

Original Paper

IPSS Score and IL-6 Before and During Treatment with Dutasteride in Patients with Benign Prostatic Hyperplasia

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REZUMAT

Relația dintre scorul IPSS și IL-6 înainte și în cursul tratamentului cu dutasteridă la pacienții cu hiperplazie benignă de prostată

Introducere: Hiperplazia benignă de prostată reprezintă una din cele mai frecvente patologii la bărbatul în vârstă, fiind asociată cu simptomatologie de tract urinar inferior.

Obiectiv: Evaluarea relației dintre statusul clinic (scor IPSS - International Prostatic Symptom Score) și valorile serice ale IL-6 la pacienții cu hiperplazie benignă prostatică înainte și în timpul tratamentului cu dutasteridă.

Material și metodă: Studiul de față este unul clinic prospectiv observațional, ce a inclus 35 bărbați adulți diagnosticați cu hiperplazie benignă de prostată. Pacienții au fost evaluați la începutul tratamentului cu dutasteridă 0,5 mg zilnic (Momentul 0) și la 6 luni de la debutul acestuia (Momentul 1).

Rezultate: Analiza statistică a arătat o relație interesantă între IL-6 și markerii clinici ai BPH. Interleukina-6 a avut o corelație pozitivă semnificativă statistic cu volumul prostatic ($r = 0,53$, $p < 0,05$) și o corelație pozitivă slabă cu scorul IPSS, semnificativă statistic ($r = 0,21$, $p < 0,05$). Scorul IPSS a arătat o îmbunătățire progresivă în timpul terapiei medicamentoase, la Momentul 1 comparativ cu valoarea inițială ($9,54 \pm 1,44$ vs $13,51 \pm 1,44$, $p < 0,05$), în timp ce interleukina-6 a prezentat o scădere semnificativă la Momentul 1 în raport cu Momentul 0 ($1,66 \pm 0,37$ pg / ml vs $15,50 \pm 2,71$ pg / ml, $p < 0,05$).

Concluzii: IL-6 poate reprezenta un marker predictor al severității simptomatice și al eficienței terapiei cu dutasteridă în hipertrofia benignă de prostată.

Cuvinte cheie: scor IPSS, IL-6, hiperplazie benignă de prostată, dutasteridă

ABSTRACT

Introduction: Benign prostatic hyperplasia is one of the most common pathologies in aging men, associated with lower urinary tract symptoms.

Objective: Evaluating the relation between clinical status (IPSS score - International Prostatic Symptom

Score) and the IL-6 serum values in patients with benign prostatic hyperplasia before and during medical treatment with dutasteride.

Material and methods: This is a clinical prospective-observational study, which included 35 adult males diagnosed with benign prostatic hyperplasia. The patients were evaluated at the beginning of the treatment with dutasteride 0.5 mg daily (Moment 0), and at 6 months (Moment 1).

Results: The statistical analysis showed an interesting relation between IL-6 and clinical markers of BPH. Interleukin-6 had a statistically significant positive correlation with prostate volume ($r = 0.53$, $p < 0.05$) and a weak positive correlation with IPSS score, statistically significant ($r = 0.21$, $p < 0.05$). The IPSS score showed a gradual improvement during medical therapy, for the Moment 1 compared to the initial value (9.54 ± 1.44 vs. 13.51 ± 1.44 , $p < 0.05$), while interleukin-6 presented a significant decrease at Moment 1 compared to Moment 0 (1.66 ± 0.37 pg / ml vs. 15.50 ± 2.71 pg / ml, $p < 0.05$).

Conclusions: IL-6 could represent a predictor marker of the severity of symptomatology, and also, of the effectiveness of dutasteride therapy.

Key words: IPSS score, IL-6, benign prostatic hyperplasia, dutasteride

INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common pathologies in aging men, associated with lower urinary tract symptoms (LUTS). This pathology has a multimodal approach depending on different factors like age, prostate size, prostate-specific antigen level, and severity of the symptoms [1].

Medical treatment is the first option in what patients with low or moderate LUTS are concerned. There are two major drug classes already established in all international treatment guidelines, 5 alpha-reductase inhibitors and alpha-blockers. 5 alpha-reductase inhibitors block the transformation of testosterone in dihydrotestosterone within the prostate, leading to the decrease of prostate volume, increased peak urinary flow rate, improvement of symptoms, decreasing the risk of acute urinary retention. Their main secondary effects are the erectile dysfunction, the decreasing of libido and of the ejaculate volume, and also gynecomastia [2]. Alpha-blockers act on alpha-adrenoceptor sites found particularly at the bladder neck, at the trigone and within the prostate. They have a fast action on the prostate gland, leading quickly to symptom relief, but without reducing the risk of acute retention or surgical treatment. As secondary effects, alpha-blockers can affect blood pressure [3-5].

These drugs are accompanied in the last years by other therapies like phytotherapy with vegetal products and/or muscarinic receptor antagonists. Severe cases are candidates for surgical treatment,

which can be performed by open or minimally invasive technique, depending on the prostate dimensions, the associated pathologies and why not, on surgeon's experience.

IPSS (International Prostatic Symptom Score) score and QOL assessments (Quality of Life) are methods for evaluating the severity of symptoms in patients with prostatic hypertrophy, benign prostatic hyperplasia, being useful in determining the indication of the medical or surgical treatment. [6, 7].

The prostate is considered an immunocompetent organ, being populated by a reduced number of inflammatory cells, which increases with age, being represented by stromal and intraepithelial cells, T and B lymphocytes, macrophages and supporting cells [8]. that Fibro muscular development in BPH it is considered to be the consequence of the inflammatory processes that appear at this level, resulting in producing local growth factors and in angiogenesis in the prostate tissue. IL-6 represents a pleiotropic cytokine and one of the main mediators of the acute phase [9]. The most important source for IL-6 and IL-1 is represented by macrophages. IL-6 is synthesized by T and B lymphocytes, by fibroblasts and endothelial cells, by keratinocytes, synoviocytes, chondrocytes, epithelial cells. Thus, IL-6 is produced as a response to bacterial and viral infections, inflammation or trauma, reaching rapidly detectable plasmatic levels, unlike many other cytokines [10-12]. Beside the pro-inflammatory actions, IL-6 mediates a series of anti-inflammatory effects, IL-6 finalizing the inflammatory cascade by inhibiting the synthesis of IL-1 and TNF, concomi-

tantly with the stimulation of IL-1RA synthesis, being important. [10]. IL-6 can also be implicated in the etiology of prostate cancer [13].

Objective

The aim of the study was to evaluate the relation between clinical status (IPSS) and the IL-6 serum values in patients with benign prostatic hyperplasia before and during medical treatment with dutasteride.

MATERIAL AND METHODS

This is a clinical prospective-observational study, which included 115 adult males diagnosed with benign prostatic hyperplasia. All patients were included in the study after signing the free informed consent, according to the 1964 Declaration of Helsinki.

Inclusion criteria:

- adult patients diagnosed with benign prostatic hyperplasia, with adequate nutritional status, without other associated diseases and without any other medication;
- age over 50 years;
- initial IPSS ≥ 12 ;
- initial prostatic volume ≥ 30 cc (TRUS);
- subjects who signed the informed consent;

Exclusion criteria:

- chronic alcoholism, drug consumption;
- neurogenic bladder;
- history of prostate cancer;
- urinary retention within 3 months before entry of the study;
- recurrent urinary tract or prostatic infection;
- treatment with antiandrogen or phytotherapy within 6 months before study enrollment;
- other associated disorders;

Study group

All the patients included in the study followed a standard diagnosis protocol: the anamnestic evaluation (IPSS score), clinical evaluation of the patient, digital rectal examination, assessment of PSA, and free PSA, transrectal ultrasonography (mean prostate volume, post-voiding residual volume (PVR)). For patients with serum prostate-specific antigen (PSA) >4 ng/mL, TRUS-guided biopsy of the prostate was performed, to exclude the presence of prostate cancer. The IPSS score can be ranged depending on the score, the symptoms being

divided into: mild (symptom score below 7 points), moderate (score ranged from 8 to 19 points), severe (score ranged from 20-35 points) [14].

Out of the total of 115 patients only a number of 35 patients diagnosed with symptomatic benign prostatic hyperplasia met all the inclusion criteria above and were treated after a standardized protocol established by the urologist according to EAU Guidelines. These 35 patients were followed-up for 6 months. The therapeutic protocol consisted of a monotherapy with dutasteride 0.5 mg (5 alpha-reductase). The evaluations were at the start of the treatment (Moment 0) and at 6 months of treatment (Moment 1).

Assessment techniques

Interleukin-6 (also known as stimulating factor 2 of B cell noted BSF-2, hybridoma growth factor/plasmacytoma, hepatocyte stimulating factor, cytotoxic T-cell differentiation factor, 2A factor inducing macrophage/ granulocyte growth) was assayed by ELISA technique – the sandwich option from the serum at the Moment 0 and at the Moment 1 of the study. The correlation with the prostatic pathology was realized because the patients did not have any other pathology at the moment of the study. The sensibility of the method was over 5 pg/ml. Based on experimental measurements, it was estimated: normal -value <8 pg/ml (mean value: 6.1 pg/ml); high- value > 8.0 pg/ml.

Statistical analysis

The statistical analysis was performed using the SPSS 16.0 software (Statistical Package for the Social Sciences Inc., Chicago, IL, USA). The ANOVA test with statistical significance level set at 0.05 was applied. The correlation was evaluated using Pearson coefficient.

RESULTS

The mean age of the 115 patients included in the study was 68.8 ± 7.4 years. From the 115 enrolled patients, 56 patients were from urban areas and 59 from rural areas.

The prostate volume was 46.7 ± 12.5 cm³ in the patients included in the study. From 115 patients with benign prostatic hyperplasia, depending on prostate volume, the following distribution occurred: 67.82% (78 patients) showed a 30-50 cm³ prostate size, 26.95% (31 patients) showed a of 50-

70 cm³ prostate size, whereas only 5.21% (6 patients) had a prostate dimension over 70 cm³ (Fig. 1).

The initial value of IPSS score was 14.2 ± 2.1 and the original PVR was 22.2 ± 15.7. Depending on IPSS classification, there was a moderate symptoms score (8-19) in a number of 111 (97.4%) patients, while a number of 4 (2.6%) patients recorded a severe symptomatology (19-35) (Fig. 2).

IL-6 (pg / ml serum) presented in our study an average of 16.84 ± 3.78 pg/ ml. There were 111 patients (96.5%) with high levels of IL-6 (over 8 pg / ml) and 4 patients (3.5%) with normal levels of IL-6 (below 8 pg / ml) (Fig. 3).

IL-6 (pg/ml serum) status was analyzed depending on prostate volume (30-50 cm³, 50-70 cm³, 70 cm³), and on IPSS score (from 12 to 19, over 19). In Table 1, we present the mean value, standard deviation and statistical significance of IL-6 in the subgroups above:

- the prostate volume for the range 30-50 cm³ - the IL-6 (pg/ml) value was 17.07 ± 2.88, for the range 50-70 cm³ - the IL-6 value was 17.52 ± 2.72, p > 0.05 and for the range of more than 70 cm³ - the IL-6 value was 23.20 ± 2.20, p <0.05;
- the IPSS score for the range of 12-19 - the IL-6 (pg/ ml) value was 16.57 ± 3.61 and for the range of over 19, the IL-6 value was 22.78 ± 2.40, p <0.05 (Table 1);

The statistical analysis using Pearson coefficient showed an interesting relation between IL-6 (pg / ml serum) and clinical markers of BPH. Interleukin-6 had a statistically significant positive correlation with prostate volume (r = 0.53, p <0.05) and a weak positive correlation with IPSS score, statistically significant (r = 0.21, p <0.05) (Table 2).

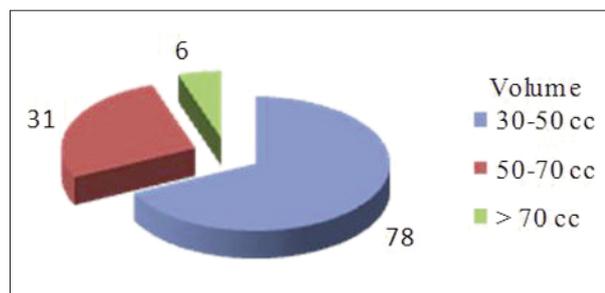


Figure 1. The distribution depending on prostate volume in patients with HBP (cm³)

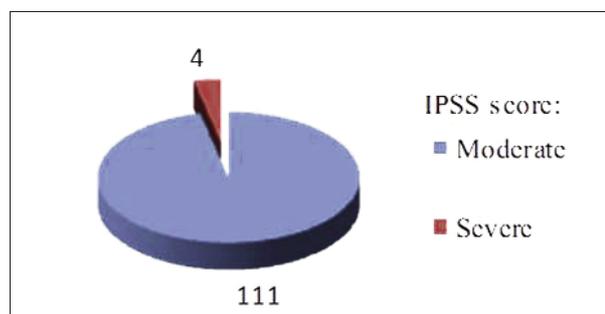


Figure 2. The distribution depending on the IPSS score in patients with BPH

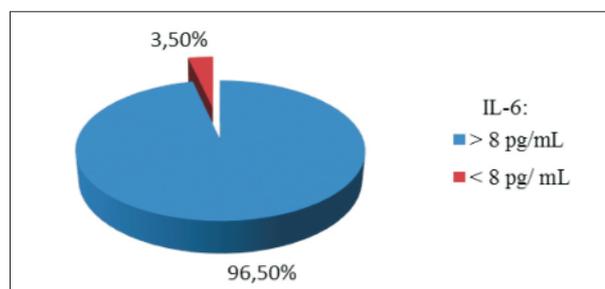


Figure 3. The distribution depending on the IL-6 value in patients with BPH

Table 1. The IL-6 value depending on prostate volume, and IPSS

Parameter	IL-6 (pg/mL)	p
Prostate volume		
30-50 cm ³	17,07±2,88	-
50-70 cm ³	17,52±2,72	0,641
>70 cm ³	23,20±2,20	0,041
IPSS		
12-19	16,57±3,61	-
>19	22,78±2,40	0,012

p1- prostate volume 50-70 cm³, >70 cm³ vs 30-50 cm³;
p2- IPSS > 19 vs 12-19

We analyzed the variations of clinical score (IPSS) for HBP, prostate volume and IL-6 at six months of treatment with dutasteride (Moment 1 - when it was considered that dutasteride had maximum efficacy) compared to the moment of the

Table 2. Statistical evaluation of IL-6 reported to prostate volume and IPSS score

Parameter	Prostate volume		IPSS	
	r	p	r	p
IL-6	r= 0,53	p=0,00	r= 0,21	p=0,00

r- correlation degree; p- statistical significance

Table 3. The IPSS score evolution during the treatment

Therapeutic moment	IPSS score	p	IL-6 (pg/mL)	p
Moment 0	13,51±1,44		15,50±2,71	
Moment 1	9,54±1,44	p=0,00	1,66±0,37	p=0,00

p - statistical significance

inclusion in the study (Moment 0) for the 35 patients group. The IPSS score showed a gradual improvement during medical therapy, statistically significant for the Moment 1 compared with the initial value (9.54 ± 1.44 vs. 13.51 ± 1.44 , $p < 0.05$) (Table 3).

Regarding the immune factors studied in the patients from our group, there was a significant decrease in interleukin-6 at Moment 1 compared to Moment 0 (1.66 ± 0.37 pg / ml vs. 15.50 ± 2.71 pg / ml, $p < 0.05$) (Fig. 4).

DISCUSSIONS

The results presented in this study reconfirm the hypothesis that inflammation plays an important role in prostate diseases initiation and progression, and sustain the author's presumption, that benign prostatic hyperplasia could be considered a immunoinflammatory disorder, characterized by systemic and sustained acute phase response. Independently of the triggers, there is an increase in the activity of some serine proteases and proteolytic enzymes in benign prostatic hyperplasia. This phenomena results in the release of active substances in the intercellular spaces which enhance the inflammatory process. In this paper we conducted a systematic analysis of the relationship between indicators of inflammation (interleukin 6) and symptoms of prostate disease (prostate volume, IPSS score) and also the biological interaction between these variables and dutasteride therapy.

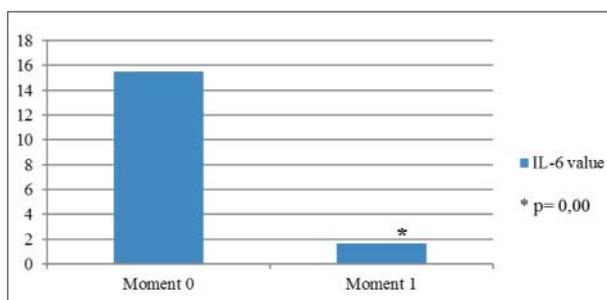


Figure 4. IL-6 serum levels during treatment with dutasteride

IL-6

IL-6 is one of the main mediators of the acute inflammatory phase. It is produced by fibroblasts, macrophages or activated monocytes, activated T-lymphocytes or B-cells, endothelial or stromal cells, representing a significant factor in the occurrence and development of prostate pathologies, including benign prostatic hyperplasia [9]. In our study, interleukin-6 showed increased levels in patients with benign prostatic hyperplasia and severe symptoms, the serum levels being significantly higher compared to those presenting mild symptoms. A statistically significant positive strong correlation between IL-6 levels and prostate volume was determined, which highlights the important inflammatory component involved in prostatic hypertrophy. Interleukin-6 also showed a statistically significant positive weak correlation with IPSS score due to the close relationship between inflammation, prostate volume and the symptoms of patients, factors leading to impaired quality of life. The main action of the interleukins and of the growth factors over the prostatic cells is represented by the mechanisms modulating the immune and inflammatory responses. Overproduction of IL-6, demonstrated during the pre-therapeutic phase in patients with benign prostatic hyperplasia, promotes prostatic cell growth, stimulates the synthesis of cytokines and chemokines in the prostate, induces the hepatic synthesis of acute phase protein, recruits inflammatory cells with an effect in the induction and maintaining a chronic inflammation, affects steroidogenesis, induces the synthesis of pituitary hormones. The analysis of clinical and inflammatory factors variation during therapy with dutasteride sustains the inflammatory pathogenesis of benign prostatic hypertrophy. IL-6 showed a significant decrease during medical treatment with dutasteride. IL-6 is a marker of inflammation, and under the action of dutasteride, medication also known with anti-inflammatory properties, according to REDUCE study, the inflammation is reduced [15].

IPSS score

IPSS score decreased significantly at 6 months of treatment with dutasteride compared to the baseline. These results were also recorded in other studies in patients on combined treatment with α -blockers and 5α -reductase inhibitors or in those with single treatment with 5α -reductase inhibitors, where a decrease with 15-30% of IPSS score could be observed. Therefore, reducing systemic inflammation during treatment with dutasteride is followed by improvement of symptoms. This fact may raise the question of associating an anti-inflammatory therapy with a 5-alpha reductase inhibitor in chronic medical treatment of benign prostatic hyperplasia [4].

CONCLUSIONS

Based on the results obtained in this clinical-prospective-observational study, we can appreciate that inflammation is an essential element involved in the onset and the evolution of BPH. Positive statistically significant correlations were showed between IL-6 titer and prostate symptoms (assessed by IPSS score) before treatment. A symptom score (IPSS) improvement together with a decrease in the IL-6 value were recorded under treatment with dutasteride. These results may be an argument for considering IL-6 as a predictor marker for the severity of symptomatology and also for the intensity of the inflammatory process. Thus, IL6 could also be a useful parameter in order to choose the best therapeutic approach and to quantify the effectiveness of medical therapy. Reducing inflammation may therefore be a rational strategy for the management of patients with benign prostatic hyperplasia.

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