1. Introduction

Both the European Association of Urology (EAU) and the American Urological Association (AUA) have recently compiled evidence-based guidelines for the assessment, management, and follow-up of men with benign prostatic hyperplasia (BPH) [1,2]. Both sets of guidelines offer a systematic framework for the evaluation of men presenting with lower urinary tract symptoms (LUTS); they are broadly concordant with each other, recommending a full patient history, a focussed physical examination (including a digital rectal examination [DRE]), urinalysis, and prostate-specific antigen (PSA) assessment in men with a life expectancy of ≥10 yr, where known prostate cancer would change management or where PSA would change management of voiding symptoms. Both guidelines also recommend the use of α-blocker therapy if LUTS are present.

Abstract

Although recent guidelines for the management of benign prostatic hyperplasia (BPH) outline evaluation of men presenting with lower urinary tract symptoms (LUTS), absolute indications for those who require surgery, and guidance for those who are eligible for watchful waiting, they do not provide concrete guidance on how to select patients for medical versus surgical versus minimally invasive therapy (MIT). The choice of medical versus MIT or surgical therapy should be thoroughly discussed with patients and the magnitude and durability of benefits and adverse events individualised. MIT offers a genuine alternative to transurethral resection of the prostate for men who are comfortable with a lower degree of benefit and a less durable outcome but who see the benefit of the reduced long-term adverse events. For men wishing to avoid surgery, the α-blockers typically provide symptom relief within 1–2 wk of starting therapy, but they do not reduce the long-term risks of acute urinary retention (AUR) and BPH-related surgery. The 5α-reductase inhibitors act on the underlying disease by reducing prostate volume; treatment results in improvements in symptoms compared with placebo with an onset typically of 3–6 mo. In contrast with the α-blockers, they also significantly reduce the risk of AUR and BPH-related surgery and are therefore suitable for men with prostatic enlargement who wish to combine symptomatic benefits with a reduction in the risk of long-term outcomes.

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of a symptom and bother index in the initial patient assessment, with the EAU guidelines also recommending a serum creatinine measurement and more active consideration of ultrasound evaluation of the urinary tract than the AUA guidelines. Although both guidelines offer clear indications for men who require surgery for BPH, and those who are eligible for watchful waiting, neither provides concrete guidance on the choice of medical therapies, or indeed which men are likely to benefit/warrant the use of combination medical therapy. Furthermore, firm guidance on the role of minimally invasive therapy (MIT) versus medical therapy versus transurethral resection of the prostate (TURP) is also lacking. This article, therefore, reviews current evidence for the roles of different medical and MIT approaches by examining their risk-benefit profiles and the role of baseline markers in selecting therapies.

2. Defining patients at risk for progressive BPH

Over the last decade, it has become increasingly evident that the natural history of BPH differs in individual men, with a significant proportion having disease that progresses with age [3–6]. Such men are more likely to fail periods of watchful waiting and are therefore candidates for a preventive approach [7,8]. Although progression of BPH can be defined in pathologic terms by an increase in prostate volume with time as a result of hyperplasia, prostate size does not necessarily correlate with symptoms [9,10]. Thus progression can be defined clinically in a number of ways, including increases in symptoms and bother, decreases in urinary flow, the development of acute urinary retention (AUR), the need for surgical intervention, urinary tract infections (UTIs), incontinence, or rarely obstructive nephropathy. From the patients’ perspective, symptom progression alone is not the only issue; the risk of AUR and the need for surgery are rated as significant concerns by patients [11].

Many studies and analyses have examined the role of baseline risk factors in predicting progression, defined as a single or composite measure from the variables listed above. One of the largest, and most recent, is the Medical Therapy of Prostatic Symptoms (MTOPS) study, which used a composite measure of any of a >4-point rise in AUA Symptom Index (AUA-SI), an episode of AUR, incontinence, UTI/urosepsis, or renal insufficiency, to define progression [12]. The MTOPS study identified that higher age, PSA, prostate volume, and postvoid residual volume were all positively associated with an increased risk of BPH progression. These risk factors, with the additional risk factor of baseline symptom score, were also useful in predicting the likelihood of undergoing surgery for BPH. However, another study has cast doubt on whether postvoid residual has value in predicting the need for invasive therapy [13]. These observations agree with a wide body of evidence from both epidemiologic studies and clinical trials demonstrating that both PSA and total prostate volume are well-defined risk factors for BPH progression [3,4,6], including progression to surgical intervention [14]. Although the combination of a number of risk factors into nomograms for the identification of men at risk for progression has clinical utility [15], it may be that PSA alone, given its strong relationship with prostate volume [16], or with the addition of baseline obstructive symptoms score, is sufficient for risk stratification [7]. Such an approach has real utility in the clinical setting, where information from DRE, transrectal ultrasound, and/or PSA testing can be used to judge the likelihood of progressive disease.

3. Optimising medical management approaches

Two principal classes of prescription medical therapies are available for BPH treatment. A large number of clinical studies have demonstrated that the α-blockers typically provide 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 [1,17]. There is no evidence that α-blockers reduce prostate volume [18]; their predominant effect appears to be on smooth muscle in the urethra, although they may also have effects on bladder function [19]. Prior to the reporting of the MTOPS study, no randomised data were available on the long-term effects of α-blockers on the incidences of AUR and need for BPH-related surgery. The 5α-reductase inhibitors (5-ARIs) act on the underlying disease by reducing prostate volume. 5-ARI treatment results in improvements in symptoms versus placebo with an onset typically from 3 to 6 mo [20]. Evidence from 2- to 4-yr studies also demonstrates that they significantly reduce the risk of AUR and BPH-related surgery [20,21].

The 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.
with placebo. The study randomised 3047 men to treatment with daily doxazosin, finasteride, placebo, or a combination of doxazosin and finasteride over a mean follow-up period of 4.5 yr [12]. Over this 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% versus 16.6% for placebo, representing a reduction in risk of 39% for doxazosin and 34% for finasteride versus placebo). 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). However, 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. From the MTOPS study it can therefore be concluded that although both 5-ARIs and α-blockers offer symptomatic benefits, only 5-ARIs have demonstrable long-term benefits in reducing AUR and the need for BPH-related surgery.

The evidence from MTOPS on AUR agrees with that from the recently published ALFuzosin in Acute Urinary Retention (ALFAUR) study, which examined the value of alfuzosin therapy first in aiding catheter withdrawal in men with AUR, and second in preventing the need for surgery in those with a successful trial without catheter (TWOC) [22]. Although the study demonstrated a significant benefit for alfuzosin in improving successful voiding following a TWOC (62% success versus 48% for placebo; \( p = 0.012 \)), the benefits of alfuzosin in preventing subsequent surgery, whether for AUR or other causes, diminished over the 6-mo course of follow-up.

Taken together, the results of placebo-controlled studies of 5-ARIs in men with BPH demonstrate their role in preventing progression, as well as affording symptom relief. Recent evidence for 4 yr of treatment with the dual 5-ARI dutasteride also demonstrates that longer durations of therapy are associated with benefits versus shorter durations with a delay in initiation [23]. Patients randomised to placebo or dutasteride at the start of the study who completed the double-blind portion of the study programme were eligible for a 2-yr open-label extension, where all patients received dutasteride 0.5 mg daily. This study plan allowed an examination of men who received placebo for the first 2 yr, but then received dutasteride, compared with those who received a total of 4 yr of dutasteride therapy. The results demonstrated that, for 4 versus 2 yr of treatment, a longer duration of therapy with dutasteride was associated with a significantly greater reduction in prostate volume and symptoms (Fig. 1). Furthermore, the proportions of men experiencing AUR or requiring BPH-related surgery were lower with a longer duration of therapy. These data strongly suggest that earlier initiation of therapy with dutasteride results in a lower risk of disease progression and better clinical outcomes in men at risk for BPH progression.

In addition to the differing efficacy profiles of the α-blockers and 5-ARIs, they also have different, but overlapping, adverse event profiles. A meta-analysis of clinical studies of 2–12 mo duration has demonstrated that rates of discontinuation due to adverse events range between 4% and 10% for alfuzosin and tamsulosin, rates that are comparable with placebo. However, for terazosin and doxazosin, an additional 4–10% of patients withdrew due to adverse events [17]. The most common adverse events observed with α-blockers at a significantly higher frequency than placebo are dizziness, postural hypotension, and asthenia, although again there may be differences between individual agents within the class [1,17]. Both the Prospective European Doxazosin and Combination Therapy (PREDICT) and MTOPS studies have examined the efficacy and tolerability of 5-ARI...
monotherapy, α-blocker monotherapy, combination therapy, and placebo in men with BPH [12,24]. In both studies, the incidence of postural hypotension and dizziness was significantly greater in the doxazosin groups versus both the placebo and finasteride groups. The incidence of postural hypotension was 4.4% in MTOPS and 5.8% in PREDICT, with rates of dizziness of 4.8% and 15.6%, respectively. Although, in general, the α-blockers are associated with a similar incidence of sexual adverse events compared with placebo, tamsulosin appears to be an exception. Placebo-controlled trials [25–27] and open-label extension studies [28] have demonstrated an incidence of abnormal ejaculation of 4.5–10% versus 0–1% for placebo.

The most common adverse events associated with 5-ARI use are erectile dysfunction, occurring in 7–8% of men (placebo, 4–5%), decreased libido, occurring in 4–6% (placebo, 2–3%), and abnormal ejaculation, occurring in 1–2% (placebo, <1%). These events are more frequent in the early stages of treatment and tend to diminish with time [12,20,21,23]. Withdrawal rates due to adverse events have been comparable with placebo in large-scale studies (11.5% for finasteride versus 10.9% for placebo over 4 yr; 8.9% for both placebo and dutasteride over 2 yr) [20,21]. There are no significant differences in the adverse events profiles between dutasteride and finasteride.

4. The role of MIT

MIT has been gaining ground as an alternative to both surgical and medical therapies. The term MIT covers transurethral microwave therapy (TUMT), transurethral needle ablation (TUNA), and stenting. In addition, a number of new surgical approaches, such as laser coagulation or elecrovaporisation, are also available. These procedures 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.

The majority of data on MIT are from studies using TUMT, which reduces AUA-SI score by about 9–11 points (Fig. 2). TUNA therapy has on average a numerically lower benefit on symptom scores, but this did not reach statistical significance in a meta-analysis conducted to support the AUA guidelines [29]. Improvements for both TUMT and TUNA are above the 5–6-point improvement seen with sham treatment and are in excess of the benefits seen with medical therapy. They are, however, significantly below the 14–15-point improvement seen with TURP. One significant caveat is that data beyond 24 mo are sparse for MIT, and therefore the durability of these outcomes is uncertain. What is clear though is that TUNA is associated with a significantly higher need for secondary procedures compared with TURP, and there is a numerically greater need compared with TUMT [29]. The use of urethral stenting is associated with symptom improvements between those of TUMT and TURP and rates of secondary treatment below those of TUNA but above those of TURP. However, the AUA does not recommend the routine use of stents because they are associated with significant complications including encrustation, infection, and chronic pain. Their placement is therefore suggested only in patients at high-risk of poor outcomes, especially urinary retention.

Intraoperative complications associated with MIT occur at a similar rate (≤3%) compared with TURP. From limited data, rates of significant haematuria appear comparable between MIT and TURP, although need for transfusion is not a recognised complication of MIT [29]. Postvoiding irritative symptoms occur at a numerically higher rate with MIT than with TURP and AUR is significantly higher with TUMT and TUNA than either TURP or sham therapy, with rates of up to 20% [29]. With regard to long-term complications, urinary incontinence rates are low (1–2%), bladder-neck contractures and urethral strictures are uncommon (2–4%), erectile dysfunction rates are also lower than with TURP (2–3%), and ejaculatory dysfunction is considerably lower than with TURP at approximately 5–15%. The need for secondary procedures is a significant issue, with approximately 10% of men following stenting or TUMT and >20% following TUNA needing further intervention, compared with
<5% following TURP. These data do not need to be interpreted with caution because the durations of follow-up and patient populations are different.

5. Conclusions

In conclusion, the choice of medical versus MIT or surgical therapy should be thoroughly discussed with patients, and the magnitude and durability of benefits and adverse events individualised. MIT offers a genuine alternative to TURP for men who are comfortable with a lower degree of benefit and a less durable outcome, but see the benefit of the reduced long-term adverse events, particularly those related to sexual function. With regard to medical therapy, MIT offers at least comparable effects on urinary flow and a greater impact on symptoms; this has to be weighed against the risk of complications and the willingness of individual men to undergo surgical intervention. For medical therapy, a significant body of evidence now demonstrates that although α-blockers provide durable symptom efficacy, they do not significantly affect the long-term risks of AUR and surgery, and that in men with severe symptoms and/or a prostate volume >40 cc (a PSA of >1.5 ng/ml), there is a significant risk of treatment failure [12,30]. For 5-ARIs, a prostate volume of <40 cc has been associated with treatment failure in early studies of finasteride [31]; for dutasteride, efficacy has been demonstrated in men with a prostate volume ≥30 cc and a PSA ≥1.5 ng/ml [20]. The current recommendation is therefore that 5-ARI use should be reserved for men with symptomatic BPH and prostatic enlargement. However, new evidence derived from the MTOPS study, presented in this supplement, challenges what may constitute prostatic enlargement, particularly with regard to the combined use of an α-blocker and a 5-ARI [32].

References

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