably lower than with TURP (5–15%) [4].

These procedures therefore differ in their profiles of efficacy, durability, adverse events, availability, and cost. In particular, there is a trade-off between the degree and durability of benefit and the risk of adverse events. They may also require later, additional interventions in comparison with the gold standard use of TURP, which has to be weighed against the less invasive nature of the procedure.
The high incidence of AUR is, however, an immediate concern. It is important, therefore, that the relative merits of these procedures be discussed with the patient to ensure that the right profile is chosen for the desired outcomes. Similarly, the profiles of these new techniques need to be examined against prostatectomy on the one hand and medical therapy on the other to ensure appropriate treatment allocations are made.

3. \(\alpha\)-blocker and 5-AR inhibitor monotherapy

A large number of clinical studies have demonstrated that the \(\alpha\)-blockers typically provide significant symptom relief within 1–2 wk of starting therapy and reduce symptom scores by 5–8 points on the AUA-SI scale, with no clear differences between the agents within the class [1,5]. Symptom relief is brought about by their action to relax smooth muscle tone in the prostate and bladder neck. In comparison, the 5-AR inhibitors, finasteride and dutasteride, act on the underlying disease by reducing prostate volume and subsequently improve symptoms and reduce the risk of long-term clinical outcomes (AUR and need for BPH-related surgery). They do this by inhibiting the conversion of testosterone to the more potent androgen, dihydrotestosterone (DHT), which acts via the androgen receptor to drive prostate disease in older men. Treatment with the 5-AR inhibitors results in improvements in symptoms compared with placebo with an onset typically from 3 to 6 months [6].

The Medical Therapies of Prostatic Symptoms (MTOPS) study has been pivotal in crystallising our understanding of the effects of medical therapies on BPH progression, because it was the first large-scale, placebo-controlled study of long duration to directly compare these treatment modalities, and their combination, with placebo [7]. The study enrolled 3047 men aged \(\geq 50\) yr with moderate to severe LUTS who were randomly assigned to receive one of the following: placebo, doxazosin, the type 2-selective 5-AR inhibitor finasteride, or combination therapy with doxazosin and finasteride. Over the 4-yr treatment period, both doxazosin and finasteride treatment were associated with a similar risk reduction for the primary end point of BPH progression compared with placebo (4-yr event rates of 9.7% and 10.2% vs. 16.6% for placebo, representing a reduction in risk of 39% for doxazosin and 34% for finasteride vs. placebo; Fig. 3). However, the nature of the progression events was different between the treatment groups. Although both finasteride and doxazosin were associated with a lower rate of symptom progression, this was more marked in the doxazosin arm (7.3% for doxazosin, 8.5% for finasteride, and 13.2% for placebo, representing a risk reduction of 45% for doxazosin and 36% for finasteride). Only finasteride was associated with a significant reduction in the long-term risks of AUR (68%) and need for surgery (64%), despite delays in time to AUR and surgery observed with doxazosin.

While the MTOPS study was ongoing, a second 5-AR, dutasteride, was undergoing phase 3a evaluation in 4325 men with moderate to severe LUTS secondary to BPH [6]. Dutasteride differs significantly from finasteride because it inhibits both type 1 and type 2 5-AR, resulting in a greater degree and consistency of DHT suppression compared with finasteride [8]. The dual 5-AR inhibition effect of dutasteride demonstrated significant benefits versus placebo in improving peak urinary flow from 1 mo of therapy, and urinary symptoms from as early as 3 mo in one study and 6 mo in the pooled analysis of the three component studies of the phase 3a programme.
Underlying this was a significant reduction in prostate volume, which was observed from 1 mo of therapy. At the end of 2 yr of therapy, dutasteride-treated men experienced a mean decrease in AUA-SI score of 4.5 points and an increase in maximum flow rate ($Q_{\text{max}}$) of 2.2 ml/s versus baseline, with an underlying decrease in prostate volume of 25.7%. Dutasteride also demonstrated significant benefits in reducing long-term disease progression risk, with a reduction of 57% in risk of AUR and 48% in risk of BPH-related surgery compared with placebo over 2 yr. The beneficial treatment effects have subsequently been shown to be durable during an additional 2-yr open-label phase [9].

To date, no long-term head-to-head comparison of dutasteride and finasteride has been performed to examine the clinical implications of the dual 5-AR inhibition achieved with dutasteride versus the type 2 5-AR inhibition of finasteride. However, within the limitations of interstudy comparisons, the improvements in symptoms and flow rates seen with dutasteride over 4 yr appear to exceed those observed with finasteride during the same treatment duration [7,10] and are similar to those seen with 6 yr of finasteride therapy [11] (Fig. 4). These observations from non-comparative studies are underscored by a greater reduction in prostate volume, which exceeds that observed with finasteride at 4 yr [7,10] and 6 yr [11] (Fig. 5). The risk of undergoing BPH-related surgery during 4 yr of dutasteride therapy is similar to that observed with finasteride, as is the risk of AUR [10].

Limited evidence has also been presented to indicate that the greater suppression of DHT achieved with dutasteride may result in more rapid onset of symptom relief [12]. A prospective study recruited 240 consecutive patients with symptomatic BPH adjudged to be suitable for 5-AR inhibitor therapy due to a prostate volume $\geq$30 cc. Symptom severity was assessed using the AUA-SI prior to therapy, and following 3 mo of treatment with either dutasteride ($n = 120$) or finasteride ($n = 120$). Age and prostate-specific antigen (PSA) were balanced between treatment groups at baseline. After 3 mo of therapy, patients receiving dutasteride had a significantly greater reduction in AUA-SI scores compared with the finasteride group; 43% versus 23% had an improvement of 1–3 points. This study is limited by its open-label nature and by the lack of baseline randomisation. Therefore, although it suggests that the onset of symptomatic benefit of dutasteride may precede that of finasteride, further randomised data would be needed to clarify this observation.

It can be concluded that whilst both 5-AR inhibitors and $\alpha$-blockers offer symptomatic benefits for men with BPH, only 5-AR inhibitors have demonstrable long-term benefits in reducing AUR and the need for BPH-related surgery. This finding from randomised clinical trials is supported by observations in real-life practice studies. A retrospective cohort study in 1430 Dutch men aged $\geq$45 yr identified men with BPH using general practitioner medical records. Patients using 5-AR inhibitors at any stage had a significantly reduced risk of surgery compared with patients using $\alpha$-blockers [13]. However, the impact of symptom status and other BPH disease parameters on this finding could not be assessed because these parameters are not routinely recorded by general practitioners in The Netherlands. In a larger retrospective study in the United States, patient records in a national managed care claims database were reviewed to determine the impact of therapy choice on rates of AUR and BPH-related surgery [14]. Of the 2959 patients included, 89% were receiving $\alpha$-blocker therapy, whereas 11% were receiving 5-AR inhibitor treatment. The rate of
AUR for patients taking 5-AR inhibitors was 8.2% versus 12.6% for those taking α-blockers; surgery was required in 3.7% of patients in the 5-AR inhibitor group compared with 6.0% for the α-blocker group. After adjustment for baseline covariates, patients taking α-blockers were 74.0% more likely to have AUR (p = 0.0088) and 80.6% more likely to have surgery (p = 0.0576) compared with those receiving 5-AR inhibitors. A further retrospective analysis using a general practice database from the United Kingdom examined the medical records of 4500 men aged >50 yr presenting with BPH or LUTS suggestive of BPH who were prescribed either the 5-AR inhibitor finasteride or an α-blocker as their first BPH treatment [15]. After a mean follow-up of 25.2 mo, patients receiving an α-blocker were significantly more likely to experience AUR or surgery than patients prescribed a 5-AR inhibitor (p < 0.001).

An analysis of medical records of 316 patients with LUTS in The Netherlands used 3-yr follow-up data to calculate retreatment rates for different α-blockers [16]. Patients receiving tamsulosin were found to have a retreatment rate of 27% compared with 37% and 49% for alfuzosin and terazosin, respectively. The high rates of retreatment found suggest that α-blockers are associated with a significant risk of treatment failure. Furthermore, it has been suggested that the widespread use of α-blockers may have contributed to a rise in the use of open prostatectomy, as symptom relief is achieved without reductions in prostate volume, eventually requiring more aggressive surgery in those that need intervention [17]. A single-centre, retrospective, cross-sectional observational study in Spain reviewed the medical history of all patients who had surgery for BPH in the first semester of 1992 (n = 85) and 2002 (n = 70). Surgery for BPH was found to have decreased by 17.6% during this decade. However, in 1992, only 46% of patients undergoing surgery were taking medical therapy, with most (89%) using phytotherapy. In contrast, >80% of the patients operated on in 2002 were on medical therapy; most of these (79%) were taking α-blockers, in most cases continuously over long periods of time. The lack of effect of α-blockers on BPH disease progression may therefore be driving an increased need for invasive surgery.

4. α-blocker and 5-AR inhibitor combination therapy

At a mechanistic level, a clear rationale exists for exploring the potential of combining α-blocker and 5-AR inhibitor therapy, given that their modes of action can be considered complimentary. The key question was whether such individual benefits were additive or even synergistic, with the potential for the magnitude and onset of symptomatic benefits to be improved whilst maintaining the long-term disease modification benefits of 5-AR inhibitors. The MTOPS study has provided support for this hypothesis, demonstrating that the combination of doxazosin and finasteride resulted in significantly better outcomes in terms of overall risk of clinical progression (defined as an increase above baseline of ≥4 points in the AUA-SI, AUR, urinary incontinence, renal insufficiency, or recurrent urinary tract infection) compared with either doxazosin or finasteride alone [7]. A subsequent examination of data from the MTOPS study suggested that combination therapy was no better than doxazosin alone in men with a baseline prostate volume <25 ml, but had clinical benefit above this level [18]. Further data on the potential of combination therapy in symptomatic BPH will be derived from the ongoing phase 3 Combination of Avodart® and Tamsulosin (CombAT) study, which is investigating the effect of combination therapy with tamsulosin and dutasteride versus tamsulosin and dutasteride monotherapies in men at high risk of BPH progression. Men eligible for inclusion in the CombAT study needed to have an International Prostate Symptom Score of ≥12 points, a transrectal ultrasound of the prostate-demonstrated prostate volume of ≥30 cc, and a serum PSA of ≥1.5 ng/ml. This contrasts with MTOPS, where men needed to have an AUA-SI score of ≥8 points, but no minimum prostate volume or PSA level. Given our understanding that men with a prostate volume of ≥30 cc and/or a PSA level of ≥1.5 ng/ml are at increased risk of BPH progression [19], the CombAT study population is at an elevated risk of progression. Another significant difference between the MTOPS and CombAT studies is that the latter study is designed to yield powered symptom end point data at 2 yr for symptoms and at 4 yr for long-term surgical and AUR outcomes. The CombAT study will, therefore, provide more detailed information beyond the composite progression end point used in the MTOPS study. It will also be the first long-term study to investigate combination therapy with a dual 5-AR inhibitor.

5. Other medical therapies

Men with LUTS often have both storage symptoms as well as voiding symptoms and, therefore, have symptoms concordant with detrusor instability. Recently, there has been interest in the potential role of anticholinergic drugs, alone or in combination
with α-blockers, to treat patients with LUTS due to BPH and concomitant overactive bladder (OAB) syndrome. Novara et al. performed a systematic review of the literature to examine the evidence to support this and found that, at present, available data, although promising, are limited [20]. The authors identified four randomised controlled trials, two prospective case series, and a few congress abstracts; however, these studies were limited by significant methodologic or clinical drawbacks such as small sample size, insufficient follow-up, or lack of symptom outcome measurements. Large-scale randomised, placebo-controlled trials will be needed to fully examine the efficacy and safety of anticholinergics in this patient population.

6. Conclusions

The choice of medical versus minimally invasive or surgical therapy should be thoroughly discussed with patients and the magnitude and durability of benefits and adverse events individualised to allow them to make a considered choice. MIT offers a genuine alternative to TURP, providing a lower degree of benefit and a less durable outcome, but with reduced potential for long-term adverse events, particularly those related to sexual function. When compared with medical therapy, MIT provides at least comparable effects on urinary flow and a greater impact on symptoms, but greater risk of immediate complications (particularly AUR).

In terms of medical therapy, α-blockers provide a rapid onset of symptomatic benefit but they do not significantly affect the long-term risks of AUR and surgery. In contrast, 5-AR inhibitors have a slower onset of symptomatic relief, but act early on the underlying disease to reduce prostate volume. They also significantly reduce the long-term risks of AUR and need for BPH-related surgery. Thus, 5-AR inhibitor monotherapy has an important role in the treatment of men with symptomatic BPH at risk of BPH progression. This is particularly relevant in light of data showing that many patients are more concerned about the long-term effects of BPH rather than rapid symptom relief [21]. With regard to combination therapy, the addition of an α-blocker to 5-AR inhibitor therapy may provide greater benefits in selected patients. However, this must be weighed against the additive adverse events profile of α-blockers and 5-AR inhibitor therapy combined. Data on the role of combination therapy in men at high risk of BPH progression will be available with accrual of the CombAT study.

In conclusion, the selection of medical therapy should be based on assessment of the likelihood of BPH progression using prostate volume and/or serum PSA level. In patients at increased risk, 5-AR inhibitors have been shown to confer significant long-term benefits over α-blockers. The magnitude and onset of symptom relief may, however, also be an important goal of therapy, and here the addition of an α-blocker to a 5-AR inhibitor may be appropriate in certain patients.

Conflicts of interests

Professor Mirone is a paid consultant for Lilly, Italy and Pfizer, Italy.

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References


