

Combination Therapy with Rofecoxib and Finasteride in the Treatment of Men with Lower Urinary Tract Symptoms (LUTS) and Benign Prostatic Hyperplasia (BPH)

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Abstract

Purpose: Cyclooxygenase-2 (COX-2) is expressed in human BPH tissue and displays either a pro-inflammatory effect or a proliferative effect on prostate cells. The aim of this study is to analyze whether combination therapy with rofecoxib, a COX-2 inhibitor, and finasteride offers an advantage compared to finasteride monotherapy in patients with BPH.

Materials and Methods: This is a single centre unblinded trial. Forty-six consecutive men with LUTS and BPH were entered into the study and were randomized to receive rofecoxib 25 mg/day plus finasteride 5 mg/day (group B) versus finasteride 5 mg/day alone (group A) for 24 weeks. Inclusion criteria included also a prostate size greater than 40 cc. The efficacy and safety of treatments were assessed at baseline and at week 4, 12 and 24.

Results: In our population, both treatments (groups A and B) produced statistically significant improvements in total IPSS and Q_{\max} from baseline during follow-up, although they were very low in particular for the finasteride alone group at 4 weeks. We found that finasteride monotherapy produces very little improvement at the 1 month interval. In comparing group A with group B, a significantly higher improvement in IPSS ($p = 0.0001$) and Q_{\max} ($p = 0.03$) was obtained in group B at 4 weeks interval (% cases with IPSS reduction >4 points: group B = 34.7, group A = 0; % cases with Q_{\max} improvement >3 ml/s: group B = 8.7, group A = 0), whereas at week 24, the differences between the two treatments were not significant ($p > 0.05$).

Conclusions: In our population, the advantage of the combination therapy compared to finasteride alone is significant in a short-term interval (4 weeks). It can be hypothesized that the association of rofecoxib with finasteride induces a more rapid improvement in clinical results until the effect of finasteride becomes predominant.

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1. Introduction

It is well known that BPH and inflammation can coexist in the prostate, and histological evidence of prostatic inflammation has been described by some

authors in approximately 90% of transurethral resection of the prostate (TURP) specimens [1]. Kessler et al. [2] suggested that immunoinflammatory stimulators might play a role in prostate cell growth and might stimulate hyperplastic changes. It is possible that inflammatory aspects associated with BPH may, in part, concur in the development of LUTS or may also influence prostate tissue growth. It is recognized that finasteride treatment is more effective on larger prostates [3]. The ideal

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patient for finasteride, therefore, would have an enlarged prostate and would have LUTS. If, however, these symptoms were moderate or severe, he might not want to wait the 3 to 6 months required for finasteride to achieve its symptomatic effect [4]. Combination medical therapy may offer the best strategy for these patients. Recently, the MTOPS study showed a significant advantage of combination therapy with finasteride and doxazosin on each monotherapy in the treatment of BPH patients [5]. Even though combination therapy is a popular treatment modality among urologists, there is a surprising lack of published reports on the subject, and the main combination therapy analyzed is that with finasteride plus α 1-adrenoceptor blockers.

Cyclooxygenase-2 (COX-2) is a pro-inflammatory and inducible enzyme which can be induced by mitogens, cytokines and growth factors in different cell types [6]. Several studies have demonstrated the expression of COX-2 mRNA in human prostate tissue [7,8], either BPH or prostate cancer. COX-2 was found to be expressed in basal epithelial cells with 60% BPH and 94% peripheral zone of the prostate [8,9]. There are multiple mechanisms through which COX-2 may play a role in prostate growth. Some of these mechanisms are likely to result from a COX-2 induced increase in prostaglandin (PG) synthesis [8]. Moreover, COX-2 has shown to upregulate Bcl-2 expression with an associated decrease in apoptosis in prostate tissue [10].

The aim of this study was to analyze whether the combination therapy of finasteride with a COX-2 inhibitor may offer an advantage over finasteride monotherapy in improving LUTS and urinary flow in patients with BPH and an enlarged prostate. Fewer data are available in the literature on the effect of finasteride at 1 and 3 months of treatment. Our analysis is particularly focused on the short term period.

The rationale of combining a COX-2 inhibitor with finasteride therapy in BPH cases with an enlarged prostate is:

- in the enlarged prostate gland, inflammatory processes are more commonly present and may condition LUTS and prostate tissue growth;
- by adding an anti-inflammatory effect to the anti-proliferative effect of finasteride, symptoms may improve more rapidly until finasteride has time to act;
- to increase the pro-apoptotic or anti-proliferative effect of finasteride in BPH tissue with the inhibition of COX-2 activity.

We tried to verify these points in the rationale for our combination therapy.

In fact, as in previous studies [11,12], we also analyzed at the BPH tissue level whether the combination of finasteride and a COX-2 inhibitor would result in a significant higher induction of prostate apoptosis or reduction in proliferation.

2. Materials and methods

2.1. Study design

This is a prospective, randomized, single-centre, 24-week unblinded trial.

Forty-six consecutive men were enrolled in this study between June 2002 and March 2003.

During a 24-week treatment phase, subjects who satisfied the inclusion criteria were randomized to receive either finasteride or finasteride plus rofecoxib treatment.

Urinary flow and symptoms were assessed at screening, baseline and weeks 4, 12, 24 or at endpoint. Prostate volume was assessed at screening and at week 24.

Blood pressure (BP), heart rate, and adverse events were assessed at each visit; standard laboratory tests and serum prostate-specific antigen (PSA) measurements were performed at screening and at final visit.

The study protocol was conducted in accordance with the declaration of Helsinki and local laws.

2.2. Screening

The initial visit included a complete history and medical examination, including a digital rectal examination (DRE), sitting and standing BP, heart rate, standard laboratory testing, PSA testing, urinary flow rate, LUTS evaluation, and prostate volume measurements.

2.3. Eligibility

The subjects were men aged 50 to 80 years with BPH and a total International Prostate Symptom Score (IPSS) greater than 12, Q_{\max} of 5 ml/s or greater but 15 ml/s or less in a total voided volume of 150 ml or greater, and a prostate volume greater than 40 cc as determined by transrectal ultrasonography of the prostate (TRUS). Individuals who had undergone previous prostate surgery or other invasive procedures for treating BPH or who had prostate cancer or a PSA level exceeding 10 ng/ml were excluded. To exclude the presence of prostate cancer further, men with a PSA of 4.1 to 10 ng/ml had to provide either a negative DRE or a negative TRUS or negative ultrasound-guided biopsy findings. Other criteria for exclusion included LUTS or reduced urinary flow rates resulting from a condition other than BPH; large bladder diverticulum, bladder stone, recurrent urinary infections, episodes of acute urinary retention (AUR) requiring catheterization during the year prior to entrance in the study; residual urinary volumes greater than 200 ml; active urinary tract infection. Men diagnosed as having serious diseases, history of uncontrolled hypertension, congestive heart failure, unstable angina, cerebrovascular accident, occult fecal blood, bleeding diathesis, active hepatitis/hepatic disease, history of drug or alcohol abuse, history of sensitivity to COX-2 inhibitors, anti-inflammatory drugs or finasteride, any illness or condition that in the opinion of the investigator might confound results or pose additional risks to the patient were excluded.

Previous or concomitant therapy with 5 α -reductase inhibitors, α -blockers, antiandrogens, plant extract preparations, COX-2

inhibitors or other drugs that are known to influence prostate growth or bladder function or concomitant therapies with anticholinergics, cholinergics, diuretics were also considered as exclusion criteria.

2.4. Treatments

Subjects were instructed to take the study medications once daily. Finasteride was administered at 5 mg/day and rofecoxib at 25 mg/day throughout the study. Patients were randomized to receive finasteride monotherapy or finasteride plus rofecoxib for the entire study period.

2.5. Efficacy measures

Urinary flow was assessed using the Dantec Urolynx 1000 rotating uroflowmeter: overall urinary symptoms were assessed using the IPSS in culturally and linguistically validated translations in the subjects' native language. Prostate volume was measured at TRUS using the ellipsoid method.

Moreover, PSA serum levels were determined by immunoassay (Hybritech Inc., San Diego) at screening and final visit.

2.6. Pathological and immunohistochemical analysis

In patients included in the study with a PSA level higher than 4 ng/ml at screening, an ultrasound guided prostate biopsy was obtained at screening and at week 12.

Formalin-fixed and paraffin-embedded prostate specimens were obtained and sectioned to 5 μ m thick prior to analysis. In each prostate sample, the histological diagnosis of BPH was confirmed.

In tissue samples obtained in the transitional zone of the prostate, the proliferative index was determined using Ki-67 nuclear antigen immunostaining with the mouse monoclonal antibody MIB1 (AMAC, Westbrook, ME, USA). Moreover, 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, USA). Apoptotic index was determined as the percentage of TUNEL-positive cells over the total number of cells (at least 200 cells) per section.

In each case examined, apoptotic and proliferative indexes were compared between tissue samples obtained at baseline and during treatments.

2.7. Statistical analysis and statistical power

Descriptive statistics were used to characterize variables in the population and in each group of treatment (mean \pm S.D., median, range). Mean changes adjusted for baseline are presented and tested using the Wilcoxon signed-rank test. Pair-wise treatment comparisons were made. All statistical tests were two-tailed with a 5% level of significance for treatment effects.

3. Results

3.1. Efficacy

Forty-six consecutive patients who responded to the inclusion criteria entered the study and were randomized to treatment. All 46 subjects completed the 24-week period of the study. Mean age was 66.43 ± 6.34 (range 53–76) and 65.91 ± 6.61 (range 54–76) years in the finasteride and finasteride plus rofecoxib groups, respectively ($p = 0.7862$).

The baseline characteristics were not significantly different statistically between the two treatment groups ($p > 0.05$) (Tables 1 and 2).

IPSS and Q_{\max} mean changes from baseline to each interval of follow-up are shown in Fig. 1A and B.

Both treatments (finasteride and finasteride plus rofecoxib) demonstrated statistically significant improvements in IPSS and Q_{\max} from baseline during follow-up ($p < 0.05$), although they were very low for the finasteride group at 4 weeks (mean change IPSS: -0.69 ; Q_{\max} : $+0.62$ ml/s).

If we compare the two treatment groups, no statistically significant differences were observed at visit 24-week ($p > 0.05$). At the 12-week visit, differences were statistically significant only for IPSS but not for Q_{\max} in favor of the finasteride plus rofecoxib treatment ($p = 0.0016$), and at the 4-week visit, a significantly higher improvement in both IPSS ($p = 0.0001$) and Q_{\max} ($p = 0.03$) was obtained in the finasteride plus rofecoxib group when compared to the finasteride group.

Moreover, at the 4-week visit, the per cent of cases with IPSS reduction greater than 4 points was 34.7% and 0% and the per cent of cases with Q_{\max} improvement greater than 3 ml/s was 8.7% and 0% in the finasteride plus rofecoxib versus finasteride group, respectively (Table 1).

A significant reduction in PSA serum levels and prostate volume ($p < 0.0001$) between baseline and the 24-week visit was found in the finasteride plus rofecoxib and in the finasteride group without significant differences between the two groups ($p > 0.05$) (Table 2).

3.2. Tolerability

Treatments were generally well tolerated. None of the 46 cases discontinued treatment and no serious adverse events were reported.

Table 3 shows the treatment-related adverse events that are known to occur with the two treatments. The side-effect distribution was as expected, with more finasteride plus rofecoxib patients having gastrointestinal events. No significant differences between the two treatment groups were reported on other side effects.

3.3. Immunohistochemical results

Ten patients were evaluated immunohistochemically at the BPH tissue level. Analysis of Ki-67 immunoreactivity revealed no significant differences from baseline to the 12-week interval of finasteride or finasteride plus rofecoxib therapy. The proliferative index in prostate cell populations remained unaffected regardless of the medication.

Table 1

IPSS and Q_{max} values at each interval in the two treatment groups: mean \pm S.D. (median), range

	Baseline		4-week		12-week		24-week	
	A	B	A	B	A	B	A	B
IPSS	16.48 \pm 2.33 (16) range 13–20	16.65 \pm 2.01 (17) range 13–20 0.78**	15.78 \pm 2.04 0.02*	13.08 \pm 2.33 <0.0001* 0.0001**	14.35 \pm 3.31 0.0072*	12.26 \pm 2.37 <0.0001* 0.0016**	11.08 \pm 1.83 <0.0001*	11.21 \pm 1.68 <0.0001* 0.80**
Q_{max} (ml/s)	11.99 \pm 1.54 (12.0) range 9.3–14.7	11.82 \pm 1.49 (12.1) range 9.5–14.6 0.46**	12.61 \pm 1.42 0.002*	13.66 \pm 1.84 <0.0001* 0.03**	14.37 \pm 2.26 <0.0001*	14.84 \pm 2.25 <0.0001* 0.48**	15.46 \pm 1.94 <0.0001*	15.24 \pm 1.87 <0.0001* 0.69**
Mean % change from baseline IPSS (range)			–4.2 (–0.6; –7.3)	–21.4 (–16.8; –25.5)	–12.9 (–6.2; –18.7)	–26.3 (–19.9; –32.1)	–32.7 (–27.1; –37.7)	–32.6 (–27.4; –37.2)
Mean % change from baseline Q_{max} (range)			5.08 (3.2; 7.3)	14.58 (10.0; 19.6)	19.8 (12.7; 27.8)	24.4 (17.8; 31.8)	28.9 (22.7; 35.9)	27.41 (21.9; 34.3)
% cases with IPSS reduction > 4 points from baseline			0	34.7	39.1	47.8	78.3	69.7
% cases with Q_{max} improvement > 3 ml/s from baseline			0	8.7	30.4	34.7	65.2	69.6

Treatment: A = finasteride; B = finasteride plus rofecoxib. * p versus placebo. ** p versus finasteride monotherapy.

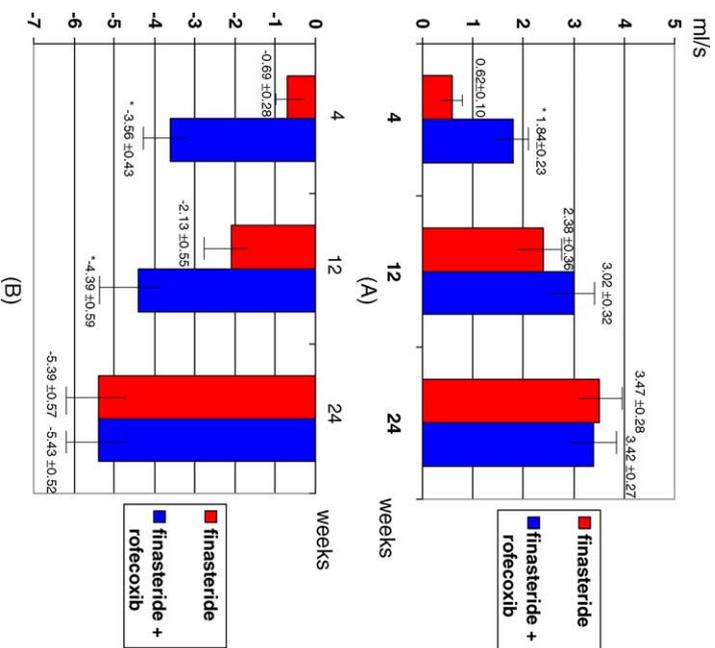


Fig. 1. (A) Mean change \pm S.E. from baseline in Q_{max} at different intervals with finasteride and finasteride plus rofecoxib. Rates adjusted for baseline values. * p < 0.001 versus finasteride monotherapy. (B) Mean change \pm S.E. from baseline in IPSS at different intervals with finasteride and finasteride plus rofecoxib. Scores adjusted for baseline values. * p < 0.001 versus finasteride monotherapy.

Upon comparison of the apoptotic index (AI) of patients in any of the treatment groups over their baseline, a significant increase was observed (finasteride alone: $p = 0.0049$; finasteride plus rofecoxib: $p = 0.0038$) (Fig. 2). There was a slightly further increase in the AI of patients on combination therapy

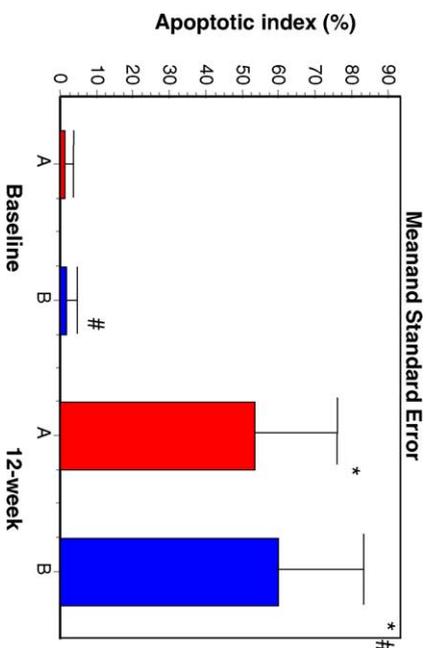


Fig. 2. Quantitative analysis of the effect of finasteride (A) and finasteride plus rofecoxib (B) in prostate apoptosis. Apoptotic index is expressed as mean percentage \pm S.E. of TUNEL-positive cells/total number of cells in prostate specimens. * p < 0.005 versus baseline. # p > 0.05 versus finasteride monotherapy.

Table 2PSA and prostate volume at baseline and visit 24-week. mean \pm S.D., (median), range

	Baseline		24-week	
	A	B	A	B
PSA (ng/ml)	2.68 \pm 1.18 (2.5) range 0.8–5.3	2.62 \pm 1.16 (2.3) range 0.9–5.1 0.87**	1.70 \pm 0.70 <0.0001*	1.69 \pm 0.76 <0.0001* 0.96**
Prostate volume (cc)	51.65 \pm 9.07 (52) range 43–78	49.65 \pm 9.47 (50) range 41–78 0.99**	42.82 \pm 7.39 <0.0001*	40.86 \pm 8.29 <0.0001* 0.98**
Prostate volume % mean change from baseline (range)			–20.2 (–18.9; –20.3)	–20.1 (–18.0; –20.2)
PSA % mean change from baseline (range)			–36.4 (–32.2; –39.1)	–35.4 (–31.0; –38.2)

Treatment: A = finasteride; B = finasteride plus rofecoxib. * *p* versus placebo. ** *p* versus finasteride monotherapy.

Table 3

Incidence of adverse events

Event	Number of cases (%)	
	Finasteride	Finasteride plus rofecoxib
Death	0 (0.0)	0 (0.0)
Discontinuation	0 (0.0)	0 (0.0)
Acute urinary retention	0 (0.0)	0 (0.0)
Reduction in sexual potency	1 (4.3)	1 (4.3)
Libido decrease	3 (13.0)	2 (8.7)
Abnormal ejaculation	2 (8.7)	2 (8.7)
Cardiovascular	0 (0.0)	0 (0.0)
Gastrointestinal	0 (0.0)	3 (13.0)

over those with finasteride alone ($p = 0.3911$) (Figs. 2 and 3).

4. Discussion

This represents the first experience in the literature using a combination therapy with a 5α -reductase

inhibitor and a COX-2 inhibitor for the treatment of BPH. The rationale to combine rofecoxib and finasteride in BPH cases is: (1) to add an anti-inflammatory effect to the proapoptotic effect of finasteride on BPH tissue that may rapidly improve symptoms and urinary flow until finasteride has time to act; (2) to increase the proapoptotic effect of finasteride in BPH tissue with the inhibition of COX-2 activity.

We selected BPH patients with an enlarged prostate (prostate volume > 40 cc) for two reasons: (1) it is recognized that finasteride treatment is more effective on larger prostates [3]; (2) inflammatory processes are present more commonly in enlarged prostate glands and may condition LUTS and prostate tissue growth [1].

Interrelationships between BPH and prostatic inflammation have been studied by several authors [13,14]. De Marzo et al. [15] showed foci of proliferative glandular epithelium occurring in association with inflammation in prostate tissue; the authors also

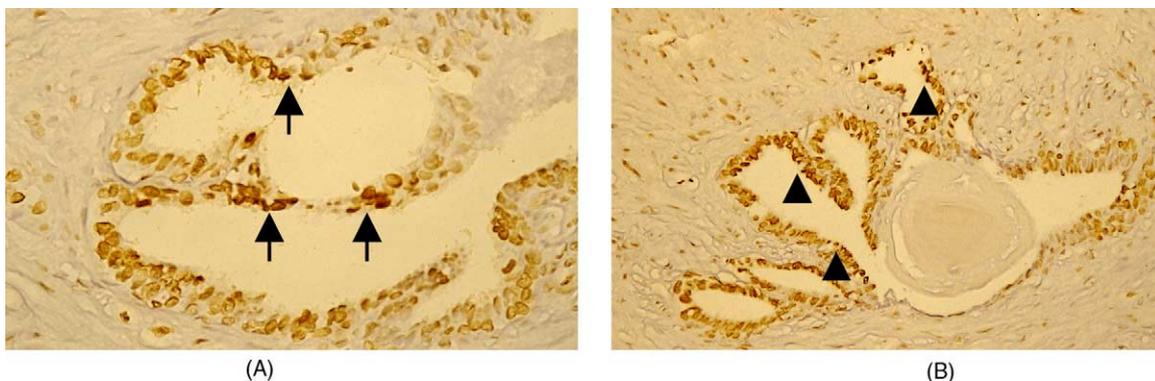


Fig. 3. Effect of finasteride (A) and finasteride plus rofecoxib (B) therapy on prostate cell apoptosis (in situ) in BPH specimens. Numerous apoptotic cells as detected by TUNEL assay were identified in prostatic cells of BPH sections either after finasteride or finasteride plus rofecoxib treatment. Darkly stained cells are prominent and indicative of apoptotic TUNEL positivity (arrow). Original magnification $\times 400$.

noted increased staining for prostate cell proliferation marker and for Bcl-2 expression in proximity of inflammation. These data may support the hypothesis that an anti-inflammatory therapy which is active on BPH tissue, may also condition prostate tissue growth.

COX-2 promotion of cell growth and modification of phenotype has been linked to its ability to increase prostaglandin production, promote angiogenesis, inhibit apoptosis, modulate inflammation in the microenvironment around cells [16,17]. COX-2 activity has been demonstrated to be significant not only in prostate cancer but also in BPH tissue. The results of these studies lead to the conclusion that COX-2 plays an important role in the proliferation of prostate cells. The COX-2 effect on prostate cell proliferation may be obtained either by modulating the inflammatory process or by directly decreasing apoptosis (upregulation of Bc-2 expression) [8].

Following the experience of previous studies [11,12], we analyzed, at BPH tissue levels, modifications in proliferative and apoptotic indexes induced by our therapy. As in the study of Glassman [12], in our study no significant differences in BPH tissue proliferative index during therapy were found in our cases. On the contrary, upon comparison of the apoptotic index, a significant increase during therapy was observed either in the finasteride or in the finasteride plus rofecoxib group. However, as in the above-cited Glassman study, it was until 6 months' therapy was given with the combination of finasteride plus rofecoxib that an only slightly but not significant further increase occurred in the apoptotic index when compared to finasteride alone. These immunohistochemical data seem to suggest that our combination therapy can slightly increase apoptotic activity in BPH tissue when compared to finasteride monotherapy. A longer term analysis (more than 3 months) may, however, be justified on the basis of these results and previous experiences [12].

The aim of our clinical study was to verify whether the combination of finasteride with rofecoxib can offer advantages in terms of efficacy (symptoms and urinary flow rates) when compared to finasteride monotherapy.

The MTOPS study [5] demonstrated a significant advantage in the combination of doxazosin plus finasteride over the individual monotherapies in either improving symptom scores, urinary flow or the risk of BPH progression. The advantage of the combination therapy was particularly evident in the long-term period whereas no significant differences with monotherapies were found in the first year of treatment. Our single centre, short-term, not controlled with placebo,

experience is not comparable with a study such as MTOPS. However, some interesting suggestions can be obtained from our study. Few data are available in the literature on the effect of finasteride at months 1 and 3 of treatment. We found that finasteride monotherapy produces very little improvement at the 1 month interval. At the interval at month 6, the results obtained in the finasteride monotherapy group are comparable to those reported in the literature [4,18], and no statistically significant differences were observed with the combination therapy group. On the contrary, in particular at the interval at month 1 as well as at month 3, a significantly higher improvement in IPSS and Q_{\max} (only in IPSS at month 3) was obtained in the finasteride plus rofecoxib group when compared to the finasteride group ($p < 0.05$).

Some studies considered an IPSS reduction of more than 4 points and a Q_{\max} improvement greater than 3 ml/s as clinically significant [18]. In our population, at the week 4 visit, the percent of cases with an IPSS reduction of more than 4 points was 34.7% and 0% and the percent of cases with Q_{\max} improvement greater than 3 ml/s was 8.7% and 0% in the finasteride plus rofecoxib versus finasteride alone group, respectively.

According to the immunohistochemical results on the apoptotic index, a significant reduction in PSA level and prostate volume was found in each treatment group with no differences. Since we limited our investigation to the first 6 months of therapy, we cannot offer results in terms of disease progression. Our results are particularly significant for the short-term period, and we focused our analysis specifically to this period. The reduced efficacy of finasteride in the first 6 months of therapy is an actual and open problem.

Tolerability of both treatments was good, none of our cases discontinued treatment, and no serious adverse events were reported. The combination of rofecoxib and finasteride produced a higher percentage of gastrointestinal events when compared to finasteride alone. However, all these events were moderate and well controlled by the patient. Long-term gastrointestinal and cardiovascular safety of rofecoxib treatment has been demonstrated in several trials with lower side effect rates compared to those obtained with other NSAIDs [19].

It can be hypothesized that the association of rofecoxib with finasteride induces a more rapid improvement in clinical results until the effect of finasteride becomes predominant. Baldwin et al. [20] showed that patients with LUTS and enlarged prostates initially receiving combination therapy with finasteride and an α -adrenoceptor blocker are likely to experience no significant symptoms deterioration after discontinuing

the α -blocker after 9 months of combination therapy. Our results may represent a basis on which to verify the effect of the discontinuation of rofecoxib after an initial 3 months of combination therapy with finasteride.

The question may be: why not just combine finasteride with an α 1-blocker as done in MTOPS? This achieves similar results, and the medication itself is similarly priced. With our pilot study we want only suggest that also a COX-2 inhibitor can be associated with finasteride, and may represent an alternative to the use of α 1-blockers in the combination with finasteride (in particular in the short term period). Our results also underline that not only a dynamic component related to the α 1-adrenergic system but also an inflammatory component inside the prostate gland, is able to condition LUTS and urinary flow rates. We must, however, underscore the limits of our study. This is a prospective but single centre unblinded study on a limited population. Although we did not use a placebo control for our study, we considered the finasteride alone group as the control to compare the effect of our combination therapy. Results on finasteride monotherapy have been extensively described in the literature and are comparable with the results we obtained. We specifically analyzed the two therapies only over short-term intervals because this is something of present and open interest. However, the analysis of long-term results may be useful from both a clinical and histological point of view.

5. Conclusions

The rationale for combining α 1-adrenoceptor blockers with finasteride is to interact with both the dynamic and mechanical component of BPH. The rationale of our combination therapy is to interact with the inflammatory in addition to the mechanical component of BPH and to sustain the effect of finasteride over a short term so as to induce a more rapid improvement in clinical results until the effect of finasteride becomes predominant. We demonstrate a slightly but not significant higher proapoptotic effect on BPH tissue obtained with the combination of a COX-2 inhibitor to finasteride in comparison to finasteride alone, but there were significantly better clinical results in terms of efficacy at 1 and 3 months.

It should be emphasized that any conclusion regarding the usefulness of this combination therapy can only be drawn from larger, randomized, controlled clinical trials. The results of our study indicate that such trials are warranted because our combination therapy had a favorable tolerability profile and offered clinical symptomatic responses.

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Editorial Comment

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The Medical Therapy for Prostatic Symptoms (MTOPS) study demonstrated that combination medical therapy utilizing the two most widely utilized classes of drugs— α -adrenergic receptor blocker and 5α -reductase inhibitors—is superior to either drug alone in terms of delaying or preventing the progression of lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) over a five-year duration of treatment. Other combination therapies offering at least theoretical advantages such as the combination of α -blockers and anticholinergics have been tested and found to be both safe and effective in selected patients. It is understandable and commendable to study other combinations for the treatment of LUTS and BPH. The presence of inflammatory infiltrates in BPH surgical specimens is well known and documented. However, there is no direct link between the *presence or severity of inflammatory infiltrates and presence or severity of LUTS and BPH-related signs and symptoms*. Thus, the rationale for the use of an anti-inflammatory agent such as the COX-2 inhibitor rofecoxib is less clear. This 24-week long study demonstrated that patients receiving rofecoxib together with finasteride had a faster onset of improvements in both symptoms and flowrate. While of interest and thought provoking, several important questions arise: why would one prefer an anti-inflammatory drug like rofecoxib or another COX-2 inhibitor in favor of using an α -receptor blocker? Would the results be the same if the study would be double-blinded and placebo controlled? One should remember that patients in a study setting tend to respond better if they receive more medications (Blackwell, Bloomfield et al. 1972). In this study medical students received unknowingly placebo tablets of different color, shape and size and different numbers of tablets and were told that they should expect either a stimulatory or a sedatory effect. Different colors of the placebo tablet caused different responses, and the responses were greater to the larger tablets and if there were more tablets given, although none of them contained any active medication. The current study requires validation in a double blind placebo controlled setting, and an economic or other

justification why the tested combination might be preferable over the standard α -blocker and 5α -reductase inhibitor combination.

Editorial Comment

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This paper addresses a plausible hypothesis that combination of a COX-2 inhibitor with a 5α -reductase inhibitor may speed the onset of relief from BPH-related LUTS. This hypothesis is plausible in that inflammation is known to co-exist with BPH in many prostate specimens (including transition zone resections from men with symptoms) and that such inflammation may contribute to LUTS. However, the significance of the associated inflammation in terms of LUTS severity has never been unambiguously established, and it is worth considering that inflammation in various zones of the prostate is essentially ubiquitous, among symptomatic and asymptomatic men. Total prostatectomy specimens removed because of cancer often show substantial inflammation histologically.

This trial shows a very modest short-term “beneficial” effect of combining rofecoxib with finasteride. The magnitude of improvement in flow rate and symptom scores observed in the combination arm in comparison to the monotherapy arm was relatively small (in a relatively small population), probably clinically irrelevant, and potentially due to the placebo-effect of taking 2 medications rather than 1. These data clearly are not definitive and do not establish the effectiveness of the combined approach over monotherapy.

A larger, placebo-controlled trial is necessary to establish the efficacy of the combination in men with LUTS due to BPH. Ideally, beyond the usual clinical end-points, this trial will also include correlative science studies measuring relevant baseline and post-treatment tissue histologic parameters and intermediary molecular markers. Only by such a study will the significance of inflammation on the presence and development of LUTS be known and will role of COX-2 inhibition in reducing those symptoms be established.