Dutasteride: 21st Century medical therapy for symptomatic benign prostatic hyperplasia

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Dutasteride is the latest addition to medical therapy for symptomatic benign prostatic hyperplasia. The safety and efficacy of dutasteride has been firmly established in high-quality, randomized, clinical trials, and in this article we discuss these key studies, along with current thoughts on its use in combination with other benign prostatic hyperplasia drugs. The role of dutasteride in chemoprevention of prostate cancer will also be discussed.

Keywords: benign prostatic hyperplasia, BPH, dutasteride, treatment, urology

Benign prostatic hyperplasia (BPH) is a common urological problem, affecting up to 70% of men aged between 60 and 70 years. It is generally accepted that approximately 80% of all men will develop BPH within their lifetime. BPH typically causes bladder outflow obstruction (BOO) which is associated with lower urinary tract symptoms (LUTS). Symptom severity can be assessed objectively using validated questionnaires, such as the American Urological Association (AUA) symptom score, or the International Prostate Symptom Score (IPSS), which attributes scores regarding BPH-related LUTS. A 2-point improvement is generally regarded as meaningful to patients [1]. Other important objective indicators of BOO include maximum urinary flow rate (Q_{max}), post-void residual volume (PVR), prostate-specific antigen (PSA) level and prostate volume. A Q_{max} of less than or equivalent to 15 ml/s requires treatment, whereas maximum flow rates of 15 ml/s or more are considered acceptable. A significant PVR is considered to be over 150 ml, and in addition to being predictive of acute urinary retention (AUR), and it also a good indicator of whether a patient will ultimately require surgery for their LUTS.

BOO due to BPH consists of two components; a static component due to the proliferation of epithelial and stromal cells, and a dynamic component in which the role of smooth muscle cells are important. The static component appears to be under the control of hormones, including testosterone, and it's more active derivative, dihydrotestosterone (DHT). DHT is synthesized from testosterone by two isoenzymic forms of 5α-reductase, and studies have shown that in BPH, there is increased activity of 5α-reductase as well as increased DHT levels in the hyperplastic tissue. This knowledge has encouraged the development of the 4-azasteroids. These are a class of drugs that inhibit 5α-reductase, and thereby preventing the production of DHT, with the aim of reversing prostatic growth without effecting testosterone-dependent functions.

Dutasteride, also known as GI198745, is one such drug, and it competitively inhibits both type 1 and type 2 isoenzymes of 5α-reductase, with the advantage of providing greater suppression of intraprostatic DHT, by 97% at therapeutic doses [2].

The efficacy and safety of dutasteride was firmly established in a combined analysis of three randomized, placebo-controlled trials (ARIA 3001, ARIA 3002 and ARIB 3003) by Roehrborn and colleagues [3]. A total of 4325 men aged 50 years or older, with clinical BPH, moderate-to-severe symptoms (AUA symptom index score ≥ 12 points), a Q_{max} of 15 ml/s, a prostate volume, measured by transrectal ultrasound, of either greater than or equivalent to 30 cm^3 and a serum PSA of 1.5–10 ng/ml, were enrolled in the three identical trials. These patients were randomzed to receive 0.5 mg dutasteride daily or placebo. After a 1-month, single-blind, placebo lead-in, patients were followed for up to 24 months with multiple interval assessments at 1, 3, 6, 12, 18 and 24 months. The main end points were change in symptom score and risk of AUR. At baseline, men had an average age of 66 years, a symptom score of 17 points, a Q_{max} of 10 ml/s and a mean prostate volume of 55 cm^3.

In total, 2951 men completed the study and dutasteride was found to be effective in terms of reduction of prostate volume and symptoms, flow rates and reduction of risk of AUR and surgery during the 24-month period.

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Specifically, the symptom score fell by 4.5 points (21.4%) with dutasteride, significantly more than the 2.3 points observed with placebo. Interestingly, the AUA symptom score was found to be improved as early as the third month, with significant improvement over placebo from 6 months onward. The Q_{max} also improved significantly – by 2.2 ml/s with dutasteride in comparison with 0.6 ml/s in placebo – over the 24-month period. Furthermore, differences were present even at 1 month in those taking dutasteride by 0.9 ml/s (0.5 ml/s in placebo) with differences between dutasteride and placebo of over 1 ml/s by month 12. In addition, prostate volume was reduced by a mean of 25.7% at 24 months in those taking dutasteride ($p < 0.001$).

A total of 39 patients taking dutasteride (1.8%) and 90 in the placebo arm (4.2%) developed AUR, and the number of patients requiring BPH-related surgical intervention was 47 in those taking dutasteride (2.2%) and 89 in those on placebo (4.1%). This represented a calculated risk reduction of AUR of 57% and BPH-related surgery was 48%. The number needed to treat with dutasteride for 2 years to prevent one episode of retention was 42 and the number needed to treat with dutasteride to prevent one surgery was 51.

In addition to being clinically efficacious, dutasteride was found to be well tolerated with minimal side effects. In general, the safety profile of dutasteride is comparable to that of placebo, with bone metabolism, density and lipid profiles not significantly affected after administration of dutasteride for a period of 1 year [3,4]. However, there were elevated incidences of impotence (4.7 vs 1.7%; $p < 0.05$), ejaculatory disorders (1.4 vs 0.5%; $p < 0.05$), decreased libido (3.0 vs 1.4%; $p < 0.05$) and gynecomastia (0.5 vs 0.2%, difference nonsignificant) in those receiving dutasteride [3,4]. It has to be appreciated that these adverse events were more marked in the first 6 months of treatment and reduced significantly after the first year of treatment (impotence 4.7–1.0%; ejaculatory disorders 1.4–0.5%; decreased libido 3.0–0.3%) and the numbers affected are extremely small. In conclusion, dutasteride is extremely well tolerated.

As well as reporting the 2-year follow up, the longer-term outcomes have also been recently published in a 2-year, open-label extension of the three randomized studies (ARIA 3001, ARIA 3002 and ARIB 3003) by Debruyne and colleagues [5]. All patients in the original study, by Roehrborn and colleagues [3] were eligible for a 2-year, open-label extension, into two groups – dutasteride/dutasteride (D/D) or placebo/dutasteride (P/D). Significant improvements in AUA symptom score and Q_{max} were observed in both arms. At month 48, the D/D group had statistically significant improvements, with respect to AUA symptom score, from -4.4 points at 24 months, to -6.5 points at 48 months, than the P/D group (-2.5 points at 24 months and -5.5 points at 48 months). Similarly, significant differences in Q_{max}, reductions in prostate volumes and PSA were noted in the D/D group. In addition, AUR- and BPH-related surgery occurred in a small percentage only in both groups and no new safety issues were observed with an extra 2 years of usage. Although it has to be appreciated that the open-labelled extension is not strictly the highest level of evidence a randomized, placebo-controlled trial can provide, Debryune and colleagues have concluded that long-term treatment with dutasteride resulted in continued improvements in urinary symptoms and flow rate and further reductions in prostate volume in men with symptomatic BPH. The relative risk of AUR and BPH-related surgery was found to be durable over a 4-year treatment period, and dutasteride was tolerated in the longer term.

Additional analyses of the 2-year, open-label extension of the three randomized, controlled trils have been reported by Roehrborn and colleagues [6] and have been termed as 'severe data'. The proportion of patients with severe symptoms declined in both study groups of the open-label extension, although these changes were more profound in those receiving dutasteride for the 4-year duration of the study. Dutasteride reduced the percentage of patients with severe symptoms from 30 to 8% over 4 years. In the 356 patients with severe symptoms, a mean improvement in symptom scores was 6.4 at 12 months, 7.2 at 24 months, 8.9 at 36 months and 10.1 at 48 months. It is generally accepted that a 6-point improvement is regarded as meaningful in severe patients [1].

Dutasteride has also been shown to possess tumor regression properties *in vitro* [7] and it has recently been announced that its role in the chemoprevention of prostate cancer will be examined and investigated in the ongoing Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial [8,9].

REDUCE is a 4-year, international, multicenter, randomzed, double-blind, placebo-controlled study to evaluate the efficacy and safety of oral, daily dutasteride 0.5 mg in men at increased risk of developing prostate cancer. The target enrolment is 8000 men who will be randomized to receive dutasteride or placebo for 4 years. Eligibility criteria include men between 50 and 75 years, PSA of between 2.5 ng/ml and 10 ng/ml (men aged 50–60 years) or between 3.0 and 10 ng/ml (men aged > 60 years). All patients must have no histological evidence of prostate cancer, based on a negative biopsy within 6 months prior to enrolment. Prostate volumes of over 80 cm^3 and those with IPSS values over 25 have been excluded to minimize the risk of BPH-related surgical intervention. After screening, eligible subjects will complete a 4-week, placebo run-in and entry biopsy slides, and all subsequent prostate biopsies will undergo central pathology review. PSA will be measured every 6 months throughout the study. Study participants will return for assessment visits at 6 months post-randomization, and every 6 months until the end of the study. Prostate biopsies will be performed at 2 and 4 years to evaluate for prostate cancer. The primary end point is biopsy-determined prostate cancer after 2 and 4 years of treatment. Several secondary end points will also be assessed including overall survival. The study will also incorporate various genetic and protein biomarkers of prostate cancer. The safety and tolerability of dutasteride will also be examined. The REDUCE study has been specifically designed to recruit men at increased risk of developing prostate cancer. By excluding men with prostate cancer detected within 6 months prior to enrolment, the study is attempting to enrol men without prostate cancer, or those with undetectable disease based on a mandatory negative biopsy. These study design elements will reduce the number of men needing to undergo biopsy before any putative effect of dutasteride can be detected.

Recently, GlaxoSmithKline have also announced the launch of The Combination of Avodart and Tamsulosin (COMBAT) study. COMBAT is a 4-year, randomzed study to be conducted in Europe, North America, Latin America and Asia–Pacific, that will investigate the efficacy and safety of dutasteride 0.5 mg, and tamsulosin 0.4 mg, administered once-daily, alone and in combination, on improving urinary symptoms and reducing the risk of BPH progression. Eligibility criteria include men (aged ≥ 50 years) with an IPSS greater than or equal to 12, a prostate volume of 30 cm^3 or more, and PSA level of 1.5–10 ng/ml or more. Baseline data from COMBAT has recently been presented in abstract form at the 21st European Urology Annual scientific conference, by Roehrborn and colleagues [10] and Montorsi and colleagues [11]. Roehrborn and colleagues analyzed baseline data to assess the relationships between body mass index (BMI) and measures of LUTS/BPH severity and indicators of metabolic syndrome. They reported that a higher BMI was associated with more severe irritative LUTS, greater Q_{max}, higher prostate volumes, greater girth, higher blood pressures and higher fasting glucose and fasting insulin levels. PSA density was also found to be lower with higher BMI. They concluded that the mechanisms responsible for these relationships were intriguing and merited further research. Montorsi and colleagues analysed the baseline data to evaluate the profiles of different racial groups enrolled in REDUCE. Baseline data collected included answers to questions regarding alcohol consumption, smoking, sexual activity, impotence and libido. Patients were divided into Caucasian, African–American, Hispanic–American and Asian subgroups. They found that there were some racial differences in baseline parameters, particularly smaller prostate volumes, but greater symptom severity in Asian men. Finally, in the same conference, Marberger and colleagues presented baseline data on the relationship between testosterone levels and measures of sexual dysfunction from the three large dutasteride BPH trials (n = 4325) and the COMBAT trial [12]. All subjects were asked about their sexual activity and any experiences of impotence or lack of libido. They reported that there was a significant relationship between baseline testosterone levels and sexual activity, impotence and lack of libido. However, the effects of testosterone levels on these sexual function parameters were not as significant as the effects of age, IPSS and BMI.

The safety and efficacy of dutasteride, in the short and long term, has been firmly established in high quality randomised clinical trials. Its use in combination treatment for BPH as well as its role in chemoprevention of prostate cancer will also become clear in the near and exciting future.

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