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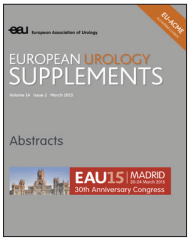

European Association of Urology

Comparison of the Effects of Hexanic Extract of *Serenoa repens* (Permixon) and Tamsulosin on Inflammatory Biomarkers in the Treatment of Benign Prostatic Hyperplasia-Related Lower Urinary Tract Symptoms

Grégoire Y. Robert [a,*]

[a] *Department of Urology, Bordeaux Pellegrin University Hospital, Université de Bordeaux, Bordeaux, France*

Article info

Keywords:
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Abstract

Context: Chronic prostatic inflammation appears to have a key role in the pathogenesis and progression of benign prostatic hyperplasia (BPH). The PERMIN study compared the effects of hexanic extract of *Serenoa repens* (Permixon; Pierre Fabre, Castres, France) and tamsulosin on inflammation-related biomarkers secreted in urine of patients with BPH-related lower urinary tract symptoms (LUTS).
Objective: To review key features of the PERMIN study as they relate to treatment effects on the messenger RNA expression of selected inflammation-related genes and proteins.
Evidence acquisition: This article is based primarily on material presented at a satellite symposium entitled, "Inflammation and Prostatic Diseases: From Bench to Bedside," held during the 2015 annual meeting of the European Association of Urology in Madrid, Spain. Current data regarding the link between inflammation and BPH were reviewed.
Evidence synthesis: Permixon showed a more pronounced effect than tamsulosin on selected inflammation-related genes and proteins. Among the 15 most frequently expressed genes in patients at baseline, 73% were favourably affected by Permixon versus 27% with tamsulosin, as indicated by the combination of downregulation and fewer upregulation effects. Expression of inflammatory proteins (CCL2/MCP-1, CXCL10/IP-10, macrophage migration inhibitory factor [MIF]) was downregulated in a higher percentage of patients and upregulated in a lower percentage of patients treated with Permixon compared with tamsulosin. In Permixon-treated patients, greater improvement in the International Prostate Symptom Score was observed at 3 months in those who overexpressed MIF protein at baseline compared with those who did not (−6.4 vs −4.5).
Conclusions: Downregulation of inflammation-related genes and proteins by Permixon brought meaningful symptomatic improvement in patients with moderate to severe LUTS. Patients with high chronic prostatic inflammation may benefit from early treatment with Permixon.
Patient summary: Downregulation of inflammation-related genes and proteins by *Serenoa repens* (Permixon) was associated with meaningful symptomatic improvement in patients with moderate to severe lower urinary tract symptoms. Patients with high chronic prostatic inflammation may benefit from early treatment with Permixon.

* Department of Urology and Kidney Transplantation, Bordeaux Pellegrin University Hospital, Université de Bordeaux, Place Amélie Raba-Léon, 33000 Bordeaux, France.
E-mail: gregoire.robert@chu-bordeaux.fr (G.Y. Robert).

1. Introduction

The transcriptome of the aging prostate stroma is characterised by upregulation of numerous genes that encode secreted inflammatory mediators shown to stimulate prostatic cell growth [1]. As such, prostatic inflammation has been proposed as an appropriate target for medical treatment of lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) [2]. In the 20 yr since the anti-inflammatory activity of hexanic extract of *Serenoa repens* (Permixon; Pierre Fabre, Castres, France) was first reported [3], a considerable body of in vitro and in vivo evidence has accumulated that demonstrates inhibition by Permixon of inflammatory cells (macrophages, T lymphocytes, B lymphocytes) [4,5] and a wide variety of inflammatory mediators and proteins [3,5–9] as well as deregulation of numerous genes known to play key roles in the proliferative, apoptotic, and inflammatory pathways of BPH [10]. Nevertheless, evidence of its anti-inflammatory activity at the clinical level was lacking.

PERMIN was a randomised clinical trial designed specifically to investigate the anti-inflammatory activity of therapy intended for the treatment of BPH-related LUTS [11]. Based on our work at the University of Bordeaux and other published articles [9,10,12–20], the 29 most significant inflammation markers in BPH were identified and selected for investigation (Table 1). To better understand the mechanisms behind the anti-inflammatory effects of Permixon, tamsulosin was selected as the comparator because of its frequent prescription, well-established mechanism of action, and absence of any known anti-inflammatory activity. The PERMIN study has recently been reported in full [11]. This review examines some key features of the study and provides a clinical interpretation of the comparative effects of Permixon and tamsulosin on inflammatory markers in men with BPH-related LUTS.

2. Evidence acquisition

This article is based primarily on material presented at a satellite symposium entitled, "Inflammation and Prostatic Diseases: From Bench to Bedside," held during the 2015 annual meeting of the European Association of Urology in Madrid, Spain. Current data regarding the link between inflammation and BPH were reviewed. The article is complemented by relevant related literature identified on PubMed and by hand searches of key references.

3. Evidence synthesis

3.1. PERMIN study: patients and methods

PERMIN was a multicentre, exploratory, double-blind, randomised, phase 4 study designed to compare the effects of Permixon and the α_{1a}-adrenergic receptor antagonist tamsulosin on inflammatory biomarkers secreted in the urine of patients with BPH-related LUTS. To monitor inflammatory status, a noninvasive method was used that allowed for collection of prostatic epithelial cells desquaming in the lumen of glands and seminal plasma fluid after digital rectal examination. As the methods are detailed in the original article [11], only a brief summary is provided in this report.

Table 1 – Selected inflammation-related genes [9–19]

IL-1β	*PLA2G2A*	*CTLA4*	*ALOX5*	*CAT*	*NFKB1*
IL-6	*CXCL10*	*FGF-2*	*ICOS*	*CCL5*	*PTGES2*
IL-8	*CCL2/MPC-1*	*CXCL6*	*SELP*	*HIF1A*	*PTGES3*
IL-15	*CD40LG*	*ALOX15*	*STAT3*	*LTC4S*	*PTGS2*
IL-17	*CCR7*	*ALOX15B*	*PTPRC*	*MIF*	

Patients eligible for inclusion were men aged 45–85 yr with a minimum 12-mo history of bothersome LUTS related to BPH. Specific criteria were International Prostate Symptom Score (IPSS) ≥12, prostatic volume ≥30 ml, maximal urinary flow rate (Q_{max}) of 5–15 ml/s for a voided volume 150–500 ml, serum total prostate-specific antigen (PSA) ≤4 ng/ml or ≤10 ng/ml with a ratio free to total PSA ≥25% or a negative prostate biopsy.

Initial screening was followed by a 28-d washout/run-in phase and further patient selection (Fig. 1). Eligible patients were randomised at a 1:1 ratio to receive Permixon 160 mg twice daily or extended-release tamsulosin 0.4 mg once daily for 90 d. Four visits were planned for each participant: selection visit, baseline visit (day 1), first assessment visit (day 30), and end-of-study visit (day 90).

The primary end point was the change from baseline to study end in messenger RNA (mRNA) expression of the selected BPH inflammation markers (Table 1). Downregulation and upregulation of gene expression were considered to have occurred when a change of twofold or more from baseline was observed. Secondary end points were the change from baseline to study end in mRNA expression of selected proteins and the clinical efficacy of medical treatments based on patients' prostatic inflammation status (change in IPSS) from day 1 to days 30 and 90.

3.2. PERMIN study: results

The PERMIN study took place between June 2012 and October 2013 at 42 centres across France, Italy, Portugal, and Spain. Of 323 patients screened, 303 patients were selected and 206 patients were randomised to treatment, 102 to Permixon and 104 to tamsulosin (101 were treated). Main reasons for noninclusion were failure to meet entrance criteria (n = 64), particularly with regard to Q_{max}, and patient's decision not to participate (n = 22). Nineteen patients withdrew from Permixon for reasons of safety (n = 7), efficacy (n = 2), safety and efficacy (n = 1), or other (n = 9). Eighteen patients withdrew from tamsulosin for reasons of safety (n = 3), efficacy (n = 2), or other (n = 13).

Groups were well matched at baseline for demographic and clinical characteristics (Table 2). Similar to the population in the Combination of Avodart and Tamsulosin (CombAT) study [21], PERMIN patients had moderate to severe BPH-related LUTS.

3.2.1. Primary end point

3.2.1.1. Change in messenger RNA expression of inflammation-related genes

Twenty-six of the 29 selected inflammation-related genes were detected in at least one patient. From baseline to

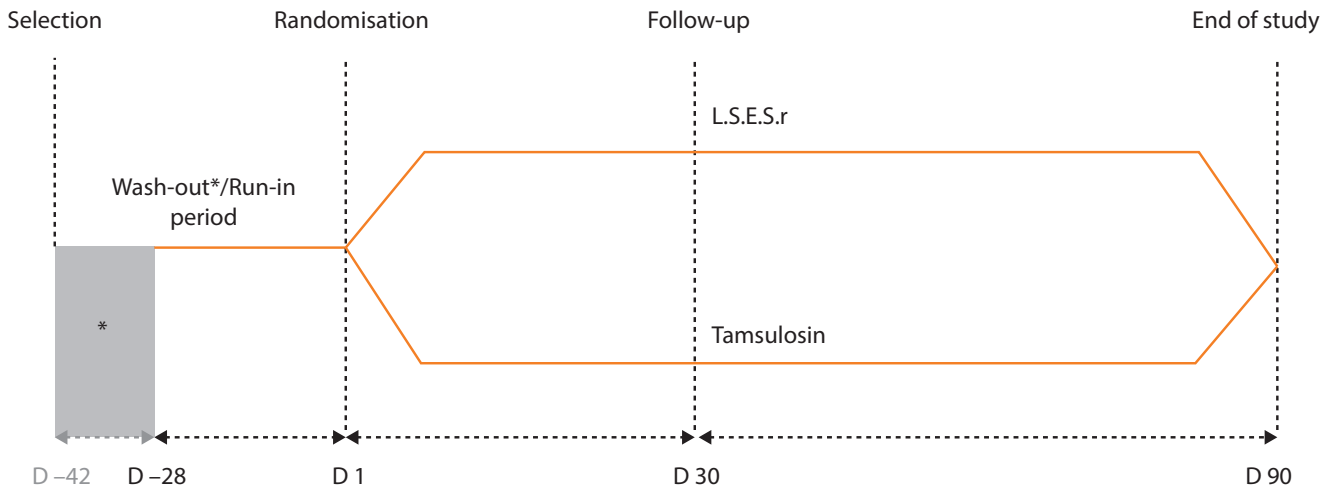

Fig. 1 – PERMIN study design. * Optional 2-wk washout period. D = day; L.S.E.r = lipidosterolic hexanic extract of *Serenoa repens* (Permixon); V = visit.

Table 2 – Baseline characteristics of patients in the PERMIN study

Parameter	Permixon (n = 102)	Tamsulosin (n = 101)
Age, years	65.4 (7.8)	66.1 (7.6)
IPSS	17.7 (4.4)	16.8 (4.5)
IPSS question 8	3.9 (0.9)	3.8 (0.9)
MSF4 score	7.4 (4.5)	6.9 (4.5)
Q_{max}, ml/s	10.88 (2.69)	10.60 (3.03)
Transrectal prostate volume, ml	48.82 (20.80)	46.29 (13.88)
Suprapubic postvoid residual volume, ml	53.82 (57.07)	42.04 (47.61)

All values are means (SD). IPSS = International Prostate Symptom Score; IPSS question 8 = patient's perceived quality of life; MSF4 score = Male Sexual Function 4-item questionnaire; Q_{max} = maximal urinary flow rate; SD = standard deviation.
Adapted with permission from Wiley-Blackwell [11].

study end, mean mRNA expression was reduced in 65.4% of genes in Permixon-treated patients and in 46.2% of genes in tamsulosin-treated patients, for a difference of 19.2% in favour of Permixon. With respect to the 15 most frequently expressed genes at baseline (*ALOX5, ALOX15B, CAT, CCL2, HIF1A, IL1B, IL8, MIF, NFKB1, PLA2G2A, PTGES2, PTGES3, PTGS2, PTPRC* and *STAT3*), mean mRNA expression was reduced in 80% of genes in Permixon-treated patients and in 33% of genes in tamsulosin-treated patients, for a difference of 47% in favour of Permixon. Analyses of the cumulative favourable effect per gene, defined as a combination of more downregulation and less upregulation, indicated a favourable effect on 73% of genes after Permixon treatment versus 27% of genes after tamsulosin treatment (Fig. 2).

3.2.2. *Secondary end points*

3.2.2.1. *Change in protein expression*

Three of the 10 selected proteins were detected in urine: monocyte chemoattractant protein-1 (CCL2/MCP-1); CXCL10/IP-10, a chemoattractant for human monocytes and T cells; and macrophage migration inhibitory factor (MIF). For CCL2/MCP-1, the proportion of patients showing expression in urine samples from baseline to study end decreased from 54.8% to 35.6% with Permixon (−19.2%) and increased from 46.5% to 47.9% with tamsulosin (+1.4%). For CXCL10/IP-10, the proportion of patients showing expression in urine samples from baseline to study end decreased from 74.0% to 63.0% with Permixon (−11.0%) and increased from 64.8% to 67.6% with tamsulosin (+2.8%). MIF was expressed in all urine samples at baseline and at study end. MIF expression was downregulated in a higher proportion (42.5% vs 23.9%) and upregulated in a lower proportion (43.8% vs 66.2%) of patients treated with Permixon compared with tamsulosin ($p = 0.007$).

3.2.2.2. *Change in International Prostate Symptom Score*

From baseline to study end, IPSS was reduced by 4.5 points with Permixon (from 17.7 to 13.2) and by 6.3 points with tamsulosin (from 16.6 to 10.3). Among Permixon-treated patients, those with greater baseline MIF expression had more pronounced symptomatic improvement (mean IPSS change) than those without MIF overexpression (Fig. 3).

3.2.3. *Safety*

Permixon and tamsulosin had similar safety profiles. Treatment-emergent adverse events (TEAEs) were reported in 10.8% of Permixon-treated patients and in 8.9% of tamsulosin-treated patients. No related TEAE occurred at a frequency >1% in the Permixon group, whereas ejaculation failure, retrograde ejaculation, and asthenia were each reported in 2% of patients treated with tamsulosin.

4. Discussion

The PERMIN study is unique in that it was designed specifically to assess, in a noninvasive manner, the anti-inflammatory effects of medical treatments on BPH-related LUTS. The anti-inflammatory activity of Permixon was greater than that of tamsulosin across all primary and secondary end points. A decrease in mean mRNA expression of detected BPH inflammation markers was observed in 65% of patients in the Permixon group versus 46% of patients in the tamsulosin group. Among the 15 most frequently

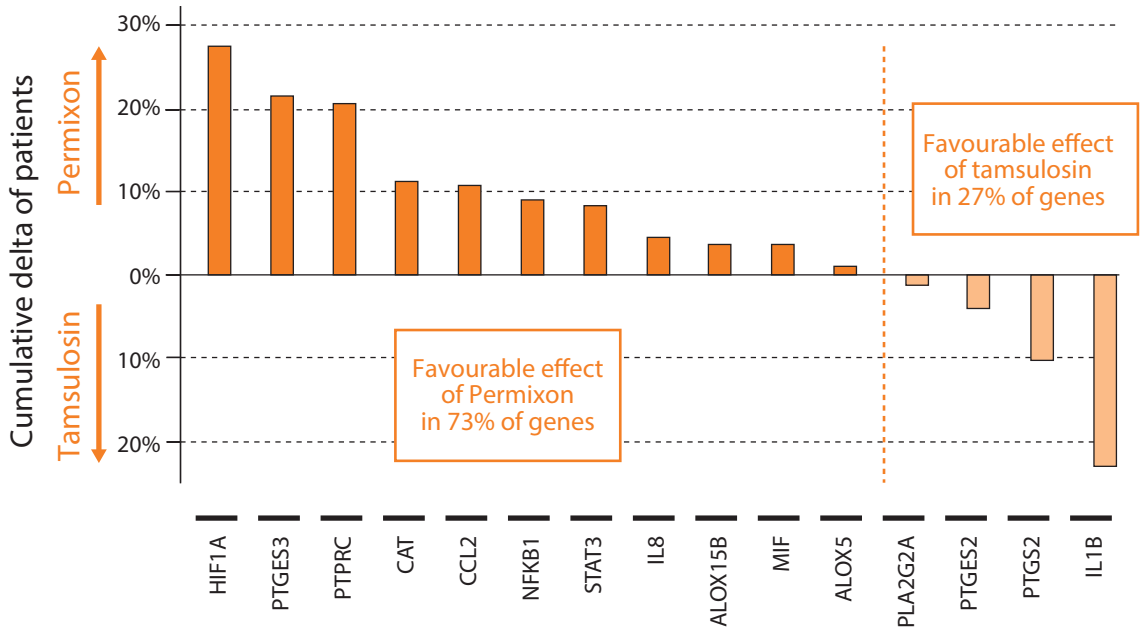

Fig. 2 – Cumulative effect of Permixon and tamsulosin on messenger RNA expression of inflammation-related genes at end of treatment (day 90). The global favourable effect corresponded to the sum of the delta of patients between treatment groups for the combination of more downregulation and fewer upregulation effects. Reproduced with permission from Wiley-Blackwell [11].

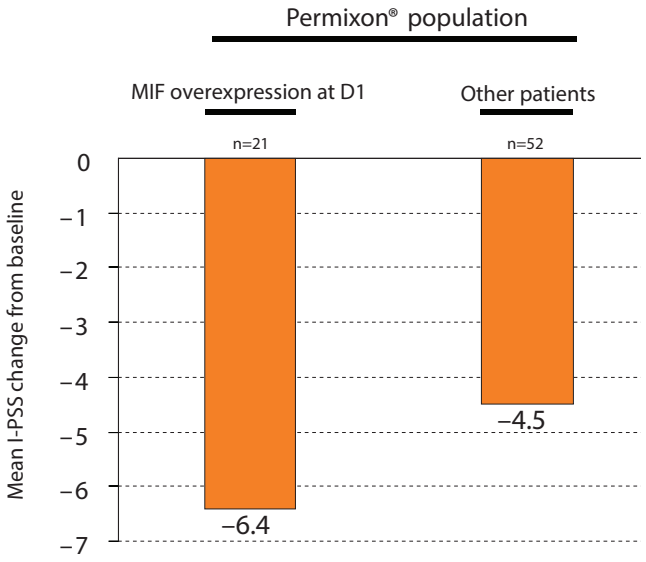

Fig. 3 – Change in the International Prostate Symptom Score from baseline to study end in Permixon-treated patients according to expression of macrophage migration inhibitory factor at baseline. Adapted with permission from Wiley-Blackwell [11]. D1 = baseline; IPSS = International Prostate Symptom Score; MIF = macrophage migration inhibitory factor.

expressed markers, Permixon had a cumulative favourable effect (more downregulation and less upregulation) on 73% of genes compared with 27% for tamsulosin.

Permixon, but not tamsulosin, decreased the proportion of patients expressing CCL2/MCP-1 and CXCL10/IP-10 proteins between baseline and study end. Between-treatment differences in MIF expression were statistically significant: MIF expression was downregulated in more patients (42.5% vs 23.9%) and upregulated in fewer patients (43.8% vs 66.2%) treated with Permixon than tamsulosin (p = 0.007). Given its role as a key player in immune response regulation with an influence on prostatic cell growth, targeting MIF may be a rational approach from clinical and therapeutic perspectives. Symptomatic improvement of LUTS was considerably more pronounced in Permixon-treated patients with than without MIF overexpression at baseline, suggesting that early treatment with Permixon may prevent unfavourable clinical evolution. Moreover, the ubiquity of MIF expression in urine samples at baseline and study end suggests that it may be a candidate biomarker to assess chronic prostatic inflammation.

The greater efficiency of Permixon in the subset of patients with MIF overexpression may be explained by benchside observations. Immunohistochemistry studies in prostate tissue samples of patients undergoing surgery for BPH have shown greater MIF expression in BPH lesions than in adjacent normal area [22]. In vitro, MIF has been shown to upregulate BPH epithelial cell line proliferation through a process involving cyclooxygenase-2 and p53 signalling [22].

The inclusion criteria of the PERMIN study also provide clues when interpreting the results for clinical practice. Eligibility was restricted to patients with moderate to severe LUTS and a high “bother” score, in contrast to other studies of plant extracts in which populations were generally limited to patients with mild to moderate symptoms. The mean improvement of 4.5 points in IPSS in Permixon-treated patients was thus a clinically meaningful result in a therapeutically challenging population.

Permixon is the only medical treatment for BPH-related LUTS with anti-inflammatory activity demonstrated in vitro, in vivo, and now in a randomised clinical trial. The favourable effect of tamsulosin observed on some genes and/or patients in the PERMIN study can likely be explained by the relief of urinary obstruction associated with effective α-blocker therapy.

5. Conclusions

Downregulation of inflammation-related genes and proteins by Permixon was associated with meaningful symptomatic improvement in patients with moderate to severe BPH-related LUTS. The greater degree of improvement in IPSS with Permixon in patients with higher baseline MIF protein expression suggests that patients with higher chronic prostatic inflammation and greater MIF overexpression may benefit most from this treatment.

Conflicts of interest

G.Y. Robert has received honoraria as a consultant and speaker from Pierre Fabre Médicament.

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