Journal of Steroid Biochemistry & Molecular Biology 125 (2011) 32–38

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

Steroid 5 α-reductase inhibitors targeting BPH and prostate cancer

Lucy J. Schmidt[a], Donald J. Tindall[a,b,*]

[a] Department of Urology Research, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN 55905, United States
[b] Department of Biochemistry and Molecular Biology, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN 55905, United States

ARTICLE INFO

Article history:
Received 9 June 2010
Received in revised form
14 September 2010
Accepted 21 September 2010

Keywords:
5 Alpha-reductase inhibition
Prostate disease
Chemoprevention

ABSTRACT

Steroid 5 alpha-reductase inhibitors (5ARIs) have been approved for use clinically in treatment of benign prostate hyperplasia (BPH) and accompanying lower urinary tract symptoms (LUTS) and have also been evaluated in clinical trials for prevention and treatment of prostate cancer. There are currently two steroidal inhibitors in use, finasteride and dutasteride, both with distinct pharmacokinetic properties. This review will examine the evidence presented by various studies supporting the use of these steroidal inhibitors in the prevention and treatment of prostate disease.

Article from the Special issue on Targeted Inhibitors.

Contents

1. Introduction

In the prostate, androgens play a crucial role in normal, BPH and cancerous growth by acting through the androgen receptor (AR), a member of the steroid nuclear receptor superfamily. The natural ligand for the AR is testosterone (T), which is produced by the testes (95%) and adrenal glands (5%) and enters prostate epithelial cells by passive diffusion. Once ligand is bound to cytoplasmic AR, the receptor undergoes homodimerization resulting in a conformational change and is translocated to the nucleus. In the nucleus, AR acts by binding to specific recognition sequences, called androgen response elements (AREs), located in or near androgen-regulated genes and thereby directs transcription of genes necessary for growth and maintenance of the prostate [1]. Consequently, the androgenic pathway has become a target of therapeutic intervention in both benign and cancerous diseases [2]. In the prostate, T is converted to the more potent ligand dihydrotestosterone (DHT) by steroid 5 alpha-reductase (5AR) isoenzymes. There are three 5AR isoenzymes in prostate tissue; 5AR Types 1 and 2 (5AR-1 and 5AR-2) are found in normal, BPH and cancerous tissue, with distribution patterns specific to each tissue type [3]. 5AR Type 3 (5AR-3) has recently been detected and described in hormone refractory prostate cancer (HRPC) and is ubiquitous in mammals, being found also in non-androgenic tissues such pancreas and brain [4]. One group, however, has identified 5AR-3 as a polyprenol reductase involved in N-linked protein glycosylation [5], as opposed to it being classified as a 5 alpha-reductase. While both T and DHT bind to the AR, DHT binds the receptor with approximately 2–10 times greater affinity, dissociates from the receptor much more slowly and results in an AR conformation that is much more resistant to degradation [6]. High levels of 5AR enzymatic activity result in large amounts of the more potent ligand available to drive prostate growth, thus inhibition of 5AR activity is a valuable tool in reducing proliferation. Table 1A lists

* Corresponding author at: Department of Urology Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Tel.: +1 507 284 8139; fax: +1 507 284 2384.
E-mail address: tindall.donald@mayo.edu (D.J. Tindall).

0960-0760/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jsbmb.2010.09.003

Table 1A
Properties of 5AR isoenzymes[a].

Properties	5AR-1	5AR-2
Size	259 amino acids	254 amino acids
Molecular weight	29.5 kDa	28.4 kDa
Optimal pH	6–8.5	5–5.5
Biochemical state	Hydrophobic	Hydrophobic
Tissue distribution	Liver, skin, brain, ovary, prostate, testis	Prostate, epididymis, seminal vesicle, genital skin, uterus, breast, hair follicle, placenta, testis
Expression in prostate	Normal (low), high in BPH and cancer	Normal and BPH (high), low in cancer
Gene name	SRD5A1	SRD5A2
Chromosome location	5p15	2p23

[a] Data for table obtained from Refs. [10] and [8].

biochemical properties and characteristics of 5AR-1 and -2 isoenzymes.

2. 5ARIs in clinical use

5AR (3-oxo-steroid-4-ene dehydrogenase {E.C. 1.3.99.5}) isoenzymes are membrane-bound microsomal proteins that act by reducing the double bond at the 4–5 position of a number of C_{19} and C_{21} steroids, such as T. They catalyze the NADPH-dependent reduction of T to yield the more potent hormone DHT [7]. Various compounds have been developed in an effort to block this conversion and inhibit the effects of DHT in prostate disease. Neither isoenzyme has been purified due to its unstable nature, so isoenzyme inhibitors have been designed by targeting their substrates. Azasteroids are chemically altered steroids that have been produced by substituting a nitrogen atom for one of the carbons at different positions in the ring; a number of these compounds have been found to inhibit 5AR activity [8]. Finasteride (chemical name 4-azaandrost-1-ene-17-carboxamide, N-(1,1-dimethylethyl)-3-oxo, (5(alpha)), 17(beta))-) and dutasteride (chemical name (5α, 17β)-N {2,5,bis(trifluoromethyl) phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide) belong to a group of compounds designated as 17β-substituted-4-azasteroids, one of the most extensively studied classes of steroidal 5AR inhibitors[8]. Both drugs display characteristics of competitive inhibitors in short-term kinetic experiments, but analysis of long-term reactions reveals they are irreversible inhibitors due to formation of very stable enzyme-bound intermediates. Interactions between 4-azasteroids and 5AR isoenzymes are best described by the two-step mechanism:

$$E + I \underset{}{\overset{K_i}{\rightleftharpoons}} EI \xrightarrow{k_3} EI^*$$

with K_i as the inhibition constant for the first step equilibrium (reached rapidly) and k_3 the rate constant for the second, time-dependent step (reached more slowly) [9,10].

Finasteride has been shown to be a mechanism-based inhibitor of 5AR-2 [9]. Finasteride acts as an alternate substrate for 5AR-2 and is initially bound in an extremely stable enzyme-bound NADP-dihydrofinasteride adduct which is ultimately processed to dihydrofinasteride. The NADP-dihydrofinasteride adduct is a potent bisubstrate analog inhibitor with a dissociation constant $K_i \leq 1 \times 10^{-13}$ M, making it one of the most potent non-covalently bound inhibitors known. Finasteride is also an inhibitor of 5AR-1, but the dihydrofinasteride adduct is formed with a much smaller rate constant compared to 5AR-2 (Table 1B). Finasteride was the first steroidal 5ARI approved by the US Food and Drug Administration (USFDA) in 1992 for treatment of BPH. It reduces the levels of plasma DHT by 70–90%, thereby reducing prostate size [8,11].

Table 1B
Inhibition of 5AR isoenzymes by steroidal drugs[a].

	k_3 (s^{-1})	K_i (IC_{50}, nM)	k_3/K_i ($M^{-1}\ s^{-1}$)
5AR-1			
Finasteride inhibition	1.4×10^{-3}	360	4×10^3
Dutasteride inhibition	1.1×10^{-3}	6	1.8×10^5
5AR-2			
Finasteride inhibition	2.2×10^{-2}	69	3.2×10^5
Dutasteride inhibition	4.9×10^{-3}	7	6.8×10^5

[a] Data for table obtained from Refs. [10] and [8].

Dutasteride is a specific dual inhibitor of 5AR. Enzymology studies indicate it is a potent irreversible competitive inhibitor of both human 5AR-1 and -2 [10,12]. Dutasteride forms a stable complex with both isoenzymes which has a slow rate of dissociation (Table 1B). Dutasteride is approximately 60 times more potent than finasteride and was approved in 2002 by the USFDA for use in treatment of BPH. Dutasteride reduces DHT levels by >90% after 1 year of oral administration, resulting in a smaller prostate volume [8].

Finasteride and dutasteride are the only two steroidal drugs in use clinically, although there are others, such as epristeride, currently in clinical trials. As summarized in Tables 1A and 1B, finasteride and dutasteride have distinct properties which may suggest their optimal use in treating prostate disease, but it has not yet been determined whether there is a significant difference in clinical applications/outcomes between the two [13]. A number of non-steroidal 5ARIs have also been developed as mimics of steroidal inhibitors, but none have been brought to clinical use [8].

3. 5ARIs in the treatment of BPH

BPH is a progressive disease, with increasing prostate volume leading to increased LUTS resulting from pressure on the urethra and accompanying decreased urinary flow. BPH is prevalent among aging men and affects up to 90% of men by the age of 80 or older, making this a vital healthcare issue with associated economic implications [14]. Medical treatment is thus focused on relieving LUTS and avoiding disease progression which could eventually result in complications such as acute urinary retention (AUR) and/or surgery. Both 5AR-1 and -2 isoenzymes are significantly over-expressed in BPH tissue as compared to normal prostate tissue, with 5AR-2 being the predominant form [3]. Thus, initial treatment options currently available for men with BPH-LUTS are to use either a 5ARI, or an α_1-adrenoreceptor antagonist (alpha-blocker) such as doxazosin or tamsulosin, or a combination of the two. While finasteride is the most widely studied 5ARI, there have been a number of clinical studies demonstrating that both finasteride and dutasteride are effective in treating BPH-LUTS either as monotherapy or in combination with an alpha blocker.

In 1998 the Proscar Long-term Efficacy and Safety Study (PLESS) verified the effectiveness of finasteride treatment alone in a trial involving 3040 men treated with placebo or 5 mg finasteride daily for a period of four years [15]. Significant reductions in the number of men experiencing AUR or ultimately requiring surgery were apparent within 4 months. For men completing the study, total prostate volume (TPV) decreased and improved symptom scores were observed in the finasteride group.

Combined data from three large ARIA studies (ARIA 3001 and 3002 in the US, ARIA 3003 in 19 countries, with over 4000 men) [16], demonstrated the effectiveness of dutasteride in reducing prostate size and LUTS. Treatment with dutasteride reduced serum DHT by 90.2% at 24 months, followed by a rapid reduction in TPV. Dutasteride reduced the risk of AUR or eventual surgical intervention by 50% within two years. This study confirmed the hypothesis that using a dual 5ARI like dutasteride to achieve nearly complete suppression of serum DHT levels can halt the progression of BPH.

Table 2A
Selected 5ARI monotherapy trials in treatment of BPH-LUTS.

Trial	Agent	Report	Duration	Q_{max} (ml/s)	ΔTPV	ΔIPSS
PLESS (Proscar Long-term Efficacy and Safety Study)	Finasteride	1998 [11]	4 years $n = 3040$	1.9 vs 0.2 for placebo	−18% vs +14% for placebo	−3.4
ARIA3001, 3002, 3003 (pooled data)	Dutasteride	2002 [8]	2 years $n = 4325$	2.2 vs 0.6 for placebo	−25.7% relative to placebo	−2.2
EPICS (Enlarged Prostate International Comparator Study)	Dutasteride vs Finasteride	2005 [12]	1 year $n = 1630$	DU: 2.1* FN: 1.8*	−27.4% in both groups*	DU: −6.2* FN: −5.8*

* No significant difference between groups.

In an effort to determine if one 5ARI was more effective than the other, the Enlarged Prostate International Comparator Study (EPICS) [17] compared treatment with finasteride and dutasteride in 1630 men over the age of 50 and concluded that after one year of treatment, both groups had statistically similar reductions in prostate volume; improvements in the International Prostate Symptom Score (IPSS) were greater with dutasteride than finasteride, but were not statistically significant. A list of key randomized monotherapy trials and results are shown in Table 2A.

Effects of 5ARIs in symptomatic relief of BPH-LUTS are presumed to be a result of a reduction in prostate volume [18], so relief requires more time (up to several months) than with the faster acting alpha-blockers, which are thought to work by relaxing the smooth muscle in the prostate and bladder neck (working within 1–2 weeks) [14]. Therefore, an argument can be made for combination therapy, wherein an alpha-blocker provides rapid relief of symptoms and a 5ARI provides for a long-term reduction in prostate volume and lessens the risk of progression to AUR and/or surgery. A number of studies have examined the effectiveness of combination therapy.

The Prospective European Doxazosin and Combination Therapy (PREDICT) [14] and the Medical Therapy of Prostate Symptoms (MTOPS) [19] trials examined the efficacy of treatment with finasteride and alpha-blocker doxazosin either alone or in combination. In the one-year PREDICT trial it was initially determined that doxazosin alone was more effective in improving urinary symptoms than finasteride alone or a combination of the two. Further secondary analysis suggested that the addition of finasteride was more effective in men with larger (>40 cm^3) prostates, as found in the PLESS, but the PREDICT trial was not designed to take this parameter into account [14]. Analysis of the longer MTOPS trial concluded that finasteride alone or in combination with doxazosin consistently resulted in clinically significant TPV reduction regardless of baseline prostate size [19–21]. There is still some debate as to the value of using combination therapy and adding a 5ARI in patients with smaller prostates, as opposed to the use of an alpha-blocker alone.

The dual 5ARI dutasteride has also been studied in combination with an alpha-blocker. The Combination of Avodart® and Tamsulosin (CombAT) [22] study concluded that dutasteride alone or in combination with the alpha-blocker tamsulosin was significantly more effective than tamsulosin alone in reducing the risk of AUR or eventual surgery. Combination therapy significantly reduced the risk of clinical progression of BPH, but it should be noted that there was no placebo arm of this study due to ethical considerations.

In a meta-analysis of four studies using randomized controlled data and a total of 10,215 patients, it was determined that at a follow-up time of ≥4 years, combinational therapy with either 5ARI and an alpha-blocker was superior to monotherapy, notably in men with moderately enlarged prostates (starting at 25 ml) and significantly better in men with moderate (25–39 ml) or large prostates (≥40 ml) [23].

Taking another approach, the Symptom Management After Reducing Therapy (SMART) [24] trial demonstrated that dutasteride and tamsulosin can be used together for six months to obtain rapid relief of symptoms, after which time the alpha-blocker can be discontinued and relief maintained using only the 5ARI. Table 2B lists selected combination therapy trials. Overall, drug-related adverse events with treatment tended to be low in these studies with the most common being dizziness (alpha-blockers) and sexual dysfunction (5ARIs) [18].

Based on the current evidence presented in these numerous and various trials, the conclusion can be drawn that the use of 5ARIs, either as monotherapy or in combination with an alpha-blocker, is effective for the treatment of BPH-LUTS in preventing disease progression and the need for invasive surgery. Whether or not there is an additional benefit from the dual 5AR inhibition offered by dutasteride over finasteride or whether there is a difference in long-term adverse outcomes has not been determined [13].

4. 5ARIs in the prevention of prostate cancer

Prostate cancer continues to be a leading cause of male deaths worldwide. In 2009, it was estimated there would be 192,280 new cases of prostate cancer with a predicted 27,360 deaths [25]. Because androgens, and specifically DHT, play a large role in both normal and cancerous prostate growth, inhibition of the andro-

Table 2B
Selected 5ARI combination therapy trials in treatment of BPH-LUTS.

Trial	Agents	Report	Duration	Q_{max} (ml/s)	ΔTPV	ΔIPSS
PREDICT (Prospective European Doxazosin and Combination Therapy)	Finasteride Doxazosin	2003 [10]	1 year $n = 1095$	PL: 1.4* FN: 1.8* DX: 3.6† Comb: 3.8†	No data	PL: −5.7* FN: −6.6* DX: −8.3† Comb: −8.5†
MTOPS (Medical Therapy of Prostate Symptoms)	Finasteride Doxazosin	2003 [14] 2010 [13]	4.5 years $n = 3047$	PL: 2.8 FN: 3.2 DX: 4.0 Comb: 5.1	PL: +24 FN: −19% DX: +20% Comb: −19%	PL: −4.9 FN: −5.6 DX: −6.6 Comb: −7.4
CombAT (Combination of Dutasteride and Tamsulosin)	Dutasteride Tamsulosin	2009 [17]	4 years $n = 4844$	DU: 2.0 TM: 0.7 Comb: 2.4	DU: −28% TM: +4.6% Comb: −27%	DU: −6.4 TM: −4.9 Comb: −7.3

* No significant difference between groups.
† No significant difference between groups.

genic pathway has been explored as an option in prostate cancer prevention. Further enabling this type of approach was the development of 5ARIs, with their much lower risk of the adverse side effects previously associated with androgen-deprivation therapy.

In the landmark Prostate Cancer Prevention Trial (PCPT) [26], the hypothesis was tested that the 5AR-2 inhibitor finasteride could reduce the risk of prostate cancer. The PCPT was a double-blind, randomized, placebo-controlled Phase III study involving 18,882 men with a low risk of developing prostate cancer based on a PSA level of $\leq$3.0 ng/ml and a normal digital rectal exam (DRE). Men received placebo or 5 mg finasteride daily for a period of seven years. PSA levels were measured and DREs were performed annually. To address concerns about potential study bias toward the finasteride or placebo group during the course of the study, an end-of-study biopsy was performed on all participants. The primary endpoint of the PCPT was the development of prostate cancer, either during the study or at the seven-year endpoint biopsy.

In the PCPT it was found that 18.4% of men in the finasteride group developed prostate cancer as opposed to 24.4% in the placebo group [27]; this was statistically significant ($P < 0.001$). Medical events and side effects were more common in the finasteride group, while LUTS, such as urinary retention, frequency, and urinary tract infection, were more common in the placebo group. Of concern, more high-grade tumors (Gleason score 7–10) were found in the finasteride group as compared to the placebo group (6.4% and 5.1%, respectively $P = 0.005$). Much debate has resulted with regards to interpretation of these data and whether finasteride treatment results in a higher incidence of high-grade prostate cancer [28]. Since the completion of the study, numerous groups have extensively examined the data and have identified potential for biases that could account for this apparent increase in high-grade tumors [29–32]. Some of these are: increased sensitivity of PSA and DREs in diagnosing cancer in the finasteride group, smaller prostate volume in the finasteride group resulting in an increased chance of detection of high-grade cancers, and the possibility that finasteride inhibits growth of low-grade cancers better than high-grade, leading to an increase in the latter. Both 5AR-1 and 5AR-2 are expressed at higher levels in localized high-grade cancers [33], which might help to explain the inability of finasteride to inhibit growth of these cancers. Additionally, there is some evidence that men with low testosterone levels, as could be achieved with 5AR inhibition, develop higher grade tumors [34]. Taken together, it has been proposed that these factors combine to level the differences between the placebo and finasteride group with respect to development of high-grade prostate tumors [35,36] and there is no associated risk of developing high-grade cancer with finasteride therapy.

Since 5AR-1 expression is increased in prostate cancer, dutasteride, which inhibits 5AR-1 in addition to 5AR-2, might be expected to deliver a better outcome than that with finasteride. To examine this, another large Phase III trial, the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial [37,38], tested the dual 5ARI dutasteride in much the same way that finasteride was used in the PCPT, but with some notable differences in study design [38].

The REDUCE trial was an international, multi-center, double-blind, randomized, placebo-controlled study designed to study the ability of dutasteride to prevent prostate cancer development in men with a *high* risk of prostate cancer. To be enrolled in the study, men needed to be between 50 and 75 years old, have a serum PSA of 2.5–10 ng/ml and needed to have a negative 6–12 core biopsy within six months of enrollment. Whereas the PCPT assumed absence of prostate cancer in participants based on clinical data such as PSA, the REDUCE trial required a negative biopsy at enrollment to exclude any men already having prostate cancer. Over 8000 subjects were randomized to receive placebo or 0.5 mg dutasteride daily and were evaluated every six months for IPSS and PSA (free and total). TPV was measured by ultrasound at baseline and 2 and 4 years, with 10 core biopsies also performed at the 2 and 4-year periods. The primary endpoint of this study, as with the PCPT, was biopsy detectable prostate cancer at 2 and 4 years after treatment. To gain further insights, several secondary endpoints were also examined including Gleason score of cancer at diagnosis, HGPIN at biopsy, tumor volume, percent of cores with cancer at diagnosis, the number of cancer positive cores, the treatment alteration score, the incidence of intervention for cancer, and overall survival. Based on knowledge gained from the PCPT, tumor aggressiveness was determined not only by Gleason score, but by additional biomarkers for apoptosis, proliferation and tumor differentiation.

During the 4-year study period, 19.9% of men in the dutasteride group developed prostate cancer as compared to 25.1% in the placebo group, which represents an absolute risk reduction of 5.1% for men taking dutasteride ($P < 0.001$). The rate of prostate cancer detection at biopsy was lower in all subgroups for those receiving dutasteride, including groups based on age, family history of prostate cancer, baseline PSA, baseline TPV, baseline IPSS, or BMI. The reduced incidence occurred primarily in men with tumors having Gleason scores of 5–6. During the first two years of the study, there was no significant difference in incidence of tumors with Gleason score of 8–10 between the placebo and dutasteride groups, but in years 3–4, only 1 tumor with a Gleason score of 8–10 was detected in the placebo group, while 12 were found in the dutasteride group. The authors of this study have speculated that this may be a reflection of the drop-out rate of men in the placebo group who developed cancers in the first two years, leading to a lower number of high grade tumors detected in this group. If, for example, the men in the placebo group who developed tumors with a Gleason score of 5–7 during the first two years of the study had remained in the study until the end (against protocol), a number of these tumors might have been upgraded to high-grade in years 3–4, reducing the differences between the two groups at the 4 year endpoint. The REDUCE study also examined the effects of dutasteride on BPH using IPSS, change in TPV from baseline, number of men progressing to surgical intervention, and evidence of BPH-related AUR or urinary tract infection. In this study, as in previous studies where dutasteride was tested in subjects with BPH (ARIA3001, ARIA3002, ARIA3003, EPIC, and CombAT), dutasteride reduced the rate of BPH progression. Upon completion of the REDUCE trial, it was concluded that dutasteride, over a 4 year period, reduced the risk of biopsy-detected cancer and also improved symptoms and reduced progression of BPH. Thus, dutasteride may be considered as a treatment option for men who have been determined to be at a higher risk of developing prostate cancer.

These two studies represent important efforts to determine the efficacy of using 5ARIs in prostate cancer risk reduction and disease prevention and have demonstrated that both finasteride and dutasteride can prevent or delay the emergence of prostate cancer [39]. Since completion and analysis of the studies, the use of 5ARIs to reduce the risk of prostate cancer has not yet been universally adopted; the benefits of therapy should be weighed against the prospect of undesirable sexual side effects and decreased quality of life. Recommendations in statements issued by the American Urological Association (AUA) and the American Society of Clinical Oncology (ASCO) ask that physicians discuss the risks and benefits of preventive therapy using 5ARIs with their patients so they can make an informed decision [36].

5. 5ARIs in the treatment of prostate cancer

A natural extension of studies demonstrating the efficacy of using 5ARIs in prevention of prostate cancer is to examine the use

Table 3
5ARI trials in chemoprevention and treatment of prostate cancer.

Trial	Agent	Report	Period	Results: PCa	Risk reduction
PCPT (Prostate Cancer Prevention Trial)	Finasteride	2003 [22]	7 years *n* = 18,882	PL: 24.4% FN: 18.4%	24.8%
REDUCE (Reduction by Dutasteride of Prostate Cancer Events)	Dutasteride	2010 [32]	4 years *n* = 8231	PL: 25.1% DU: 19.9%	22.8%
REDEEM (Reduction by Dutasteride of Clinical Progression Events in Expectant Management)	Dutasteride	Expected 2010	3 years *n* = 302	Expected 2010	
TARP (Therapeutic Assessment of Rising PSA)	Dutasteride + Bicalutamide	Expected 2010	18 month + 2 year *n* = 150	Expected 2010	
ARTS (Avodart® after Radical Therapy for Prostate Cancer Study)	Dutasteride	Expected 2010	2 year *n* = 276	Expected 2010	

of these inhibitors in the treatment of prostate cancer. Expression of both 5AR-1 and -2 are increased in hyperplastic prostate tissue and 5AR-1 expression is increased in prostate cancer as compared to BPH [3,33]. 5AR-2 expression has been shown to be lower in prostate cancer than in normal tissue [40]. Pre-clinical studies have demonstrated that inhibition of 5AR isoenzymes by finasteride or dutasteride can kill prostate cancer cells and increase apoptosis *in vitro* [41–43] and *in vivo* [44–47]. The first clinical trial examining the use of finasteride in patients after radical prostatectomy was performed in 1995 and demonstrated that a regimen of 10 mg/d finasteride for 1 year delayed the increase in serum PSA for approximately 9 months as compared to placebo [48]. The results of this study indicated that treatment with a 5ARI delays, but does not prevent, a rise in serum PSA after radical prostatectomy.

Several tertiary prevention studies are currently underway examining the use of dutasteride for prostate cancer treatment: (1) during expectant management of prostate cancer, (2) after radical prostatectomy in men at high risk for relapse, and (3) in men with metastatic disease. The Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) [49] trial is a 3-year study testing whether dutasteride can be used in men with localized prostate cancer to delay progression to a more aggressive form. To avoid the complications of unwanted side effects, men in this study with low-grade cancer are undergoing "watchful waiting" or what is currently termed expectant management of their disease, with the possibility of intervention upon evidence of disease progression. This is a randomized, double-blind, placebo-controlled study involving 302 men enrolled in 2006–2007. To be enrolled, men must have low-grade, low-risk, localized prostate cancer (Gleason score ≤ 6, PSA ≤ 10 ng/ml) and a TPV of <80 cm^3. Men were randomized to receive placebo or 0.5 mg/d dutasteride and have been followed up with visits every 3 months for the first year and every 6 months for the remaining 2 years. The primary endpoint for the REDEEM trial is the interval to disease progression,

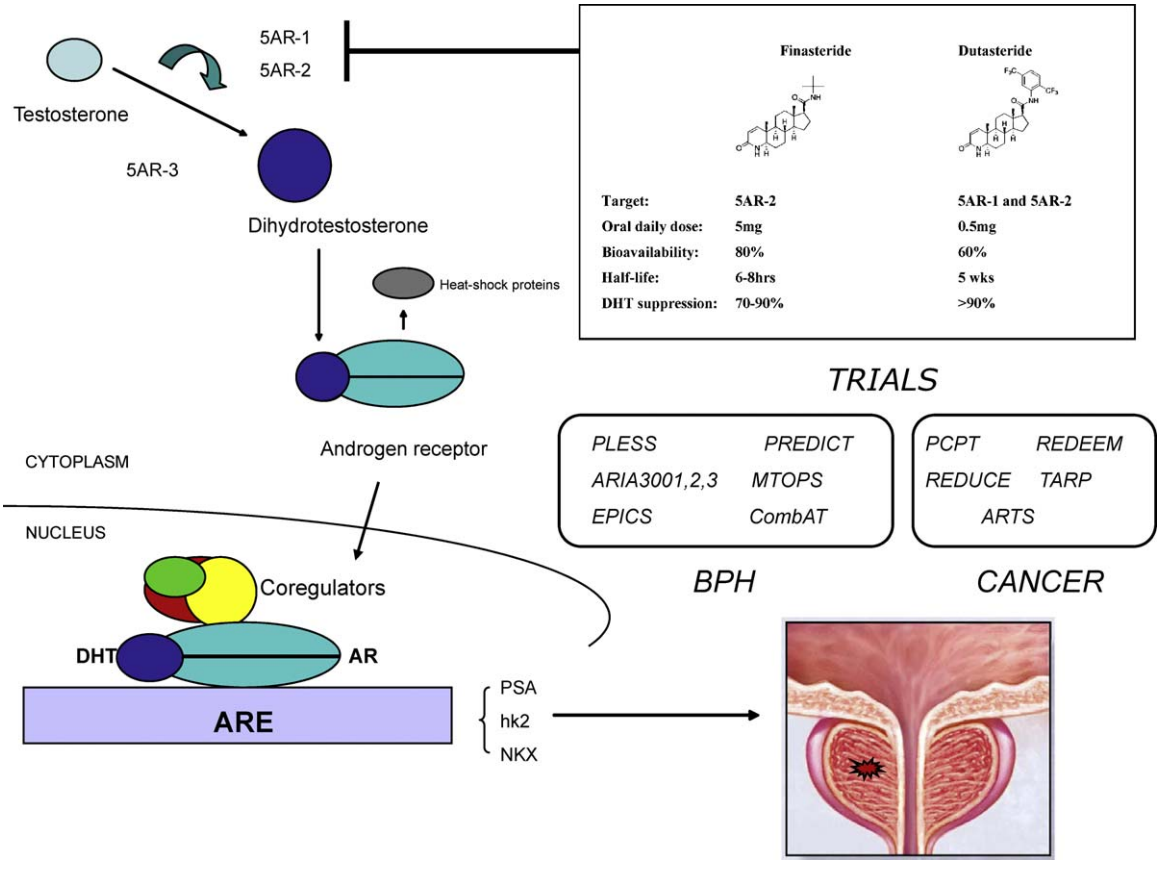

Fig. 1. Schematic of androgen action in the prostate and some of the key trials using 5ARIs in treatment and prevention of prostate disease.

which has been defined as either initiation of therapy for prostate cancer or pathologic progression. The results and evaluation of data are expected in 2010 and if proven successful, dutasteride could become an effective treatment for men undergoing expectant management.

Two other studies are looking at dutasteride treatment in patients who have failed previous therapies. The Avodart® after Radical Therapy for Prostate Cancer Study (ARTS) [50] is exploring the use of dutasteride in patients who have increasing PSA levels after either radical prostatectomy or radiotherapy, but have not yet progressed to metastatic disease. Study endpoints are time to PSA doubling, time to disease progression, treatment response (PSA decrease), changes in PSA and PSA doubling time, and changes in anxiety, as measured by the Memorial Anxiety Scale for Prostate Cancer.

Combination therapies with 5ARIs and various agents are also being explored. The Therapy Assessed by Rising PSA (TARP) [51] study will be examining the use of combination therapy in patients with castrate-refractory prostate cancer (CRPC). This is a multicenter trial in the US and Canada where patients will be randomized to receive treatment with bicalutamide alone or bicalutamide plus dutasteride. The primary endpoint of this study will be time to disease progression. This will be the first trial using both an antiandrogen and a 5ARI in an attempt to reduce the rate of progression in CRPC.

A Phase II study of 57 patients with CPRC receiving dutasteride in addition to ketoconazole, which was reported last year, concluded that dutasteride may improve the response rate to ketoconazole and also increases the duration of the response significantly [52]. Ketoconazole is one of a group of inhibitors of CYP17A1, the enzyme that mediates androgen precursor synthesis. This study demonstrated the validity of combining therapies targeting multiple steps in the androgen synthesis pathway and supports the concept of further combination trials. Table 3 lists the major chemoprevention trials and a number of the ongoing prostate cancer treatment trials using 5ARIs. The results of several studies are expected to be reported this year that may add to our knowledge regarding use of 5ARIs in treatment of prostate cancer.

6. Gene expression analysis of 5ARI action in prostate cells

Gene expression analyses are enhancing knowledge of the mechanism(s) of action of 5ARIs in prostate cells. A number of laboratories, including our own, have examined changes in gene expression in prostate cancer cells treated with finasteride and/or dutasteride. These studies have discovered pathways in addition to the androgen pathway that are affected with treatment, such as those involved in cytoskeletal remodeling, cell cycle, and Rho GTPase signaling [43,47,53–56]. Recently, gene expression patterns were examined in benign epithelium of patients with localized prostate cancer. It was found that pre-treatment AR levels may predict the response to or success of chemoprevention with dutasteride [56] and that patients with high levels of AR can compensate for androgen depletion better than those having lower endogenous levels, leading to differing responses to 5AR inhibition. A carefully designed clinical study can determine if these levels do indeed predict response to therapy. Gaining insights into the pathways affected by finasteride and dutasteride within the prostate tumor microenvironment should lead to development of additional agents that can be used in combination with 5ARIs leading to more effective use in prevention or treatment of prostate cancer in the near future.

7. Conclusion

There have been multiple clinical trials and pre-clinical studies that have tested the utility of 5ARIs in treating prostate disease, as summarized in Fig. 1. Inhibiting androgen action through the use of finasteride and dutasteride has been established as a valuable resource for physicians. These two inhibitors have already been proven safe and effective for treatment of LUTS and inhibiting BPH disease progression; both finasteride and dutasteride have also shown promise in preventing prostate cancer in men at risk for developing the disease. The year 2010 should be exciting, since results from three dutasteride trials will be reported. As more information becomes available regarding the mechanism(s) of action of 5ARIs at the molecular level and how a patient's genetic profile can predict drug-response, it is anticipated that the efficacy of 5ARIs in treating prostate disease will be enhanced.

References

[1] S.M. Dehm, D.J. Tindall, Molecular regulation of androgen action in prostate cancer, J. Cell Biochem. 99 (2) (2006) 333–344.
[2] D.J. Tindall, R.S. Rittmaster, The rationale for inhibiting 5alpha-reductase isoenzymes in the prevention and treatment of prostate cancer, J. Urol. 179 (4) (2008) 1235–1242.
[3] C. Iehle, et al., Differences in steroid 5alpha-reductase iso-enzymes expression between normal and pathological human prostate tissue, J. Steroid Biochem. Mol. Biol. 68 (5–6) (1999) 189–195.
[4] M. Uemura, et al., Novel 5 alpha-steroid reductase (SRD5A3, type-3) is overexpressed in hormone-refractory prostate cancer, Cancer Sci. 99 (1) (2008) 81–86.
[5] V. Cantagrel, et al., SRD5A3 is required for converting polyprenol to dolichol and is mutated in a congenital glycosylation disorder, Cell 142 (2) (2010) 203–217.
[6] Z.X. Zhou, et al., Specificity of ligand-dependent androgen receptor stabilization: receptor domain interactions influence ligand dissociation and receptor stability, Mol. Endocrinol. 9 (2) (1995) 208–218.
[7] D.W. Russell, J.D. Wilson, Steroid 5 alpha-reductase: two genes/two enzymes, Annu. Rev. Biochem. 63 (1994) 25–61.
[8] S. Aggarwal, et al., An overview on 5alpha-reductase inhibitors, Steroids 75 (2) (2010) 109–153.
[9] H.G. Bull, et al., Mechanism-based inhibition of human steroid 5a-reductase by finasteride: enzyme-catalyzed formation of NADP-dihydrofinasteride, a potent bisubstrate analog inhibitor, J. Am. Chem. Soc. 118 (1996) 2359–2365.
[10] S.V. Frye, et al., Discovery and development of GG745, a potent inhibitor of both isozymes of 5 alpha-reductase, Pharm. Biotechnol. 11 (1998) 393–422.
[11] D. Vaughan, et al., Long-term (7 to 8-year) experience with finasteride in men with benign prostatic hyperplasia, Urology 60 (6) (2002) 1040–1044.
[12] G. Tian, et al., Mechanism of time-dependent inhibition of 5 alpha-reductases by delta 1-4-azasteroids: toward perfection of rates of time-dependent inhibition by using ligand-binding energies, Biochemistry 34 (41) (1995) 13453–13459.
[13] J.C. Nickel, Comparison of clinical trials with finasteride and dutasteride, Rev. Urol. 6 (9 (Suppl.)) (2004) S31–S39.
[14] R.S. Kirby, et al., Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial, Urology 61 (1) (2003) 119–126.
[15] J.D. McConnell, et al., The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia Finasteride Long-Term Efficacy and Safety Study Group, N. Engl. J. Med. 338 (9) (1998) 557–563.
[16] C.G. Roehrborn, et al., Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia, Urology 60 (3) (2002) 434–441.
[17] P. Gilling, et al., Efficacy of dutasteride and finasteride for the treatment of benign prostate hyperplasia: results of the 1-year Enlarged Prostate International Comparator Study (EPICS), BJU Int. 95 (1 (Suppl.)) (2005) 1–38.
[18] S. Gravas, M. Oelke, Current status of 5alpha-reductase inhibitors in the management of lower urinary tract symptoms and BPH, World J. Urol. 28 (1) (2010) 9–15.
[19] J.D. McConnell, et al., The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia, N. Engl. J. Med. 349 (25) (2003) 2387–2398.
[20] S.A. Kaplan, et al., Combination therapy with doxazosin and finasteride for benign prostatic hyperplasia in patients with lower urinary tract symptoms and a baseline total prostate volume of 25 ml or greater, J. Urol. 175 (1) (2006) 220–221 (discussion).
[21] S.A. Kaplan, et al., Long-term treatment with finasteride results in a clinically significant reduction in total prostate volume compared to placebo over the

full range of baseline prostate sizes in men enrolled in the MTOPS trial, J. Urol. 180 (3) (2008) 1030–1032 (discussion).
[22] C.G. Roehrborn, et al., The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study, Eur. Urol. 57 (1) (2010) 123–131.
[23] J.M. Hollingsworth, J.T. Wei, Does the combination of an alpha1-adrenergic antagonist with a 5alpha-reductase inhibitor improve urinary symptoms more than either monotherapy? Curr, Opin. Urol. 20 (1) (2010) 1–6.
[24] J. Barkin, et al., Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5alpha-reductase inhibitor dutasteride, Eur. Urol. 44 (4) (2003) 461–466.
[25] A. Jemal, et al., Cancer statistics, 2009, CA Cancer J. Clin. 59 (4) (2009) 225–249.
[26] I.M. Thompson, C. Tangen, P. Goodman, The prostate cancer prevention trial: design, status, and promise, World J. Urol. 21 (1) (2003) 28–30.
[27] I.M. Thompson, et al., The influence of finasteride on the development of prostate cancer, N. Engl. J. Med. 349 (3) (2003) 215–224.
[28] P.T. Scardino, The prevention of prostate cancer—the dilemma continues, N. Engl. J. Med. 349 (3) (2003) 297–299.
[29] Y.C. Cohen, et al., Detection bias due to the effect of finasteride on prostate volume: a modeling approach for analysis of the Prostate Cancer Prevention Trial, J. Natl. Cancer Inst. 99 (18) (2007) 1366–1374.
[30] P. Pinsky, H. Parnes, L. Ford, Estimating rates of true high-grade disease in the prostate cancer prevention trial, Cancer Prev. Res. (Phila Pa) 1 (3) (2008) 182–186.
[31] M.W. Redman, et al., Finasteride does not increase the risk of high-grade prostate cancer: a bias-adjusted modeling approach, Cancer Prev. Res. (Phila Pa) 1 (3) (2008) 174–181.
[32] S.A. Kaplan, et al., PCPT: evidence that finasteride reduces risk of most frequently detected intermediate- and high-grade (Gleason score 6 and 7) cancer, Urology 73 (5) (2009) 935–939.
[33] L.N. Thomas, et al., Levels of 5alpha-reductase type 1 and type 2 are increased in localized high grade compared to low grade prostate cancer, J. Urol. 179 (1) (2008) 147–151.
[34] S. Ishikawa, et al., Prognostic factors in survival free of progression after androgen deprivation therapy for treatment of prostate cancer, J. Urol. 141 (5) (1989) 1139–1142.
[35] E.D. Crawford, et al., Reduction in the risk of prostate cancer: future directions after the Prostate Cancer Prevention Trial, Urology 75 (3) (2009) 502–509.
[36] S.A. Strope, G.L. Andriole, Update on chemoprevention for prostate cancer, Curr. Opin. Urol. 20 (3) (2010) 194–197.
[37] G.L. Andriole, et al., Effect of dutasteride on the risk of prostate cancer, N. Engl. J. Med. 362 (13) (2010) 1192–1202.
[38] G. Andriole, et al., Chemoprevention of prostate cancer in men at high risk: rationale and design of the reduction by dutasteride of prostate cancer events (REDUCE) trial, J. Urol. 172 (4 (Pt. 1)) (2004) 1314–1317.
[39] R.S. Rittmaster, N.E. Fleshner, I.M. Thompson, Pharmacological approaches to reducing the risk of prostate cancer, Eur. Urol. 55 (5) (2009) 1064–1073.
[40] J. Luo, et al., Decreased gene expression of steroid 5 alpha-reductase 2 in human prostate cancer: implications for finasteride therapy of prostate carcinoma, Prostate 57 (2) (2003) 134–139.
[41] B.J. Long, et al., Antiandrogenic effects of novel androgen synthesis inhibitors on hormone-dependent prostate cancer, Cancer Res. 60 (23) (2000) 6630–6640.
[42] C.B. Lazier, et al., Dutasteride, the dual 5alpha-reductase inhibitor, inhibits androgen action and promotes cell death in the LNCaP prostate cancer cell line, Prostate 58 (2) (2004) 130–144.
[43] L.J. Schmidt, H. Murillo, D.J. Tindall, Gene expression in prostate cancer cells treated with the dual 5 alpha-reductase inhibitor dutasteride, J. Androl. 25 (6) (2004) 944–953.
[44] C. Cayatte, et al., Protein profiling of rat ventral prostate following chronic finasteride administration: identification and localization of a novel putative androgen-regulated protein, Mol. Cell Proteomics 5 (11) (2006) 2031–2043.
[45] S.E. Eggener, et al., Enhancement of intermittent androgen ablation by "off-cycle" maintenance with finasteride in LNCaP prostate cancer xenograft model, Prostate 66 (5) (2006) 495–502.
[46] Y. Xu, et al., Pharmacologic basis for the enhanced efficacy of dutasteride against prostatic cancers, Clin. Cancer Res. 12 (13) (2006) 4072–4079.
[47] L.J. Schmidt, et al., Effects of the 5 alpha-reductase inhibitor dutasteride on gene expression in prostate cancer xenografts, Prostate 69 (16) (2009) 1730–1743.
[48] G. Andriole, et al., Treatment with finasteride following radical prostatectomy for prostate cancer, Urology 45 (3) (1995) 491–497.
[49] N. Fleshner, et al., Delay in the progression of low-risk prostate cancer: rationale and design of the Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) trial, Contemp. Clin. Trials 28 (6) (2007) 763–769.
[50] F.H. Schroder, et al., Can dutasteride delay or prevent the progression of prostate cancer in patients with biochemical failure after radical therapy? Rationale and design of the Avodart after Radical Therapy for Prostate Cancer Study, BJU Int. 103 (5) (2009) 590–596.
[51] O. Sartor, et al., Dutasteride and bicalutamide in patients with hormone-refractory prostate cancer: the Therapy Assessed by Rising PSA (TARP) study rationale and design, Can. J. Urol. 16 (5) (2009) 4806–4812.
[52] S.K. Shah, et al., Phase II study of dutasteride for recurrent prostate cancer during androgen deprivation therapy, J. Urol. 181 (2) (2009) 621–626.
[53] L.J. Schmidt, K.V. Ballman, D.J. Tindall, Inhibition of fatty acid synthase activity in prostate cancer cells by dutasteride, Prostate 67 (10) (2007) 1111–1120.
[54] M. Biancolella, et al., Effects of dutasteride on the expression of genes related to androgen metabolism and related pathway in human prostate cancer cell lines, Invest. New Drugs 25 (5) (2007) 491–497.
[55] J. Li, J. Kim, Molecular profiles of finasteride effects on prostate carcinogenesis, Cancer Prev. Res. (Phila Pa) 2 (6) (2009) 518–524.
[56] E.A. Mostaghel, et al., Variability in the androgen response of prostate epithelium to 5alpha-reductase inhibition: implications for prostate cancer chemoprevention, Cancer Res. 70 (4) (2010) 1286–1295.