Combined Effect of Terazosin and Finasteride on Apoptosis, Cell Proliferation, and Transforming Growth Factor-β Expression in Benign Prostatic Hyperplasia

Deborah T. Glassman,[1] Joanna K. Chon,[1] Andrew Borkowski,[2] Stephen C. Jacobs,[1] and Natasha Kyprianou[1,3]*

[1]Division of Urology, Department of Surgery, University of Maryland School of Medicine, Baltimore, Maryland
[2]Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland
[3]Department of Biochemistry and Molecular Biology, University of Maryland School of Medicine, Baltimore, Maryland

BACKGROUND. Medical treatment of benign prostatic hyperplasia (BPH) targets relief of symptoms by causing either relaxation of the prostatic smooth muscle with α_1 adrenergic blockade, or shrinkage of the gland with 5α-reductase inhibitors. We recently demonstrated that α_1-blockers, such as terazosin, induce apoptosis in prostatic cells. In this study, we examined the combined effect of finasteride and terazosin on the rate of apoptosis and cellular proliferation to investigate their potential synergy at the cellular level.

METHODS. Prostate specimens were obtained from men who were treated with either finasteride (n = 24), terazosin (n = 42), or combination therapy (n = 10) for varying time periods (1 week to 36 months) for the relief of the symptoms of BPH. The proliferative and apoptotic indices of both stromal and epithelial prostatic cell populations were determined. Antibodies against TGF-β_1 and TβRII were used to examine the immunoreactivity of TGF-β_1 and TβRII, respectively, in all prostate tissue sections.

RESULTS. The apoptotic index in both prostate cell populations was significantly higher following the combination treatment compared to terazosin or finasteride alone. There were no significant changes in the rate of cellular proliferation with any treatment. Furthermore, there was a significant increase in TGF-β_1 expression in the prostates of patients treated with terazosin or combination therapy, while there was no change in TβRII expression.

CONCLUSIONS. These results support the concept that induction of prostate apoptosis is a potential molecular mechanism underlying the combination effect of α_1 blockade with 5α-reductase inhibitors in the effective treatment of BPH. The upregulation of TGF-β_1 implies a role for this ligand as an effector of apoptosis induction in response to α_1-blockade or finasteride therapy of BPH patients. *Prostate 46:45–51, 2001.*

KEY WORDS: **terazosin; finasteride; apoptosis; cell proliferation; BPH; TGF-β**

INTRODUCTION

Approximately 85% of men over age 50 will have benign prostatic hyperplasia (BPH). By the ninth decade of life, half of these men will require treatment for symptomatic relief of urinary obstructive symptoms associated with BPH [1]. In 1976, Caine proposed the theory that symptoms related to BPH were due to both a static and dynamic component of the prostate gland [2]. Hyperplasia of the gland provided a physical blockade of the bladder outlet, the static component, while an increase in the smooth muscle tone of the gland provided the dynamic component.

Abbreviations: BPH, benign prostatic hyperplasia; TGF-β_1, transforming growth factor β-1; TβRII, transforming growth factor beta receptor type II; DHT, dihydrotestosterone; TUNEL, terminal transferase/uridine nick end labeling.

*Correspondence to: Dr. Natasha Kyprianou, Division of Urology, University of Maryland Medical Center, 22 S. Greene St., Baltimore, MD 21201. E-mail: nkyprianou@smail.umaryland.edu

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This theory gave impetus to target both components by causing either relaxation of the smooth muscle or shrinkage of the gland for the management of BPH [3]. Two major classes of medications have consequently emerged in the treatment of men who suffer from symptoms related to BPH. The first, alpha1 adrenoreceptor antagonists (α_1-blockers), originally were thought to work by causing relaxation of the stromal smooth muscle by blocking the receptors found in the prostate and its capsule [4]. Recent studies from this laboratory demonstrated the ability of α_1-blockers, such as doxazosin and terazosin, to induce apoptosis of the prostate stromal smooth muscle and epithelial cells, which correlates with symptom improvement [5,6].

Androgens influence growth and function of the prostate, and castration-induced androgen ablation causes involution of the prostate gland [7,8]. Finasteride, a clinically used 5α-reductase inhibitor (5αR), prevents the conversion of testosterone (T) to dihydrotestosterone (DHT) in the prostate, leading to a reduction of gland size via induction of apoptosis [9]. Finasteride is used in the treatment of BPH to relieve symptoms of outlet obstruction and reduce the risk of acute urinary retention [10].

Androgens maintain prostate homeostasis through the regulation of several growth factors, including epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF), and TGF-β_1 [11]. Androgen deprivation also causes a decrease in these growth factors as well as a decrease of vascular endothelial growth factor (VEGF) and angiogenesis of the prostate, preventing glandular growth [12,13]. Induction of TGF-β_1 expression has been shown to inhibit cellular proliferation and promote apoptosis in the prostate gland [14,15]. TGF-β_1 exerts its antiapoptotic effects by binding to its high-affinity TβRII. TβRII then interacts with TβRI to initiate a signaling cascade, via which it asserts its mechanism of action [16,17]. TGF-β_1 inhibits target cells from entering the S phase of the cell cycle via induction of key cell cycle regulators, such as the cyclin-dependent kinase inhibitors, $p21^{Waf\text{-}1}$ and $p27^{Kip\text{-}1}$ [18]. In the prostate gland, TGF-β_1 signaling appears to be negatively modulated by androgens [20].

Both α_1-blockers and 5α-reductase inhibitors induce apoptosis in the prostate gland, without affecting cellular proliferation [5,9]. In this study, we hypothesized that a combination of terazosin and finasteride would result in a significant induction of prostate apoptosis through a potential synergistic effect. To gain a mechanistic insight into the α_1-blockade-mediated induction of apoptosis in BPH tissue, expression of TGF-β_1 and its receptor, TβRII, was investigated in BPH patients following treatment.

MATERIALS AND METHODS

Patient Selection

A retrospective analysis was performed on patients treated with terazosin, finasteride, or both medications at the University of Maryland Medical Center and the Baltimore Veterans Affairs Medical Center. Archival tissue specimens (Departments of Pathology) were selected patients who were concurrently on terazosin, finasteride, or both for treatment of lower urinary tract symptoms (LUTS) and were selected on the basis of availability of posttreatment prostate biopsy specimens (for clinically suspicious elevated PSA) or surgical specimens (for BPH- transurethral resection of the prostate (TUR) or for low-grade prostate adenocarcinoma-radical prostatectomy) Treatment periods ranged from 1 week to 36 months. The doses for patients on terazosin ($n = 42$) were from 2–10 mg per day. Patients on finasteride ($n = 24$) were given 5 mg per day. Those patients on both ($n = 10$) took a combination of these medications at the indicated doses. The groups were then stratified by length of treatment into two ranges: 1 week–6 months and greater than 6 months. A group of men diagnosed with BPH on pathologic examination, who were untreated, served as a control ($n = 56$). All specimens were examined by a pathologist (A.B.) to establish the histopathological presence of benign hyperplasia in prostate sections. Only those sections determined to be consistent with the histological appearance of BPH were used in the study (cancerous areas were not included in the analysis).

Immunohistochemical Analysis

Specimens were formalin-fixed, paraffin-embedded, and sectioned to 5 μm thick prior to analysis. The proliferative index of each sample was determined using Ki-67 nuclear antigen immunostaining with the mouse monoclonal antibody, MIBI (AMAC, Westbrook, ME), as previously described [21]. The incidence of apoptosis in situ was evaluated by the terminal transferase TdT-mediated dUTP-biotin end labeling (TUNEL) assay, using the ApoTag kit (Oncor, Inc., Gaithersburg, MD). Apoptotic index was determined as the percentage of TUNEL-positive cells over the total number of cells (at least 200 cells) per section. Three different fields per section were counted by two independent investigators (D.T.G. and N.K.), and the average value was taken as the apoptotic index.

Analysis of TGF-β_1 and TβRII immunoreactivity was performed on serial sections using mouse polyclonal antibodies against TGF-β_1 and TβRII, respec-

tively (Santa Cruz Biotechnology, Santa Cruz, CA). An avidin-biotin complex with 2,2-diaminobenzidene for color development was used, according to the manufacturer's instructions. Each slide was evaluated at 400 × magnification under light microscopy. Positively stained cells (regardless of the intensity and diffuse nature of the staining) were counted in the epithelial and stromal compartments of the prostate in three separate, randomly selected fields, by two independent investigators (D.T.G. and N.K.). The mean percentage of immunoreactivity was determined by the ratio of positively stained cells over the total number of cells in each cellular population, and the average value was taken from the two sets of data to be subjected to statistical analysis.

Statistical Analysis

All values are expressed as mean value ± standard error of the mean (SEM). Statistical significance was determined using the Student *t*-test, assuming unequal variance, and also using a two-way analysis of variance for nonparametric distribution (ANOVA). All *P*-values less than 0.05 were considered statistically significant. Linear regression analysis was applied to correlate TGF-β_1 expression with the apoptotic index of the different cell populations.

RESULTS

Quantitative analysis of Ki-67 immunoreactivity revealed no significant differences in the epithelial proliferative indices between patients treated with terazosin, finasteride, or combination treatment vs. untreated patients. As shown in Figure 1, the proliferative index of prostate cell populations in the epithelial cell component remained unaffected, regardless of the medication or length of treatment. There was a transient increase in the stromal proliferative index for patients on short-term combination therapy.

Upon comparison of the apoptotic index (AI) of patients in any of the treatment groups over the control group, a significant increase was observed (Fig. 2). There was an even further increase in the AI of patients on combination treatment over those on terazosin alone ($P < 0.05$). As shown in Figure 2, this significant difference in apoptosis induction among epithelial cells was maintained for short- and long-term treatment periods. There was also a statistically significant difference between the epithelial AI of patients on finasteride alone (short-term therapy) vs. those on terazosin ($P < 0.05$) (Fig. 2). For patients

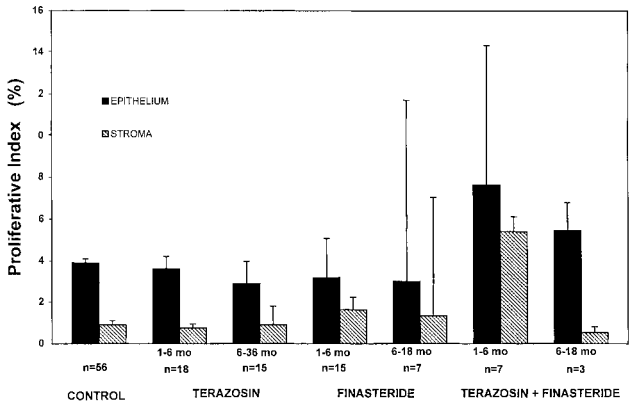

Fig. 1. Effect of terazosin, finasteride, or combination treatment on prostate cell proliferation. Epithelial and stromal cellular compartments in prostate glands from treated BPH patients showed no significant differences in cellular proliferation rate when compared to an untreated control or to each other. Values represent mean ± SEM.

treated with finasteride for longer than 6 months, a decrease in AI was observed, though it was not significantly higher than that observed for terazosin treatment alone ($P > 0.05$). Changes in AI of the stromal smooth muscle cells were comparable to those observed in the prostatic epithelium. As shown in Figure 2, there was a higher rate of apoptosis in the combination therapy group compared to terazosin alone ($P < 0.05$). Similarly, there was also an increase in AI when compared to finasteride alone, especially in the 6–18-month treatment group.

Figure 3A reveals a characteristic distribution of TGF-β_1 immunoreactive cells in prostate epithelium and stromal compartments of a patient treated with

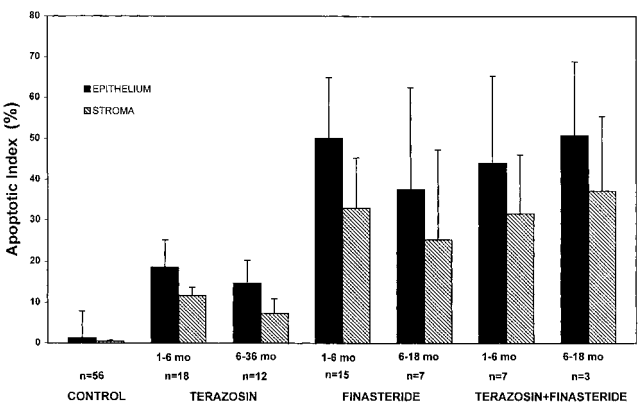

Fig. 2. Induction of apoptosis in response to terazosin, finasteride, or combination therapy in BPH patients. A significant increase in epithelial and stromal apoptotic indices in patients on combination treatment was observed compared to those taking terazosin alone, in both long- and short-term treatment groups ($P < 0.05$), but not to those on finasteride alone ($P > 0.05$). Values represent mean ± SEM.

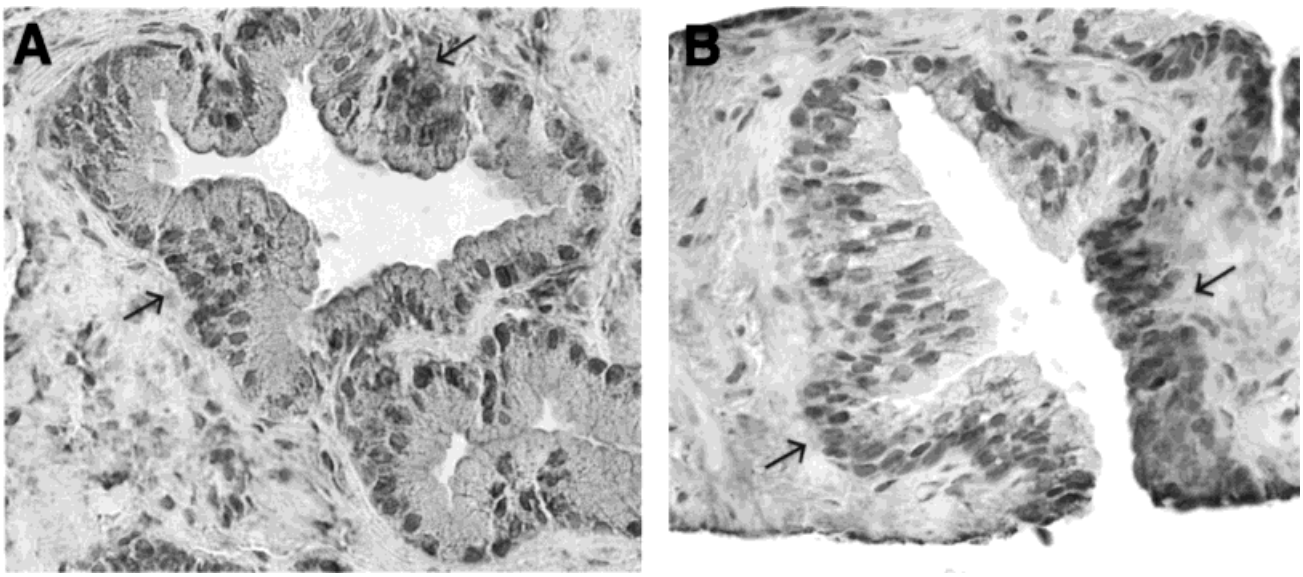

Fig. 3. TGF-β_1 immunoreactivity in prostatic tissue from BPH patients treated with either terazosin or combination therapy. **A:** Terazosin-treated BPH. **B:** Characteristic immunostaining terazosin + finasteride-treated BPH tissue. Note an increased intensity of TGF-β_1 immunoreactivity among epithelial cells in B compared to A (arrows). There is minimal stromal smooth muscle staining in both sections (magnification, × 130). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

terazosin. A considerably stronger intensity in TGF-β_1 staining was observed in the epithelial prostate tissue from a patient on combination therapy (Fig. 3B). Quantitative analysis of the immunoreactivity indicated that a relatively low expression of TGF-β_1 was detected in the epithelium as well as in the prostatic smooth muscle cells of untreated control patients (Fig. 4). In all treated patients, a significantly higher TGF-β_1 immunoreactivity was observed in both epithelial and stromal compartments, when compared to controls ($P < 0.05$).

Interestingly enough, there was no statistical difference in the mean level of epithelial TGF-β_1 expression between patients on terazosin alone compared to those on combination treatment; however, there was a trend towards higher levels of expression in the combination group. Furthermore, TGF-β_1 expression levels in prostatic smooth muscle cells were not significantly different between the terazosin and combination groups ($P > 0.05$). No significant differences were detected in epithelial levels of TGF-β_1 expression for those patients on finasteride when compared to either of the other groups. Stromal levels were lower in patients treated with finasteride when compared to those on terazosin for less than 6 months (Fig. 4). Linear regression analysis revealed a strong positive correlation between TGF-β_1 levels with rate of epithelial apoptosis induction for patients on combination therapy ($R = 0.66$), but no correlation between TGF-β_1 levels with the epithelial apoptotic index for patients on terazosin or finasteride alone.

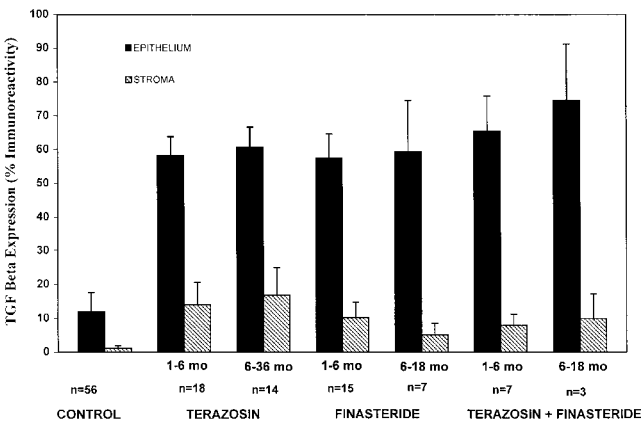

Fig. 4. Quantitative analysis of TGF-β_1 expression in prostatic tissue from BPH patients treated with terazosin, finasteride, or combination therapy. The increase in epithelial TGF-β_1 expression in patients on combination therapy vs. those on terazosin alone in long- and short-term treatment groups was not statistically significant ($P > 0.05$). Values represent mean ± SEM.

The results shown in Figure 5 indicate a decrease in TβRII expression in the epithelium of patients on combination treatment for the short term when compared to those on terazosin alone. Patients who were treated for longer periods had levels of expression that were uniformly equivalent in the epithelium. In the stroma, there was a significantly higher expression of TβRII in patients treated with combination therapy, or finasteride alone, for a short time compared to terazosin ($P < 0.05$) (Fig. 5). None of the

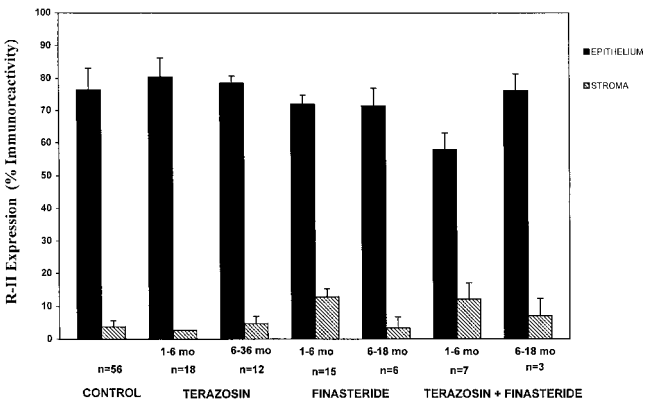

Fig. 5. Effect of terazosin and finasteride (as single agents and in combination) on expression of TβRII receptor in BPH patients. There was no significant increase in TβRII immunoreactivity in prostates from treated patients compared to untreated controls ($P > 0.05$). Values represent mean ± SEM.

therapeutic regimens had a significant effect on TβRII receptor expression in the epithelium compared to untreated controls (Fig. 5).

DISCUSSION

Previous studies from this laboratory showed that both doxazosin and terazosin induced apoptosis in prostate stromal and epithelial compartments without affecting cellular proliferation [6]. In the present study, we examined a potential mechanism through which apoptosis is initiated in response to pharmacological treatment of BPH patients with terazosin and finasteride, either as single agents or in combination. Finasteride shrinks prostate volume and causes epithelial involution via induction of apoptosis [9,22]. Our findings indicate that finasteride alone has no effect on cellular proliferation, while it causes an increase in the rate of apoptosis. This correlates well with the concept that inhibition of dihydrotestosterone (DHT) production in the prostate induces apoptosis without affecting DHT-stimulated cellular proliferation [23]. In addition, this might also be consistent with the fact that patients with 5α-reductase deficiency never develop prostate cancer. The induction of epithelial apoptosis observed in this study is in accordance with previously established evidence [7,24]. Our findings indicate increased apoptosis in the prostatic stromal component after treatment with finasteride. Interestingly enough, in patients on long-term finasteride treatment (longer than 6 months), there was a reduction in apoptotic index (not significantly higher than that observed for terazosin alone). This observation suggests that the apoptotic effect may become muted with longer treatment periods, potentially due to cellular tolerance to the drug with long-term treatment.

We also demonstrated that terazosin causes an induction of apoptosis without affecting cellular proliferation, in accordance with previous observations [6,15]. On the basis of these results we postulated that the molecular mechanism underlying α_{1a}-blockade in the treatment of BPH may be due to apoptosis in the stromal and epithelial prostatic components. The relief of symptoms associated with BPH may be due to a combination of the relaxation of stromal smooth muscle and apoptosis induction in the prostate gland. Direct support for this concept stems from previous work from this clinical center, indicating that both α_1-adrenoceptor antagonists doxazosin and terazosin induced apoptosis in both prostate cell populations [5,6], and that this elevated apoptotic index correlates with improvement of the clinical symptoms associated with BPH [5]. This evidence has taken on significant clinical dimensions, as it provides a molecular basis for the long-term response of BPH patients to α_1-blockade totally independent of prostatic smooth muscle relaxation. The present data suggest a potential combination effect of terazosin and finasteride in enhancing the rate of prostate apoptosis.

A higher level of TGF-β_1 expression was observed in the prostates of patients on combination therapy than with either terazosin or finasteride alone. The induction of TGF-β_1 expression is consistent with evidence that doxazosin, an α_1-blocker, increases TGF-β_1 expression in mouse prostate reconsititutions [15], a model of BPH. Significantly enough, a correlation between TGF-β_1 expression and epithelial apoptosis induction was seen in those patients treated with combination therapy. Molecular studies are required to determine whether the increased protein expression is due to deregulation of mRNA expression or is a posttranscriptional event, such as increased cleavage of the inactive native protein to its active state. Since TGF-β has a dual effect on proliferation and apoptosis of prostate cells [25], increased levels of TGF-β_1 may play a role in the transient increase in cellular proliferation observed in the 1–6-month combination therapy group.

In BPH, the prostate secretory epithelial and stromal elements exhibit TGF-β_1 immunoreactivity [15,26–28]. In the present study, the increase in prostatic TGF-β_1 expression in patients on combination therapy was higher than in patients on either monotherapy; however, this did not reach statistical significance, possibly due to the relatively small sample size. This elevated TGF-β expression may become statistically different with a larger patient cohort. Since the size of the prostate influences the clinical response to finasteride treatment [10], one may

consider the possibility that in some patients on combination therapy, or even in some treated with finasteride alone, the prostate size was not ''large enough'' to be affected by the medication. As a cellular consequence, the apoptotic status of the epithelial and stromal populations may not have been significantly affected.

No increase in epithelial expression of TβRII was observed in response to any of the apoptosis-driven treatment regimens in this study. This is somewhat in contrast with previous findings that androgen-ablation-induced apoptosis is associated with an upregulation of TβRII epithelial expression in the prostate [7,20,29]. Short-term studies might reflect a transient increase in TβRII levels, which may level off with persistent absence of androgens. In accordance with such a concept is evidence that at 10 days postcastration, TGF-β receptor expression may be restored to control levels in the involuting prostate epithelium [30]. Since none of our samples were taken within the first 2 weeks of finasteride treatment, the possibility exists that potential changes in receptor expression were bypassed in the time frame of treatment in the present study.

Our data suggest that the increase of prostatic epithelial apoptosis in patients on combination treatment may have been due to the increase in TGF-β_1 ligand and not its receptor. Complex paracrine and autocrine interactions between the stromal and epithelial cells may play a role in the increase of epithelial apoptosis in response to TGF-β_1 [11]. This may explain the upregulation of stromal TβRII in the absence of changes in the receptor levels in epithelial cells. One could speculate that increased ligand binding to stromal cells may promote stromal and epithelial apoptosis through cross-talk between the prostatic epithelial and stromal compartments.

The binding of the ligand to the TβRII receptor is crucial to the recruitment and phosphorylation of the TβRI subunit, to form a ternary complex that activates the intracellular signaling pathway [31]. A recent preliminary analysis demonstrated that there is upregulation of $p27^{Kip-1}$, a downstream intracellular effector of TGF-β_1 apoptotic signaling, in response to α_1-blockade in BPH patients (unpublished data). This TGF-β_1-induced apoptosis in the prostate may involve activation of the caspase cascade [32].

An aspect of treatment of prostatic hyperplasia that has been underestimated is the role of angiogenesis in the regulation of prostate growth and its potential involvement in the development of BPH. Since androgen deprivation inhibits vascular endothelial growth factor (VEGF) [12], finasteride treatment may affect the vascularity of the gland, and this action may drive the therapeutic response. Although a recent study suggests that androgen ablation does not appear to affect angiogenesis in prostatic adenocarcinoma [33], examining microvessel density in patients treated with α_1-blockers and/or finasteride for BPH may provide further indication of another potential mode of action.

Recent clinical studies indicate that patients on a combination regimen do not respond better symptomatically than those on terazosin alone, in the treatment of BPH [34]. One has also to consider, however, the evidence that efficacy of treatment of BPH patients with finasteride is dependent on prostate size [28]. The present study did not examine the clinical parameters (AUA symptom scores or urine flow rates); our data, however, support the concept that combination therapy leads to enhanced apoptosis of prostate epithelial and smooth muscle cells, over treatment with terazosin alone. Based on these findings, we are currently considering the feasibility of a future clinically directed randomized study that would correlate reduction of symptoms with prostate apoptosis in patients with BPH treated with finasteride and α_1 blockade.

CONCLUSIONS

In summary, this descriptive study provided the first evidence that combination treatment with terazosin and finasteride results in enhanced apoptosis over either treatment alone, potentially via a TGF-β_1-mediated pathway. Despite the small number of patients in this retrospective study, our results establish the molecular basis for a clinical trial of BPH patients in order to optimize their medical management.

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