5-Alpha-Reductase Inhibitors and Combination Therapy

Claudius Füllhase, MD, PhD[a,*], Marc P. Schneider, MD[b]

KEYWORDS

• 5-Alpha-reductase inhibitors • Finasteride • Dutasteride • Combination drug therapy
• Prostatic hyperplasia • Lower urinary tract symptoms

KEY POINTS

- In men suffering from benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS), 5-alpha reductase inhibitors (5ARIs) are a treatment option when prostate size is greater than 30 to 40 mL and medical treatment is intended for longer than 1 year.
- In the same patients, combination of 5ARIs with alpha-adrenergic-blockers (ABs) is a better option in regard to symptomatic improvement and reduction of disease progression if they are suitable for potential AB-related side effects.
- Potential sexual side effects of 5ARIs and 5ARI/AB combinations might be an individual exclusion criterion and should be openly discussed with each patient.
- 5ARIs are not recommended for the prevention of BPH/LUTS or prostate cancer (PCa). Patients with BPH/LUTS undergoing 5ARI therapy should be routinely screened for PCa, at which time the serum prostate-specific antigen level should be doubled.
- Combination of phosphodiesterase type 5 inhibitors with 5ARIs might be the best medical treatment option for some patients; however, more clinical evidence is needed.

INTRODUCTION

5-Alpha-reductases (5ARs) are enzymes converting testosterone into dihydrotestosterone (DHT).[1] DHT is the most important hormone for the development and function of male sex organs.[2] Genetic defects of 5ARs can result in pseudohermaphroditism, meaning a female phenotype despite the presence of XY genotype.[3] In 1940, Charles Huggins first reported the relationship between testosterone and benign prostatic hyperplasia (BPH) development.[4] In the 1970s, the crucial role of 5AR-depending testosterone to DHT transformation in BPH development became apparent by the seminal works of Jean Wilson.[5,6] Realizing the therapeutic potential of DHT regulation resulted in a quest for an 5AR-inhibitor (5ARI), which ended in 1992 with the approval of finasteride (FIN; Proscar) by the US Food and Drug Administration (FDA).[7] In 2002, the FDA approved dutasteride (DUT; Avodart) as another 5ARI.[7] According to current guidelines, both 5ARIs can be used in the treatment of BPH with lower urinary tract symptoms (LUTS), either alone or in combination with other drugs targeting BPH/LUTS.[8,9]

5-ALPHA-REDUCTASE INHIBITOR MONOTHERAPY

Finasteride

After several animal experiments, MK-906 (which later became FIN) was successfully tested for

Disclosures: Nothing to disclose.
[a] Department of Urology, University of Rostock, Ernst-Heydemann-Str. 6, Rostock 18057, Germany; [b] Department of Health Science and Technology, Swiss Federal Institute of Technology Zurich, Brain Research Institute, University of Zurich, Winterthurerstrasse 190, Zürich 8057, Switzerland
* Corresponding author.
E-mail address: Claudius.fuellhase@uni-rostock.de

Urol Clin N Am 43 (2016) 325–336
http://dx.doi.org/10.1016/j.ucl.2016.04.003

safety, tolerability, and biochemical activity in 350 volunteers.[10] In healthy men, MK-906 reduced serum DHT levels by −62% to −82% without affecting serum testosterone levels.[11,12] Intraprostatic DHT levels were reduced by −92% in men awaiting prostate surgery.[13]

In a phase III clinical trial, 895 men with BPH received either placebo (PBO) or FIN 1 to 5 mg for 1 year.[14] The Boyarski score (a precursor of the American Urological Association symptom score [AUA-SS] or the international prostate symptom score [IPSS]) was significantly reduced by −2.7 with 5 mg FIN compared with no changes with PBO and 1 mg FIN.[14] The urinary flow rate (Q_{max}) significantly increased from 5.6 to 6.4 mL/s with 5 mg FIN and from 5.3 to 6.1 mL/s with 1 mg FIN but remained at baseline with PBO (5.6 and 5.8 mL/s).[14] Prostate size was reduced by −19% compared with baseline with 5 mg FIN, by −18% with 1 mg FIN, and insignificantly by −3% with PBO.[14] In an open-label extension 186 men continued to take 5 mg FIN for 4 more years.[15] Prostate volume reached a nadir at 24 months (−24% of initial size) and was maintained for the rest of the study. Similarly the symptom score improvement of −4.3 points and the increase of Q_{max} by 2.3 mL/s were maintained for 4 years.[15]

In another trial, 3040 men with BPH received either FIN 5 mg or PBO for 4 years.[16] AUA-SS was reduced by −3.3 with FIN and by −1.3 with PBO. Prostate volume was reduced by −18% with FIN and increased by 14% with PBO. Q_{max} improved by 1.9 mL/s with FIN and remained at 0.2 mL/s with PBO.[16] However, the most remarkable findings were a −57% risk reduction of acute urinary retention (AUR) and a −55% risk reduction to undergo prostate surgery when taking FIN.[16] This effect was confirmed and sustained in an open-label extension, in which 908 subjects took part for another 2 years.[17] Subjects who switched from PBO to FIN during extension showed at study end the same AUR reduction and prostate surgery incidence as the continuous FIN arm.[17]

Various other clinical trials compared FIN 5 mg versus PBO and reported similar outcomes, which means a reduction of prostate size by −15% to −21%, an IPSS (or similar score) reduction by −13% to −38%, and an increase of Q_{max} by 1.6 to 2.2 mL/s.[18–22] In all studies, these effects were measurable after 6 to 12 months. Meta-analysis revealed that the difference in improvement between FIN and PBO becomes significant when the prostate volume is greater than 40 mL at baseline.[23] According to a Cochrane systematic database review, the symptomatic improvements of FIN occur distinctly later than the effects of alpha-blockers (ABs).[24] However, when taken longer than 1 year, FIN reduces BPH progression and the risk to undergo prostate surgery, which is not an effect of ABs.[24]

Summing up all evidence, and according to current guideline recommendations, FIN monotherapy is a treatment option in men with moderate to severe LUTS and an enlarged prostate (>40 mL).[8,9] FIN should not be used in men with LUTS without prostatic enlargement.[8] Furthermore, FIN can be used to prevent disease progression in regard to AUR and the need for surgery.[8,9] Due to the low onset of action, FIN is only suitable for long-term treatment.[9]

Dutasteride

In a study, 4325 men with clinical BPH received either DUT 0.5 mg or PBO over a 2 year period. At study end, serum DHT was reduced by −92%, prostate size by −25%, AUA SS by −4.5 points, and Q_{max} was increased by 2.2 mL/s with DUT.[25] Risk reduction for AUR was −57%, and −48% for prostatic surgery compared with PBO.[25] In an open-label extension, 1570 subjects were enrolled. After 2 more years, prostate size was reduced by −26%, AUA-SS by −6.1, and Q_{max} increased by 2.8 mL/s with DUT.[26] The values for subjects, who switched from PBO to DUT were −20% prostate size, −5.3 AUA-SS, and +1.8 mL/s Q_{max}.[26] The effects of DUT were faster and more pronounced the greater the prostate volume was at baseline.[27] In a post hoc analysis of the Reduction by DUT of Prostate Cancer Events (REDUCE) study, 1617 men with a prostate greater than 40 mL were evaluated.[28] Clinical progression, as defined by either AUR, need for prostatic surgery, or symptom deterioration defined by an IPSS increase greater than 4, occurred in 36% of PBO and 21% of DUT subjects, translating into an absolute risk reduction by −15% and a relative risk reduction of −41%.[28]

Whereas FIN inhibits the 5AR isoform type II, DUT inhibits 5AR isoform type I and type II; therefore it is called a dual inhibitor. Post hoc analysis suggests that the effects of DUT, in contrast to FIN, are also significant in subjects with a prostate size between 30 to 40 mL.[29] However, different inclusion criteria in the clinical trials evaluating FIN and DUT make it difficult to directly compare these 5ARIs. The Enlarged Prostate International Comparator Study (EPICS) was designed to evaluate differences between DUT and FIN.[30] In this trial, 1630 men with BPH received either DUT 0.5 mg or FIN 5 mg for 1 year. There were no significant differences in regard to prostate size, AUA-SS reduction, Q_{max} improvement, or the timely onset of their effects.[30] Hence, the