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REVIEW

Role of 5α-reductase inhibitors in benign prostatic diseases

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Testosterone is the most abundant androgen in serum. Intracellularly, testosterone is converted to dihydrotestosterone, the preferred ligand for androgen receptor transactivation, by the enzyme 5α-reductase. Three 5α-reductase isozymes have been discovered and they are expressed ubiquitously in human tissues. Testosterone and dihydrotestosterone have different but complimentary functions. Dihydrotestosterone has 2–5 times higher binding affinity for the androgen receptor than testosterone, and 10-fold higher potency of inducing androgen receptor signaling than testosterone. The role of dihydrotestosterone was discovered after the description of 5α-reductase type 2 deficiency in 1974, where affected males have normal internal but ambiguous external genitalia. Neither BPH nor prostate cancer has been reported in these patients. Currently, two 5α-reductase inhibitors are available for clinical use. This review will discuss the important clinical trials of 5α-reductase inhibitors in the treatment of benign prostatic diseases.

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INTRODUCTION

Testosterone (T) is the most abundant androgen in serum. T stimulates *in utero* differentiation of the Wolffian duct into male internal genitalia and pubertal development of libido, enlargement of the vocal cords, skeletal muscles, penis and scrotum and the initiation of spermatogenesis.[1,2] Intracellularly, T is converted to dihydrotestosterone (DHT), the preferred ligand for androgen receptor (AR) transactivation, by the enzyme 5α-reductase (5α-R).

Three 5α-R isozymes have been discovered and they are expressed ubiquitously in human tissues. Type 1 is expressed mainly in skin and liver. Type 2 is expressed mainly in prostate. Type 1 and type 2 are the most well-studied and involved mainly in 5α-reduction of steroids.[3] Type 3 is responsible mainly for N-glycosylation of nascent proteins.[4] Congenital deficiency of type 3 has been linked to a rare, autosomal recessive disorder in which patients are born with mental retardation, cerebellar and ophthalmological defects. The presumed defect involves the reduction of the terminal double bond of polyprenols to dolichols, an important step in protein N-glycosylation. Protein N-glycosylation facilitates proper folding and trafficking of nascent proteins and occurs in the membranes of endoplasmic reticula. This disorder is part of the family of congenital disorders of glycosylation and was first described by Cantagrel.[4] *In vitro* studies proved the ability of type 3 at steroid 5α-reduction; however, the clinical significance of this latter effect remains unknown.

DHT has 2–5 times higher binding affinity for AR than T, and 10-fold higher potency of inducing AR signaling than T.[5] DHT is important for *in utero* differentiation and growth of the prostate gland, penis and scrotum, and pubertal growth of facial and body hair. DHT has an important role in several human diseases, which include acne, hirsutism, male pattern baldness, benign prostate enlargement/hypertrophy (due to BPH) and prostate cancer (CaP).[6] The role of DHT was discovered after the description of 5α-R type 2 deficiency in 1974.[7] Affected males have normal internal genitalia, however, their external genitalia are ambiguous. The prostate is hypoplastic, nonpalpable on rectal examination and is barely discernible on transrectal ultrasound or MRI. Prostate biopsy reveals fibrous connective tissue, smooth muscle and no identifiable epithelial tissue, which suggests atrophic epithelium or lack of epithelial differentiation. Serum PSA level is low or undetectable. Neither BPH nor CaP has been reported in these patients.[8]

Interest in development of 5α-reductase inhibitors (5ARI) started after appreciation of the implications of 5α-R type 2 deficiency. Numerous compounds have been developed, but only two drugs have been FDA-approved. Finasteride was approved for treatment of BPH and male pattern baldness, and dutasteride was approved for BPH treatment.

5ARI are beneficial in treatment of lower urinary tract symptoms (LUTS) due to BPH, prevention of BPH-clinical progression and treatment of BPH-related hematuria. 5ARI have been tested for treatment of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), prevention and treatment of CaP. This review will discuss the role of 5ARI in benign prostatic diseases.

BACKGROUND

5ARI

Numerous steroidal and non-steroidal compounds with different mechanisms of 5α-R inhibition have been developed. The steroidal class has more inhibitors, which include 4-, 6- and 10-azasteroids. 4-Azasteroids are the most extensively studied 5ARI and include finasteride (MK-906), dutasteride (GG745), turosteride, MK-386, MK-434 and MK-963.[9] Finasteride and dutasteride are the only 5ARI approved for human use.

Non-steroidal inhibitors are derived from azasteroidal inhibitors by removing $\geqslant 1$ rings from the 4-ring steroid nucleus, and include the most potent and selective 5α-R type 1 inhibitors.[9]

Finasteride is a potent competitive inhibitor of 5α-R type 2 but inhibits less effectively 5α-R type 1. Finasteride at 1 mg or 5 mg daily doses decreased mean serum DHT levels by 71% and 72%, respectively, after 6 weeks of use.[10] Seven-day treatment with

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finasteride (1 or 5 mg daily) has been reported to suppress intraprostatic DHT levels in men with BPH by approximately 85% relative to placebo.[11] Finasteride has a half-life of 6–8 hours and is approved for treatment of male pattern baldness and BPH at daily doses of 1 mg and 5 mg, respectively.

Dutasteride has a half-life of nearly 5 weeks and is approved only for treatment of BPH. Dutasteride is more potent at inhibiting 5α-R types 1 and 2 than finasteride; dutasteride is three times more potent than finasteride at inhibiting 5α-R type 2 and more than 100 times as potent at inhibiting 5α-R type 1.[12] Dutasteride 0.5 mg daily reduced mean serum DHT levels at 24 weeks better than finasteride (92 vs 73%) and caused 97% reduction in intraprostatic DHT levels in men with CaP treated with 5 mg daily for 6–10 weeks.[13] In another trial, dutasteride 3.5 mg daily for 4 months prior to radical prostatectomy decreased intraprostatic DHT by 99%.[14] Finasteride and dutasteride effectively inhibit 5α-R type 3 *in vitro*,[15] and near-maximal suppression of intraprostatic DHT with dutasteride 3.5–5 mg daily suggest that development of a triple 5ARI may not be necessary.

Effect of 5ARI on PSA

PSA production by prostatic epithelial cells is androgen-stimulated and hence serum PSA is affected by anti-androgen therapy. The effect of 5ARI on serum PSA is complex and variable. The median reduction in serum PSA in response to finasteride therapy is 50% after 3–12 months of continued use (range: 81% decrease to 20% increase at 12 months),[16–18] and is 57% after 48 months.[19] Dutasteride decreases serum PSA by a median of 60% at 2 years (range: 10–82% reduction) and 66% at 4 years (range: 9–87% reduction).[20]

The 5ARI-induced reduction in serum PSA is greater and more sustainable in men with BPH than in those with CaP.[18] Men whose serum PSA doesn't decrease by 50% or increases after steady use of 5ARI ($\geqslant$3 months) need to be carefully followed and assessed for occult CaP.

Adverse effects (AE)

5ARI are usually well-tolerated[20–22] and most AE are mild and transient. Drug-related AE occur in $\leqslant$20% of patients and most occur in the first year of use. Drug discontinuation due to AE is rare and occurs in 4–5% of users. Sexual AE are the most common AE, occur in $<$10% of users, and include impotence, decreased libido, decreased ejaculate volume and ejaculation disorders. Sexual AE decrease over time and their incidence (after year 1) is similar to placebo. Gynecomastia and breast tenderness occur in nearly 1–2% of users, gradually increase in incidence with continued use, and are mostly irreversible.

Effect of 5ARI on risk of CaP

Two large chemoprevention trials (the Prostate Cancer Prevention Trial 'PCPT' and the Reduction by Dutasteride of Prostate Cancer Events 'REDUCE') studied the effect of daily use of a 5ARI on the incidence of CaP.[23,24] PCPT was a 7-year-long trial that enrolled nearly 19 000 men who were at low risk for CaP. REDUCE was 4-year-long and enrolled nearly 8000 men, who were at increased baseline risk of CaP. Either drug decreased the incidence of CaP by 23–25%. The prevented CaP diagnoses were low-grade (Gleason score $<$7 in PCPT and Gleason score $\leqslant 3+4=7$ in REDUCE). In PCPT, there was an increase in Gleason score $\geqslant$7 CaP in the finasteride arm (6.4% of participants vs 5.1% in the placebo arm, relative risk 1.27, $P=0.005$). In REDUCE, there was no difference in Gleason score 8–10 CaP between the two arms at study end (0.9% of men in the dutasteride vs 0.6% of men in the placebo groups, $P=0.15$). However, during years 3–4 of REDUCE, there was a significant increase in Gleason 8–10 cancers in the dutasteride arm (0.5% vs $<$0.1%, $P=0.003$). Numerous secondary analyses tried to explain the increase in high-grade CaP in PCPT and REDUCE; however, all are considered hypothesis-generating. Whether 5ARI truely induce high-grade CaP remains unknown. In January 2011, the FDA voted against recommending either drug for CaP risk reduction because of the potential increased risk of high-grade disease, which is now listed on the label of both drugs. (http://www.auanet.org/content/media/pcredinh.pdf).

Monitoring men on 5ARI

Men on 5ARI need to be monitored for AE and for changes in serum PSA. At treatment initiation, a baseline PSA level should be obtained, followed by determination of the nadir value, which is reached after 3–12 months of continued use. Thereafter, the actual PSA level is calculated by multiplying by a correction factor. The most widely used correction factor is 2. However; there are two major problems with this approach. First, the effect of 5ARI on serum PSA is continuous and increases with time,[19,23] therefore multiplying by 2 may over-estimate and under-estimate the actual PSA value in those in whom treatment duration is either short or prolonged, respectively. Marks *et al.*[25] performed an extensive review of available studies and concluded that doubling of serum PSA concentration in men who have received 5ARI for 6–9 months overestimated actual PSA, correctly estimated actual PSA during 1–3 years of treatment and underestimated it thereafter. The authors proposed that a PSA increase $\geqslant 0.3\ \mathrm{ng\,ml^{-1}}$ from the new baseline should be used as a biopsy trigger. In PCPT, the authors doubled serum PSA in the finasteride arm in the first 3 years of the study, and thereafter multiplied by 2.3, in order to ensure an equal number of prostate biopsies in the two study arms. In REDUCE, the authors used a multiplying factor of 2 in the treatment arm. Finally, the effect of 5ARI on serum PSA varies among men. In finasteride users in the VA study, serum PSA decreased by 40–60% in 34% of men and by $>$60% in 29%. In 37%, PSA either decreased by $<$40% or increased.[26] Therefore, the perfect correction factor for men on 5ARI remains unknown. The safest policy to adopt in 5ARI users is to monitor serum PSA, calculate PSA velocity, perform regular digital rectal examinations and have a low threshold for performing prostate biopsies.

Cost-effectiveness of 5ARI-use in benign prostatic diseases

Any discussion of cost-effectiveness of the various treatment modalities of benign prostatic diseases should consider all aspects related to patients, society, disease natural history and treatment specifics, such as the cost of each treatment, its effect on disease progression, risks of hospitalization and operation, reoperation rate, incidence and treatment of AE, patient preferences, heterogeneity, expectations and life expectancy. There are few available cost-effectiveness studies comparing the various treatment options for BPH. In a review article, Nickels[27] reported that alpha-1 adrenergic blockers (A1B) are more cost-effective than 5ARI and comparable in cost to TURP and minimally invasive therapies for BPH. In another study, DiSantostefano *et al.*[28] used a Markov model over a 20-year time horizon and found A1B and transurethral microwave therapy to be more cost effective for treating moderate LUTS (compared with watchful waiting, 5ARI and TURP), and TURP to be the most cost-effective treatment for severe LUTS. More studies are needed to better clarify cost-effectiveness of all treatment options for BPH, and should consider emerging newer treatments, cost of generic drugs and patient preferences.

ROLE OF 5ARI IN BENIGN PROSTATIC DISEASES

I. BPH

Histological evidence of BPH is found in 50% of males by age of 50 years and 90% of males by age of 90 years.[29] Even though 5α-R types 1 and 2 isozymes are over-expressed in BPH tissue compared with normal prostate tissue; type 2 is the predominant

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form.[30,31] BPH is a progressive disease. In the Olmsted county survey, a randomly selected cohort of 2115 men, aged 40–79 years, were followed for up to 12 years. There was an average increase in the International Prostate Symptom Score (IPSS) of 0.18 points per year, a decrease in peak flow rate (Q_{max}) of 2% per year, and a median prostate growth of 1.9% per year.[32–34] Baseline risk factors for progression were old age, severe LUTS, low Q_{max}, high post-void residual urine volume, enlarged prostate and high serum PSA levels.[35,36] Progression of BPH can manifest as LUTS deterioration, recurrent urinary tract infections, urinary incontinence, BPH-induced renal impairment, acute urinary retention (AUR) and the need for BPH-related surgery.[37,38] In addition, BPH is a common cause of hematuria that can lead to anemia, clot urinary retention, blood transfusion and prostate surgery.[39]

Ia. Prevention of BPH clinical progression. Available medical treatment options for BPH-induced LUTS include 5ARI and/or alpha-1 blockers (A1B). A1B work promptly by relaxing bladder neck and prostatic smooth muscles, which reduces the dynamic element of bladder outlet obstruction. 5ARI work more slowly by decreasing the static element of bladder outlet obstruction (prostate volume). 5ARI decrease prostate volume (PV) and serum PSA via induction of prostate epithelial atrophy and apoptosis, effects that are sustainable and may gradually increase with treatment continuation.

Several clinical trials studied the impact of A1B and 5ARI on BPH symptoms and clinical progression (Table 1). In MTOPS, PLESS and ARIA trials, 5ARI decreased the risk of BPH progression, by decreasing the risks of AUR (by 57–68%), BPH-related surgery (by 48–64%) and LUTS deterioration, defined as worsening of IPSS $\geqslant$4 points, (by 30%), compared with placebo.[20,21,38] The only impact of A1B on BPH progression was through 45% (or 30%) risk reduction (RR) in LUTS deterioration observed with doxazosin (or alfuzosin) vs placebo, respectively.[38,40] In MTOPS, combination therapy of doxazosin and finasteride yielded the greatest RR in AUR (81%), BPH-related surgery (67%) and LUTS deterioration (64%), compared with placebo.[38] However, the small difference in favor of combination therapy over finasteride alone for reduction of AUR and BPH-related surgery was not statistically significant. Similar results were seen in CombAT. Combination therapy of tamsulosin and dutasteride yielded greater reduction in risks of AUR (RR 18%) and BPH-related surgery (RR 31%) vs dutasteride, however, the difference was not statistically significant.[41] In MTOPS and CombAT, 5ARI monotherapy was superior to A1B monotherapy in decreasing the risks of AUR and BPH-related surgery. 5ARI were inferior to A1B in decreasing risk of LUTS deterioration in MTOPS (RR 30% vs 45%), but not in CombAT where they were similar (incidence 13.1% vs 14.2%), due to higher risk of BPH progression in CombAT participants, given their larger baseline PV and higher PSA.

The above data indicates that combination therapy has greater impact on BPH progression than either drug alone, and should be considered in men with BPH and risk factors for progression.

Ib. Treatment of LUTS. MTOPS and CombAT had follow-up of 4 years each, and showed the combination therapy to be the most effective modality in improving IPSS (6.3–7.4 points) and Q_{max} (2.4–3.7 ml s^{-1}). Different results were seen in PREDICT and the VA studies, where combination therapy was no more effective than A1B monotherapy in improving IPSS and Q_{max}, however, follow-up was shorter (1 year).[42,43] In MTOPS, PREDICT and the VA studies, finasteride was superior to placebo, but inferior to combination therapy and to A1B in decreasing IPSS and improving Q_{max}.[38,42,43] However; in CombAT, dutasteride was superior to tamsulosin in improving IPSS (-5.3 vs -3.8 points) and Q_{max} (2 vs 0.7 ml s^{-1}).[41] In fact, the improvement in Q_{max} in the tamsulosin arm was similar to placebo in the ARIA studies (0.6 ml s^{-1}). Dutasteride-induced improvements in LUTS and Q_{max} exceeded those of tamsulosin, starting at 15 months and 6 months, respectively, and continued until end of study. CombAT participants benefited more from 5ARI as they were at higher risk of BPH progression (baseline PV 49 ml, serum PSA 4 ng ml^{-1}) compared with men in MTOPS, PREDICT and the VA studies (PV 36–38 ml, serum PSA 2.2–2.6 ng ml^{-1}).

There is no clinical evidence that one 5ARI is better than the other for treatment of BPH. The EPICS trial showed that dutasteride was no more effective than finasteride in decreasing serum PSA, PV, IPSS and improving Q_{max}, after 12 months of treatment.[22]

A practical algorithm to treat men with BPH is based on LUTS severity and bothersomeness, and on the presence of risk factors for BPH progression, such as enlarged prostate ($>$30–40 ml) and increased serum PSA ($\geqslant$1.5 ng ml^{-1}). In those with mild LUTS and little/no bother, watchful waiting is advised, whereas those with moderate-severe LUTS or bothersome LUTS, an A1B is recommended. Those with PV$>$30–40 ml and PSA$\geqslant$1.5 ng ml^{-1}, a 5ARI is added to halt BPH progression.[44] A1B can be discontinued in men on combination therapy, as early as 6 months after initiation of combination treatment, once LUTS are satisfactorily ameliorated.[45]

Tables 2 and 3 list the European Association of Urology and American Urological Association guidelines on 5ARI use in BPH. (http://www.uroweb.org/gls/pdf/12_Male_LUTS.pdf, http://www.auanet.org/content/clinical-practice-guidelines/clinical-guidelines.cfm?sub = bph).

Ic. BPH-related hematuria. BPH-related hematuria is probably related to increased prostatic vascularity.[46] These blood vessels are friable and highly permeable.[47] As a result, hematuria happens frequently. The incidence of gross hematuria in BPH is unknown, however, gross hematuria was the reported indication for TURP in 12% of men with BPH.[39] In men with hematuria, BPH is the only pathological condition identified in 20% of men.[48] Marshall *et al.*[49] postulated that angiogenesis is critical in BPH and that androgen deprivation leads to suppression of angiogenesis. Multiple pro-angiogenic growth factors that are increased in BPH[50,51] are suppressed by 5ARI, such as hypoxia-inducible factor,[52,53] basic fibroblast growth factor[54] and vascular endothelial growth factor.[53,55,56] Prostatic suburothelial microvessel density, which is increased in patients with BPH-related hematuria compared with patients with BPH alone,[46] is decreased by 5ARI.[13,57,58] In animal and human studies, 5ARI significantly decrease prostatic blood flow.[59,60] Time to significant reduction in microvessel density and expression of pro-angiogenic factors after 5ARI initiation is inconsistent, and ranges from 2 to 10 weeks.[13,52,53,56]

The exact mechanism of action of 5ARI in treatment of BPH-related hematuria remains unclear. Probably, 5ARI causes decrease in androgenic stimulation of prostate tissue via suppression of intraprostatic DHT levels, which leads to decreased pro-angiogenic factors, microvessel density and angiogenesis. Over time, the prostate atrophies due to apoptosis,[59] which leads to decreased PV, metabolic requirements and blood flow.

Clinical evidence supporting finasteride use in BPH-related hematuria is more robust than for dutasteride. Several trials confirmed the efficacy of finasteride in decreasing recurrence and severity of BPH-related hematuria, effects that persisted with long-term follow-up and were independent of prior prostatectomy and anticoagulant drug status. Finasteride 5 mg per day for more than 3 months improved the severity of gross BPH-related hematuria in 11 of 12 patients. The benefit was observed regardless of prostatectomy status.[61] When follow-up was extended to 31 months, the benefit of finasteride persisted.[62] In another study, BPH-related hematuria resolved within 2 weeks in all patients following finasteride 5 mg per day, and none experienced recurrence while on treatment.[63] A prospective study of 57 patients with intermittent BPH-related hematuria randomized participants to finasteride 5 mg per day or watchful waiting for 1 year. In all, 63% of patients in the control group experienced recurrence of BPH-related hematuria that was moderate or severe in 59% (using a 3 grade classification system of gross hematuria).

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Table 1. Key trials of medical therapy for BPH

	IC and BD	*Results*
Proscar Long-Term Efficacy and Safety Study (PLESS):[21] Protocol: Fin 5 mg vs PL Length: 4 years No. of men: 3040	IC: Moderate - severe LUTS (q-AUASS) Enlarged prostate on DRE $Q_{max} < 15$ cm^3 s^{-1} with VV $\geqslant 150$ cm^3 Serum PSA < 10 ng ml^{-1} BD: Age 64 years, q-AUASS 15 Q_{max} 11 cm^3 s^{-1} Serum PSA 2.8 PV 55 cm^3	(1) Mean change in q-AUASS: −1.3 points (PL), -3.3 (fin) (2) Mean change in Q_{max}: 0.2 ml s^{-1} (PL), 1.9 cm^3 s^{-1} (fin) (3) Mean change in PV: 14% (PL), −18% (fin) (4) incidence of AUR: 7% (PL), 3% (fin, 57% RRR) (5) incidence of BPH-related surgery: 10% (PL), 5% (fin, 55% RRR) (6) AE: DL: PL (2.6%), Fin (2.6%), PS only in year 1 ED: PL (5.1%), Fin (5.1%), PS only in year 1 Ej dys: PL (0.5%), Fin (1.5%), PS only in year 1 Gyne: PL (1.1%), Fin (1.8%), PS only in year 1
ARIA 3001-3003:[20] Protocol: Dut 0.5 mg vs PL Length: 2 years No. of men: 4325	IC: Age > 50 years PSA 1.5 - 10 ng ml^{-1} BPH on DRE PV $\geqslant 30$ cm^3 by TRUS (AUA-SI > 11) $Q_{max} < 16$ ml s^{-1} with VV $\geqslant 125$ cm^3 BD: Age 66 years AUA-SI 17 Q_{max} 10.1 - 10.4 ml s^{-1} Serum PSA 4 ng ml^{-1} TPV 54 - 55 cm^3 TZV 26.8 cm^3	(1) change in AUA-SI: −2.3 points (PL), −4.5 points (Dut) (2) change in Q_{max}: 0.6 ml s^{-1} (PL), 2.2 ml s^{-1} (Dut) (3) change in TPV: 1.7% (PL),−25.7% (Dut) (4) change in TZV: 12.4% (PL), −20.4% (Dut) (5) incidence of AUR: 4.2% (PL), 1.8% (Dut, 57% RRR) (6) incidence of BPH-related surgery: 4.1% (PL), 2.2% (Dut, 48% RRR) (7) change in PSA: 15.8% (PL), −52.4% (Dut) (8) AE: at study end DL: 2.1% (PL), 4.2% (Dut), PS only in year 1 ED: 4% (PL), 7.3% (Dut), PS only in year 1 Ej dys:0.8% (PL), 2.2% (Dut), PS only in year 1 Gyne: 0.7% (PL), 2.3% (Dut), PS y1, y2
Veterans Affairs Cooperative Studies BPH Study Group (VA study):[43] Protocol: Ter 10 mg vs Fin 5 mg vs com vs PL At study end, 80% of men in Ter group were on 10 mg Length: 1 year No. of men: 1229	IC: 45 - 80 years AUAI-S $\geqslant 8$ Q_{max} 4-15 ml s^{-1} with VV $\geqslant 125$ ml Mean PVR < 300 ml PSA < 10 ng ml^{-1} No threshold PV BD: 65 years PV 36-38 cm^3 (by TRUS) IPSS 16 Q_{max} 10.5 ml s^{-1} PSA 2.2-2.4 ng ml^{-1}	(1) change in AUA-SI: in points −2.6 (PL),−3.2 (Fin),−6.1 (Ter),−6.2 (com) Decline in IPSS reached nadir at 13 weeks in terazosin and combination groups (2) change in Q_{max}: in ml s^{-1} 1.4 (PL), 1.6 (Fin), 2.7 (Ter), 3.2 (com) Maximal change in Q_{max} reached at 4 weeks in terazosin and combination groups (3) AE: PS vs other groups Asthenia: Ter (14%), com (14%) Dizziness: Ter (26%), com (21%) hypoTN: Ter (8%), com (9%) DL: Fin (5%), com (5%) ED: Fin (9%), com (9%) Ej dys: com (7%)
The Prospective European Doxazosin and Combination Therapy Trial (PREDICT):[42] Protocol: Dox 8 mg vs Fin 5 mg vs Com vs PL Mean final Dox dose = 6.4, 6.1 mg in dox and com groups Length: 1 year No. of men: 1095	IC: 50 - 80 years IPSS > 11 Q_{max} 5 - 15 ml s^{-1} with VV $\geqslant 150$ ml Enlarged prostate (by DRE) PSA < 10 BD: 64 years IPSS 17 PV 36 cm^3 (by DRE) PSA 2.6 ng ml^{-1} Q_{max} 10.5 ml s^{-1}	(1) Change in IPSS: in points −5.7 (PL),−6.6 (Fin),−8.3 (Dox),−8.5 (com) (2) change in Q_{max}: in ml s^{-1} 1.4 (PL), 1.8 (Fin), 3.6 (Dox), 3.8 (com) (3) AE: PS vs other groups Asthenia: Dox (11%), Com (9%) Dizziness: Dox (16%), Com (14%) hypoTN: Dox (5%), com (3%) ED: com (11%) DL, Ej dys: PNS among all groups
Medical Therapy of Prostatic Symptoms Trial (MTOPS):[38] Protocol: Dox 8 mg vs Fin 5 mg vs Com vs PL Length: 4.5 years No. of men: 3047	IC: $\geqslant 50$ years AUA-SI $\geqslant 8$ - 30 Q_{max} 4 - 15 ml s^{-1} with VV $\geqslant 125$ ml PSA < 10 ng ml^{-1} BD: 63 years AUA-SI 17 PV 36 ml Q_{max} 10.5 ml s^{-1}	(1) Incidence of overall BPH progression: 17% (PL), 10% (Fin, RRR 34%, PS), 10% (Dox, RRR 39%, PS), 5% (com, RRR 66%, PS against placebo and monotherapy) (2) LUTS deterioration $\geqslant 4$ points: (RRR vs placebo), all PS: 45% (Dox), 30% (Fin), 64% (com) (3) AUR: (RRR vs placebo) 38% (Dox, PNS), 64% (Fin, PS), 81% (com, PS) (4) BPH-related surgery: (RRR vs placebo): 26% (Dox, PNS), 64% (Fin, PS), 67% (com, PS)

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Table 1. (Continued)

	IC and BD	*Results*
	PSA 2.4 ng ml^{-1} PVR 68 ml	(5) LUTS improvement: in points −4.9 in PL, −5.6 in Fin (PS vs PL), −6.6 in Dox (PS vs Fin, PL), −7.4 in com (PS vs all 3 groups) (6) Q_{max} improvement: in ml/s, all PS vs PL: 1.4 (PL), 2.2 (Fin), 2.5 (Dox), 3.7 (com, PS vs all 3 groups) (7) main AE: Asthenia, dizziness, hypoTN: Dox, com ED, DL, ej dys: Fin, com Peripheral edema, dyspnea: com
The Combination of Avodart and Tamsulosin Study (COMBAT):[41] Protocol: Tam 0.4 mg vs Dut 0.5 mg vs Com Length: 4 years No. of men: 4844	IC: ⩾50 years IPSS >11 PV⩾30 ml (by TRUS), PSA 1.5-10 ng ml^{-1} Q_{max} 5-15 ml s^{-1}, with VV ⩾125 ml BD: 66 years IPSS 16.5 PV 49 ml PSA 4 ng ml^{-1} PVR 68 ml	All comparisons favor combination therapy vs either drug monotherapy (1) BPH progression: Com vs Tam: 44% more RR (PS) Com vs Dut: 31% more RR (PS) (2) LUTS deterioration ⩾4 points: Com vs Tam: 41% more RR (PS) Com vs Dut: 35% more RR (PS) (3) incidence of AUR: Com vs Dut: 68% more RR (PS) Com vs Tam: 18% more RR (PNS) (4) incidence of BPH-related surgery: Com vs Tam: 71% more RR (PS) Com vs Dut: 31% more RR (PNS) (5) improvement in LUTS: in points −3.8 (Tam), −5.3 (Dut), −6.3 (com, PS vs either monotherapy) (6) improvement in Q_{max}: in ml s^{-1} 0.7 (Tam), 2 (Dut), 2.4 (com, PS vs either monotherapy) (7) AE: More pts withdrew in tam (39%) vs Dut (33%) and comb (31%) due to lack of efficacy DL, ED, ej dys: mainly in comb (4-9%) Dizziness: mainly in tam, comb (2%) Gyne, breast tenderness: mainly in Dut, com (2%, 1%)
Enlarged Prostate International Comparator Study (EPICS):[22] Protocol: Dut 0.5 mg vs Fin 5 mg Length: 1 year No. of men: 1630	IC: Same as ARIA BD: Age 67 years AUA-SI 17 Q_{max} 10 ml s^{-1} PVR 68 ml PSA 4.3 ng ml^{-1} PV 52-54 m	(1) change in PV: −26.3%, Dut (22.6% if PV<40, 27.6% if PV⩾40 cm^3) −26.7%, Fin (24.2% if PV<40, 27.7% if PV⩾40 cm^3) (2) change in AUA-SI: in points −5.8 (Dut), −5.5 (Fin) (3) change in Q_{max}: in ml s^{-1} 2 (Dut), 1.7 (Fin)4) change in PSA: −49.5% (Dut),−47.7% (Fin)5) AE: ED (9% Fin, 8% Dut) DL (6% Fin, 5% Dut) Ej dys (2% each) Gyne (1% each)

Abbreviations: AUA, American Urological Association; AUR, acute urine retention; BD, baseline demographic information; com, combination of alpha blocker and 5α-R inhibitor; DL, decreased libido; DRE, digital rectal examinations; dox, doxazosin; ED, erectile dysfunction; ej dys, ejaculatory dysfunction; fin, finasteride; Gyne, gynecomastia; hypoTN, hypotension; IC, inclusion criteria; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; PL, placebo; PNS, $P>0.05$; PS, $P<0.05$; PV, prostate volume (ml); PVR, post void residue (ml); q-AUASS, quasi AUA symptom score; RRR, relative risk reduction; tam, tamsulosin; ter, terazosin; TPV, total prostate volume; TRUS, transrectal ultrasonography; TZV, transitional zone volume; VV, voided volume (ml).

Surgery for BPH-related hematuria was required in 26%. BPH-related hematuria recurred in only 14% of patients on finasteride (mild in 75%) and none required surgery for BPH-related hematuria. BPH-related hematuria resolved in all patients on finasteride within 4 weeks.[64] In a retrospective chart review on 53 patients with BPH-related hematuria, the severity of hematuria improved in 94% of patients and 77% of patients experienced no recurrence while on finasteride. Time to resolution of BPH-related hematuria correlated with prostate size, ranging from 2.7 days for prostates <40 g, to ⩾45 days for prostates >150 g. Patients on Coumadin or aspirin experienced a similar degree of improvement in BPH-related hematuria as patients not on anticoagulants. Patients with a history of TURP benefited more than patients without such a history, as BPH-related hematuria resolved faster (5.5 vs 18.6 days) and recurrence was less (16% vs 32%). Mean follow-up was 38 months.[65]

Another potential use of 5ARI is to decrease intraoperative blood loss in patients with BPH undergoing prostate resection. Out of four prospective, randomized, placebo-controlled trials, two trials of dutasteride 0.5 mg per day for 2–4 weeks prior to TURP and another of finasteride 5 mg per day for 3 months prior to TURP found no significant difference in intraoperative blood loss between treatment and placebo groups.[66-68] The only prospective, randomized, placebo-controlled study to show a significant reduction in intraoperative blood loss was reported with 2 weeks finasteride 5 mg per day prior to TURP.[69] However, blood loss in the placebo group was unusually high (4.65 g of hemoglobin per gram prostatic tissue resected (g Hg per g)). A series of up to 700 patients undergoing TURP reported blood loss of 2.3 g Hg per g.[70] Other prospective studies of 5ARI use to decrease intraoperative bleeding in TURP patients had contradictory results and methodological issues.[71-73]

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Table 2. Levels of evidence and guideline statement grading

EAU	*AUA*
1a: Evidence obtained from meta-analysis of randomized trials	1. Standard: A guideline statement is a standard if: (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions and (2) there is virtual unanimity about which intervention is preferred.
1b: Evidence obtained from at least one randomized trial	2. Recommendation: A guideline statement is a recommendation if: (1) the health outcomes of the alternative intervention are sufficiently well known to permit meaningful decisions, and (2) an appreciable but not unanimous majority agrees on which intervention is preferred.
2a: Evidence obtained from one well-designed controlled study without randomization	3. Option: A guideline statement is an option if: (1) the health outcomes of the interventions are not sufficiently well known to permit meaningful decisions, or (2) preferences are unknown or equivocal. Options can exist because of insufficient evidence or because patient preferences are divided and may/should influence choices made.
2b: Evidence obtained from at least one other type of well-designed quasi-experimental study	
3: Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports	
4: Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities	

Abbreviations: AUA, American Urological Association; EAU, European Association of Urology.

Table 3. EAU and AUA guidelines on 5ARI use in BPH

Guidelines

EAU 2011

1. 5ARI use should only be considered in men with LUTS and an enlarged prostate (>30–40 ml). However; due to the slow onset of action, 5ARI are only suitable for long-term treatment (LE 1b).
2. Combination therapy with A1B and 5ARI is superior to either drug alone in reducing LUTS and preventing BPH-progression, at the expense of more AE. Therefore, combination therapy should be offered to men with moderate-severe LUTS who are at high-risk of BPH progression (LE 1b).
3. Discontinuation of the A1B after 6 months might be considered in men with moderate LUTS (LE 1b).
4. Finasteride can be used to reduce intraoperative blood loss during TURP (LE 1b).

AUA 2010

1. 5ARI are a reasonable preventive measure against BPH-clinical progression in men with LUTS due benign prostatic enlargement (>25–40 ml) (optional).
2. 5ARI are an appropriate treatment alternative in men with LUTS due benign prostatic enlargement (>25–40 ml) (optional).
3. 5ARIs should not be used in men with LUTS secondary to BPH without prostatic enlargement (recommendation).
4. Combination therapy is considered an appropriate treatment for patients with LUTS associated with demonstrable prostatic enlargement (>25–40 ml) (optional).
5. Finasteride is an effective treatment alternative in men with refractory hematuria, presumably due to prostatic bleeding (after exclusion of other causes of hematuria) (optional). A similar LE is lacking for dutasteride; however, the AUA expert panel believes that dutasteride functions in a similar fashion to finasteride in treatment of prostatic bleeding.
6. Evidence is insufficient to recommend use of 5ARI preoperatively to decrease intraoperative blood loss and the need for blood transfusions during or after TURP.

Abbreviations: AE, adverse effects; 5ARI, 5α-reductase inhibitor; AUA, American Urological Association; A1B, alpha-1 adrenergic blockers; EAU, European Association of Urology; LE, level of evidence; LUTS, lower urinary tract symptoms.

One study suggested a benefit of finasteride in decreasing blood transfusions and clot retention after TURP in those with >30 g of resected prostate tissue,[74] and another suggested less intraoperative blood loss in those with >18.6 g of resected prostate tissue.[68] These findings require confirmation in larger studies.

II. Prostatitis

Prostatitis is a common condition, with an estimated prevalence of 5–9% for men of age ⩾18 years.[75] Prostatitis accounts for nearly 2 million ambulatory care encounters annually in the US. Prostatitis represents a heterogeneous mix of conditions, and has been classified traditionally into acute and chronic bacterial prostatitis, nonbacterial prostatitis and prostatodynia. However, the reference standard classification system for prostatitis is the NIH-CPSI (National Institute of Health chronic prostatitis symptom index) that categorizes prostatitis into four categories, with category III CP/CPPS (formerly nonbacterial prostatitis) being the most common (90–95% of cases).[76] CP/CPPS, is defined as urological pain or discomfort in the pelvic region, associated with urinary symptoms and/or sexual dysfunction, lasting for at least 3 of the previous 6 months. CP/CPPS is a diagnosis of exclusion that can be made after ruling out urinary tract infection, urogenital cancer, urethral stricture, or neurological disease affecting the lower urinary tract. CP/CPPS can diminish quality of life and impair physical and psychological function. The etiology of CP/CPPS is uncertain but may include inflammatory (category IIIA) or noninflammatory (category IIIB) etiologies. An inciting agent may cause inflammation or neurological damage in or around the prostate and lead to pelvic floor neuromuscular and/or neuropathic pain. Predisposing factors for CP/CPPS may include heredity, infection, voiding abnormalities, hormone imbalance, intraprostatic urine reflux, immunological or allergic triggers and psychological traits. A wide variety of therapies including A1B, antibiotics and anti-inflammatory medications are used routinely.[77]

As prostate growth and function are influenced by androgens, 5ARI theoretically could be beneficial in treatment for CP/CPPS. 5ARI cause regression of prostatic epithelium (where inflammation is believed to start), improve voiding parameters (especially in men with BPH and prostatitis) and potentially reduce intraprostatic ductal reflux and pressure.[78] Additionally, 5ARI suppress angiogenesis, decrease prostatic blood flow and therefore, could decrease inflammation.

A small case series reported clinically significant symptom improvement after 6 week–3 month treatment with finasteride 5 mg per day in four patients with CP/CPPS.[79] Leskinen *et al.*[80]

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(1999) randomized 41 patients (1:3) with CP/CPPS to placebo or finasteride for 1 year. Finasteride significantly reduced pain, assessed by visual analogue scale, and other symptoms of prostatitis, assessed by the Prostatitis Symptom Severity Index and IPSS, compared with baseline. No statistically significant differences were noted in the placebo group in pain score, Prostatitis Symptom Severity Index and IPSS compared with baseline. However, the baseline characteristics of the two groups were not comparable, and the enrolled patients consisted of an unknown mixed population with inflammatory and noninflammatory prostatitis. Kaplan *et al*.[81] randomized 64 men with CP/CPPS to finasteride 5 mg per day or saw palmetto for 12 months. At 3 months, significant improvements (compared with baseline) were noted in the overall NIH-CPSI, pain domain, quality of life domain and question 4 of the pain domain scores in both groups. However, these improvements persisted only in the finasteride group after 12 months. No significant effect on the urination domain score was noted in either group. This trial is difficult to interpret because of the lack of a placebo arm. A double-blinded controlled trial compared the reduction of NIH-CPSI in 64 men with inflammatory CP/CPPS (category IIIA) who were randomized to finasteride 5 mg per day or placebo for 6 months. Finasteride resulted in a numerically larger but statistically insignificant reduction in symptoms compared with placebo. The study concluded that finasteride cannot be recommended as monotherapy for CP/CPPS except perhaps in men with associated BPH.[82] In 2005, an International committee of experts in prostatic diseases reviewed the evidence on the management of CP/CPPS and didn't recommend finasteride as a therapeutic option.[83] To our knowledge, no clinical trials of dutasteride for treatment of symptomatic prostatitis have been conducted.

The EAU guidelines list finasteride as an acceptable treatment for category IIIA prostatitis, (http://www.uroweb.org/gls/pdf/15_Urological_Infections.pdf) despite the lack of statistical significance in the trial on which the recommendation was based.

CONCLUSIONS

Treatment of BPH-induced LUTS and prevention of BPH progression

BPH-clinical progression includes LUTS deterioration, AUR and BPH-related surgery. Risk factors for BPH-clinical progression include older age, enlarged prostates ($>30-40$ ml), higher PSA ($\geqslant 1.5$ ng ml^{-1}), lower Q_{max}, larger post-void residual urine volume, and severe LUTS. Whether the goal is to treat BPH-induced LUTS or to prevent BPH-clinical progression, available evidence suggests that 5ARI are beneficial only in men with enlarged prostates ($>30-40$ ml), whereas A1B are useful in all patients regardless of PV. A1B are more effective than 5ARI in treatment of BPH-induced LUTS in those with PV <50 ml. 5ARI are more effective than A1B in decreasing the risks of progression to AUR- or BPH-related surgery. A1B are more effective than 5ARI in preventing LUTS deterioration in those with PV <50 ml. At $\geqslant 50$ ml prostates, 5ARI are more effective than and as effective as A1B in treatment of LUTS, and prevention of LUTS deterioration, respectively. The onset of action of A1B starts within hours, whereas 5ARI require months for full effect. Therefore; combination therapy is appropriate in men with enlarged prostates and is the most effective treatment/prevention for BPH-induced LUTS and BPH-clinical progression, respectively.

Treatment of BPH-related hematuria and prevention of perioperative bleeding in those undergoing TURP

5ARI decrease the frequency, severity and recurrence of BPH-related hematuria. 5ARI could be valuable in men suffering from refractory prostatic bleeding (after all other causes of hematuria are excluded) and in those who are poor surgical candidates. Evidence is insufficient to justify 5ARI use in the perioperative setting of TURP and is not recommended.

Treatment of prostatitis

5ARI are not recommended for CP/CPPS treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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