REVIEW

Medical treatment of benign prostatic hyperplasia

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Pharmaceutical preparations are commonly used for benign prostate hyperplasia. This article reviews the current understanding of the natural history of the condition and the literature regarding medical treatment.

Benign prostate hyperplasia (BPH) is an age-related and androgen-related phenomenon, and an increasing incidence within an ageing population has been confirmed by many observational studies. Lower urinary tract symptoms (LUTS) due to BPH pose a very common problem for urologists, with LUTS having a proved detrimental effect on quality of life for both affected men and their partners.^{1–2}

The health and economic implications of BPH are indisputable, extending beyond pure symptomatology. The rate of transurethral prostatectomy has been considerably reduced from the level reported by an American national survey of urologists in 1989, largely facilitated by the development of non-operative management of BPH.^{3–6} In particular, the development of adrenoceptor blockade and hormonal manipulation has moved increasing numbers of men away from surgery and towards pure medical management of BPH. In 2006, any treatment of BPH must be evidence based.⁷ Increasing volumes of research each year makes constant revision of our understanding of this topic essential. In this review of medical treatments for BPH, we analyse the evidence for any treatment, the current status of medical management and the correct selection of treatment.

NATURAL HISTORY OF BPH

Knowledge of the natural history of BPH is essential for those providing care to affected men, and has been reviewed in detail elsewhere.⁸ Lack of a precise clinical definition of BPH presents a significant obstacle. Various combinations of symptoms, urinary flow rates (voided ml/s), measures of prostate size and post-void residual volumes of urine in the bladder have all been used to provide a working epidemiological definition for clinically relevant BPH, but no universal consensus has ever been reached.^{9–10} As a histopathological diagnosis, autopsy studies across different continents suggest an age-related prevalence, with 90% of men affected by their ninth decade.^{11–12} Ethnic variability exists in prostate size, and likewise variability in the prevalence of BPH-related symptoms has also been observed.^{13–15} The best information regarding the natural history of BPH is provided by longitudinal observational studies of untreated or unaffected men, although

the placebo arms of controlled studies provide an alternative, but less reliable sources of information. The use of the placebo arms of controlled trials to gain information relating to the natural history of disease depends on the assumptions that the placebo effect is negligible and that the selection criteria (often the most severe cases) for enrolment will not produce a powerful “regression to the mean” bias. In fact, the placebo/sham effect for symptomatic improvement with BPH has been calculated to be approximately 40%.¹⁶ Although currently consensus exists that placebo-controlled trials must be considered mandatory for all new treatments of BPH,¹⁷ extrapolation of natural history from such studies should be done only with caution.

The most frequently quoted longitudinal study of BPH is that based on 2115 randomly selected Caucasian males in Olmstead County, Minnesota, USA.^{18–21} Over a 12-year period of observation through much of the 1990s, men with symptoms caused by BPH were shown to have deterioration in symptoms (average increase in International Prostate Symptom Score (IPSS) of 0.3 points per year), and prostate size increased over time (1.9%/year). Symptomatic deterioration was the most common event indicating “progression” of BPH, and the incidence of acute urinary retention (AUR) was low, at a rate of 2.7% over 4 years.^{22–23} Progression was largely age-related, with 0.1% of men aged 40–49 years requiring prostatectomy during the period of follow-up, in contrast with 9.5% of men aged 70–79 years.²⁴ The uncommon nature of AUR was further documented in 1% of 6100 healthcare professionals reported in the Health Professionals Follow-up Longitudinal Study.²⁵ Both studies are susceptible to the criticism of non-representation of the general population. The Finasteride (Proscar) Long-term Efficacy and Safety Study group (PLESS) study allowed placebo-control observation of 1500 men with BPH. Perhaps reflecting a bias of the enrolment criteria, this study reported 10% requiring prostatectomy and 7% encountering acute urinary retention in the 4-year study period, significantly higher progression rates than in the longitudinal studies.²⁶ The Medical Therapy of Prostatic Symptoms (MTOPS) study allowed placebo observation of 737 men and showed a progression rate of 17%, with AUR in 2% and invasive treatment

Abbreviations: ALTESS, Alfuzosin Long-Term Efficacy and Safety; AUR, acute urinary retention; BPH, benign prostate hyperplasia; DHT, dihydrotestosterone; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; MTOPS, Medical Therapy of Prostatic Symptoms; PLESS, Finasteride (Proscar) Long-term Efficacy and Safety Study group; PSA, prostate-specific antigen

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due to BPH in 5% over the 4.5-year mean observation period.²² Until recently, little data existed on the natural history of BPH defined by strict urodynamic criteria of bladder outlet obstruction. Defining bladder outlet obstruction as the obstructed zone on the International Continence Society pressure-flow nomogram, Thomas *et al*²⁷ have reported little urodynamic or symptomatic deterioration in men who initially opted for no treatment (29 of 170 men progressed to require prostatectomy, with acute urinary retention in only 4%). In that series, 83% of men did not need treatment after a minimum of 10 years' follow-up after the urodynamic diagnosis of obstructing BPH.

Predicting response to medical treatment for BPH has been extensively analysed and such factors can be baseline or dynamic.²⁸⁻²⁹ From the Olmstead County population, baseline variables including older age, poor symptom severity, low-peak flow rates (maximum volume of voided urine per second), enlarged prostate size and high post-void residual volumes (volume remaining in the bladder after micturition) are all factors which increase significantly the risk of development of acute urinary retention or progression to BPH-related surgery.²³ The placebo arm of controlled trials such as PLESS and MTOPS provided insight that higher prostate-specific antigen (PSA) levels and larger prostate volumes predict BPH progression.³⁰ A subset of 1197 men undergoing prostate biopsies as part of the MTOPS study allowed further identification of the presence of inflammatory infiltrate within the prostate as another predictive variable for poor outcome (progression rate increased from 13% to 21%; incidence of AUR increased from 0 to 5.6%). The reason for this finding is unclear and is likely to be the subject of future work. The Alf-One study, an important open-label study designed to evaluate alfuzosin in a "real life setting", used deliberately broad inclusion criteria (no IPSS or peak flow restriction).³¹ Never previously reported, but intuitively appreciated, a history of acute urinary retention (managed non-operatively) was by far the most powerful predictive factor for future retention. Further, symptomatic deterioration while receiving alfuzosin and a (IPSS) bother score >3 also conferred an increased risk of acute urinary retention.³²

Despite the evidence above, it can remain difficult to predict those men in whom BPH-related surgery will become a necessity.³³ Many factors, such as bother, high residual volume and poor flow, have been independently shown to predict benefit from prostatectomy.³⁴⁻³⁶ For each individual case, however, an element of unpredictability remains regarding response to treatment.

ADRENOCEPTOR BLOCKADE STRATEGY

Obstruction due to BPH is caused by a static component of epithelial glandular tissue, and a dynamic component of stromal mesenchyme, mainly smooth muscle.³⁷⁻³⁸ The lack of clinical utility of hormonal manipulation of the glandular portion of the prostate has been attributed to the intrinsic resistance to hormonal influence of stromal, smooth muscle cells, which may comprise up to 40% of the total prostate volume.³⁹ Adrenoceptors are found in high concentration within the dynamic component of the prostate gland, and are thought to influence the resting tone of the smooth muscle within the prostate and bladder neck.⁴⁰ Adrenoceptor blockade was a concept originally developed for the treatment of hypertension. The first reports of α adrenoceptor influence on benign prostatic obstruction in the 1970s were based on the non-specific α blockade of phenoxybenzamine.⁴¹ Since then, much research has allowed the description of four subtypes of the α 1 adrenoceptor, with the highest affinity for prostate stromal tissue in the α 1A receptor.⁴²

Terazosin, although selective for the α 1 receptor, shows no preferential specificity for any of the four subtypes of this

receptor.⁴³ A number of randomised prospective controlled trials including a meta-analysis of this drug have been reported, showing durable efficacy compared with placebo.⁴⁴⁻⁴⁵ Somewhat surprisingly, tachyphylaxis is not seen with this drug, and speculation exists that this is related to a non-class specific stromal apoptotic effect of this drug, or perhaps to more central-mediated effects.⁴⁶⁻⁴⁸

Doxazosin shows a similar receptor profile as terazosin.⁴⁹ A number of prospective randomised studies have shown its efficacy in symptom relief and improvement of urinary flow parameters irrespective of prostate volume.⁵⁰⁻⁵¹ Analysis, however, within the MTOPS study (discussed in detail later) has called into question the capacity of doxazosin as a monotherapy to alter the natural history of the condition, specifically to prevent acute urinary retention or obviate the need for prostatectomy.²² With adrenoceptors not confined to the prostate, doxazosin has been the object of much research into the collateral benefits of adrenoceptor antagonism, such as lowering blood pressure and lipid profiles, and enhancing erectile function.⁵²⁻⁵⁴ Sometimes criticised for the mainly vascular-mediated side effects, the new gastrointestinal therapeutic system preparation of doxazosin minimises the side effects and makes dose titration largely unnecessary.⁵⁵

Although a selective α 1 antagonist, alfuzosin is not a subselective agent and is therefore similar to its predecessors described above.⁵⁶ Recently, the Alfuzosin Long-Term Efficacy and Safety (ALTESS) study reported by Roehrborn has become the most important study analysing the effect of this drug.⁵⁷ Over 1500 men were randomised to placebo or treatment with 10 mg alfuzosin once daily, and analysis of progression was performed after 2 years of treatment. The overall clinical progression rate for the group treated with alfuzosin was significantly reduced from 22.1% to 16.3% when compared with placebo, including a reduction in symptomatic deterioration (≥ 4 points IPSS) from 16.8% to 11.7%. As in other studies allowing an insight into natural history, the most common event indicating progression was symptomatic deterioration. Interestingly, the overall risk of developing AUR was unaffected by alfuzosin (2.1% v 1.8% with placebo), but the need for BPH related surgery was reduced from 6.5% with placebo to 5.1% with alfuzosin ($p = 0.18$). Before ALTESS, the main basis for the evidence-based popularity of alfuzosin has been derived from men with acute urinary retention undergoing trial without catheter. The Alfuzosin for Acute Urinary Retention study reported by McNeill examined 360 men with first episode of spontaneous AUR prospectively randomised to placebo or alfuzosin 10 mg once daily. Successful trial without catheter was recorded in 61.9% of men receiving alfuzosin versus 47.9% receiving placebo ($p = 0.012$).⁵⁸ In a second phase of the study reporting the effect of sustained treatment of the same group over a 6-month period, treatment with alfuzosin resulted in a reduction in BPH-related surgery from 24.1% to 17.1%.⁵⁹ McNeill further reported a multivariate analysis showing that residual volume exceeding 1 l and age >65 years conferred increased risk of failed trial without catheter. No other α blocker has proved efficacy in the setting of AUR. Claims of an enhanced vasculature-related side-effect profile for alfuzosin have provided a further distinguishing feature from competitors.⁶⁰⁻⁶¹ In both the ALTESS and Alfuzosin for Acute Urinary Retention studies, only a few patients reported adverse events and the overall incidence of treatment discontinuations due to adverse events was low and very comparable to placebo.

Unlike the quinazoline-derived agents described above with no α 1 subselectivity, tamsulosin was developed and remains the only α 1A selective adrenoceptor antagonist currently available.⁶²⁻⁶³ Since tamsulosin first reached a European market in 1995, multiple studies including meta-analyses have shown

efficacy in terms of improved symptoms and urodynamic parameters including increased flow rates.⁶⁴⁻⁶⁸ Abnormal ejaculation remains the only consistent side effect of this well-tolerated drug.

Only recently has ALTESS provided the first substantial evidence that alfuzosin may affect the natural history of BPH as defined by clinical progression, which predominantly consists of symptomatic deterioration. Before this study, it had been thought that the addition of a further treatment, complementary to adrenoceptor blockade, is required to change the natural history and progression of symptomatic BPH, particularly for those men with large prostate volumes. It should, however, be remembered that the ALTESS study is a relatively young study and longer term results are awaited to confirm the long-term effects of alfuzosin on BPH progression.

Hormonal manipulation in combination with adrenergic blockade is discussed at length in the next section. Alternatives to hormonal therapy for combination therapies have included the addition of anticholinergic therapy based on the knowledge that detrusor overactivity in men often accompanies bladder outlet obstruction due to BPH. Athanasopoulos *et al*⁶⁹ reported a series of 50 men with urodynamic-proved detrusor instability concomitant with bladder outlet obstruction and showed considerably improved quality of life produced by combination therapy of tamsulosin with tolterodine without any detrimental effect on bladder emptying. Further, placebo-controlled and comparative studies have now shown that the addition of an anticholinergic agent in the conventional treatment of patients with bladder outlet obstruction is safe.⁷⁰ Anticholinergic therapy is unlikely to significantly interfere in the voiding phase of bladder function, and the likelihood of acute urinary retention is low.

HORMONAL MANIPULATION AND COMBINATION THERAPIES

The epithelial component of the prostate depends on androgenic stimulation for growth and development, and 5- α -reductase catalyses the intracellular conversion of testosterone to the much more active dihydrotestosterone (DHT) responsible for genomic transcriptional changes at a cellular level.⁷¹ An observation in 1974 that men deficient in 5- α -reductase had hypoplastic prostates led to the first research into this enzyme as a therapeutic target for BPH.^{72 73}

Since the first description in 1986 of finasteride producing a reduction in DHT levels in the canine prostate, it has evolved to become the established 5- α reductase inhibitor in clinical use.^{74 75} The MTOPS study published in 2003 has superseded all previous analyses of finasteride, in its detailed investigation and duration of follow-up.²² This multi-centre study analysed a series of >3000 men randomised to placebo, either doxazosin or finasteride alone, or a combination of both, and examined for progression of disease defined as quantifiable symptom deterioration (>4 American Urological Association Symptom Index points), AUR, incontinence, renal insufficiency or the development of recurrent infection, over a mean 4.5-year observation period. The results showed a significantly greater reduction in the rates of progression or the need for invasive treatment with the combination therapy compared with either single agent alone. The adrenoceptor-alone arm had no significant effect over placebo on BPH progression, but conferred symptomatic benefit and quantifiably improved the flow rates. In a preplanned secondary analysis, optimum benefit from combination therapy was found in men with prostate volume >40 cm³ or PSA >4 ng/ml, both indicative of men with a larger prostate volume. The benefit from combination therapy in this study has served as a basis for the current practice of similar regimens of therapy in the treatment of BPH.

Previous notable studies, by the PLESS reported by McConnell, and by the Proscar Worldwide Efficacy and Safety Study group reported by Marberger, had predicted the efficacy of finasteride, but only in direct comparison with placebo, neither study having included adrenergic-blocker or combination arms.^{26 76} Some prior studies had examined the efficacy of finasteride over a shorter period of up to 1 year, and had failed to show therapeutic benefit from the drug either alone or in combination with an α -adrenergic antagonist.⁷⁷⁻⁷⁹ With the benefit of hindsight, these earlier negative studies may have been flawed by a small mean prostate volume in addition to brevity of follow-up, both of which may be key negative features for predicting benefit from 5- α reductase inhibitor.⁸⁰

The ancillary effects of finasteride, such as the successful treatment of BPH-related haematuria, have been shown in a number of prospective randomised studies, but the numbers remain small.⁸¹⁻⁸³ This effect on the vascularity of the prostate may be mediated by vascular growth factors,⁸⁴ and further extrapolation of this effect has been shown to suggest a benefit for patients undergoing transurethral prostatectomy in terms of reducing intraoperative blood loss.⁸⁵ The effect of finasteride in proportionally reducing the molecular forms of PSA has been well described.⁸⁶ Further, finasteride had been hoped to also confer a benefit in terms of prostate cancer prevention. In the prostate cancer prevention trial involving over 18 000 men with follow-up for 7 years, the incidence of prostate cancer was found to be reduced, but the increased incidence of high-grade prostate cancers in the finasteride-treated group was of major concern.⁸⁷ The true implications of this finding are as yet unclear and remain the topic of further investigation.⁸⁸

The search for an alternative to the selective type II 5- α reductase inhibition provided by finasteride has led to the production of the combined type I and II 5- α reductase inhibitor dutasteride. The two forms of 5- α reductase inhibitors, type I and II, are encoded by different genes located on chromosomes 5 and 2, respectively.⁸⁹ The distribution of each enzyme differs, with type II found almost exclusively in prostate tissue, whereas type I is also present in skin, liver and other organs.⁹⁰ Selective type II 5- α reductase inhibition by finasteride fails to reduce circulating DHT levels below 20–40% of normal levels.^{91 92} In-vitro studies and in-vivo serum assays of DHT have shown considerably greater potency with dutasteride than was evident with its class predecessor in the inhibition of both 5- α reductase inhibitor enzymes.⁹³⁻⁹⁶ It is only recently that the first long-term clinical efficacy data have emerged in relation to dutasteride. In a 4-year analysis reported by Roehrborn *et al*, comprising an initial 2-year randomised double-blind placebo-controlled phase followed by a 2-year open-label extension completed by >2000 patients, considerable and sustained improvements in LUTS were shown with dutasteride as monotherapy for LUTS attributed to BPH.⁹⁷ Before this data, much of the clinical application of dutasteride had been justified by a class effect.⁹⁸ Long-term data based on other end points, such as acute urinary retention or need for prostatectomy, are still awaited, as is a direct comparison of finasteride and dutasteride in clinical use.

PHYTOTHERAPY

No comprehensive discussion of non-operative treatments for BPH can be complete without some mention of phytotherapeutics, which currently have a market share of up to one third of all preparations used for the treatment of symptomatic BPH in Western countries, particularly mainland Europe and North America.⁹⁹ Numerous agents such as palm plant, nettle, rye grass, pumpkin seed and cactus flower derivatives have been used over the centuries, each containing single or combinations of active compounds perhaps derived from

identical or very similar classes.^{100–102} Many such agents are hypothesised to produce their beneficial effect through hormonal effects and interference with normal cellular metabolism, but for many the precise mechanism of action remains unknown.^{103–105} Many specific natural extracts such as “*Serenoa repens*” (an extract from berries of the American dwarf plant) and “*Pygeum africanum*” have been scrutinised as the topic of meta-analyses and now have a significant market share in mainland Europe.^{106–109} Meta-analyses, however, do not always reliably predict the results of large-scale prospective randomised controlled trials.¹¹⁰ Large prospective randomised trials have shown a comparable efficacy for phytotherapy when compared with both adrenoceptor blockade and finasteride, above what would be expected from a placebo effect, but they unfortunately lack real placebo control.^{111–113} As such, expert panels of critics continue to think that gold-standard clinical investigations remain deficient.¹¹⁴ The lack of gold-standard investigation may be explained at least in part by the fact that these products cannot be patented, and thus it does not seem worthwhile for the pharmaceuticals industry to invest large resources into such products. In truth, this deficiency may only distract from a possible genuine benefit of these agents, and attention may need to be refocused on this aspect in the future.

CONCLUSIONS

Not all men with BPH require medical therapy, but treatment may allow symptomatic relief and may prevent features of progression such as the development of AUR. Standard current medical management strategies use either an adrenoceptor antagonist or hormonal manipulation (5- α reductase inhibitor), or indeed a combination of both. Adrenoceptor antagonism works quickly to produce symptomatic relief, and the recent ALTESS study has shown that alfuzosin can reduce the clinical progression of BPH. Larger prostates probably do require the addition of a 5- α reductase inhibitor to significantly reduce the risk of urinary retention and BPH-related surgery. The effect of any hormonal manipulation on PSA levels in an era of ongoing cancer-screening debate, and the further unclear effect on prostate cancer development both currently hinder the widespread selection of 5- α reductase inhibitor class drugs as the preferred drug of choice in all but those men with large prostate volumes who are most likely to benefit from such treatment. Unlike 5- α reductase inhibitors, α blockers produce symptomatic benefit irrespective of gland volume. The adverse effect of hormonal manipulation on erectile function and libido may provide a further sustained impetus to the ongoing role of adrenoceptor therapy. A case for both agents can be made in many instances, and the ultimate choice of first-line treatment will remain at the discretion of the prescribing doctor for the foreseeable future.

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