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Association of CYP3A4*1B, CYP3A4*22 and CYP3A5*3 polymorphisms carriage with efficacy and safety of tamsulosin in patients with benign prostatic hyperplasia

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Tamsulosin is a first-line drug in the treatment of lower urinary tract symptoms (LUTS) in benign prostatic hyperplasia (BPH). Despite high estimates of its efficacy and safety, it rates may vary due to genetic polymorphisms of genes for the enzymes involved in the drugs metabolism.

The aim of the work was to evaluate the carriage influence of genes polymorphisms of the CYP3A enzymes group of tamsulosin metabolizers on the efficacy and safety of therapy in patients with LUTS in BPH.

Materials and methods. A total of 142 patients with LUTS, with an established BPH diagnosis (N40 according to ICD-10) were included in the study and underwent all stages. All patients received monotherapy with tamsulosin 0.4 mg/day for at least 8 weeks. An IPSS questionnaire with the definition of quality of life, a prostate ultrasound with the determination of the prostate volume and residual urine, as well as uroflowmetry, were used to evaluate the results of the treatment. Controls were performed at 2, 4 and 8 weeks from the start of the therapy. The carriage of polymorphic markers CYP3A4 (*1B, *22) and CYP3A5*3 was determined in patients; HPLC was used to determine drug concentrations in blood plasma and levels of cortisol and its metabolite 6-beta-hydroxycortisol in urine to assess the phenotypic activity of CYP3A.

Results. No statistically significant associations between CYP3A phenotype (defined by CYP3A4 and CYP3A5 genotypes) and clinical parameters of the tamsulosin therapy efficacy and the safety assessment in the studied sample of patients were found (p >0.05). Similar data were obtained for individual variants of CYP3A4*1B, CYP3A4*22, CYP3A5*3 (p >0.05). The comparison of the tamsulosin residual equilibrium concentration values in patients in the study sample with respect to the carriers of CYP3A4 and CYP3A5 gene variants did not reveal the presence of significant differences in either CYP3A phenotypes and carriers and non-carriers of individual CYP3A4*1B (p=0.57), CYP3A4*22 (p=0.37) and CYP3A5*3 (p=0.76) variants. No association was found between the metabolic ratio of 6-beta-hydroxycortisol / cortisol in urine and the CYP3A phenotype encoded by a combination of genotypes of CYP3A4 and CYP3A5 gene variants (p >0.05).

Conclusion. A possible association between the carriage of CYP3A4*1B, CYP3A4*22, CYP3A5*3 variants, a CYP3A activity assessed by the content of an endogenous substrate of this isoenzyme and its metabolite in urine, the level of plasma concentration of the drug, and the efficacy and safety of tamsulosin, has not been confirmed. The contribution of CYP3A4 and CYP3A5 genetic polymorphisms to clinical parameters of the tamsulosin therapy requires a further study.

Keywords: tamsulosin; pharmacogenetics; CYP3A4; CYP3A5; tamsulosin concentration

Abbreviations: LUTS – lower urinary tract symptoms; BPH – benign prostatic hyperplasia; HPLC – high-performance liquid chromatography; ARs – adverse reaction; BPH – benign prostatic hyperplasia; CUA – common urine analysis; GBA – general blood analysis; BBA – biochemical blood analysis; PSA – prostate-specific antigen test; TRUS – transrectal ultrasound; RUV – residual urine volume UFM – uroflowmetry; IPSS – International Prostate Symptom Score; QoLS – Quality of Life scale; EM – “extensive” metabolizers; IM – “intermediate” metabolizers; PM – “poor” metabolizers; NSAIDs – non-steroidal anti-inflammatory drugs; iACEs – angiotensin-converting enzyme inhibitors; OS – IPSS subscale to assess the severity of obstructive symptoms; IS – IPSS subscale to assess the severity of irritative symptoms.

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Ассоциация носительства полиморфизмов CYP3A4*1B, CYP3A4*22 и CYP3A5*3 с эффективностью и безопасностью тамсулозина у пациентов с доброкачественной гиперплазией предстательной железы

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Тамсулозин является препаратом первой линии в лечении симптомов нижних мочевых путей (СНМП) при доброкачественной гиперплазии предстательной железы (ДГПЖ). Несмотря на высокие оценки эффективности и безопасности, показатели могут варьироваться из-за генетических полиморфизмов генов ферментов, участвующих в метаболизме препарата.

Цель. Оценка влияния носительства полиморфизмов генов ферментов группы CYP3A метаболизаторов тамсулозина на эффективность и безопасность терапии у пациентов с СНМП при ДГПЖ.

Материалы и методы. В исследование было включено и прошли все этапы 142 пациента с СНМП при установленном диагнозе ДГПЖ (N40 по МКБ-10). Все пациенты получали монотерапию тамсулозином 0,4 мг/сут на протяжении как минимум 8 недель. Для оценки результатов лечения использовали опросник IPSS с определением качества жизни, ультразвуковое исследование предстательной железы с определением объема простаты и остаточной мочи, а также урофлоуметрию. Контроль осуществляли в сроки 2, 4 и 8 недель от начала терапии. У пациентов определялось носительство полиморфных маркеров CYP3A4 (*1B, *22) и CYP3A5*3, с помощью ВЭЖХ определяли концентрации препарата в плазме крови и уровни кортизола и его метаболита 6-бета-гидроксикортизола в моче для оценки фенотипической активности CYP3A.

Результаты. Статистически значимых ассоциаций между фенотипом CYP3A (определяемого по генотипам CYP3A4 и CYP3A5) и клиническими параметрами оценки эффективности и безопасности терапии тамсулозином в исследованной выборке пациентов установлено не было (p >0,05). Аналогичные данные были получены для отдельных вариантов CYP3A4*1B, CYP3A4*22, CYP3A5*3 (p >0,05). Сравнение значений остаточной равновесной концентрации тамсулозина у пациентов в исследуемой выборке относительно носительства вариантов генов CYP3A4 и CYP3A5 не выявил наличия значимых различий как между фенотипами по CYP3A, так и носителями и неносителями отдельных вариантов CYP3A4*1B (p=0,57), CYP3A4*22 (p=0,37) и CYP3A5*3 (p=0,76). Не было обнаружено связи между метаболическим отношением 6-бета-гидроксикортизол / кортизол в моче и фенотипом CYP3A, кодируемым по сочетанию генотипов вариантов генов CYP3A4 и CYP3A5 (p >0,05).

Заключение. Возможная связь между носительством вариантов CYP3A4*1B, CYP3A4*22, CYP3A5*3, активностью CYP3A, оцениваемой по содержанию в моче эндогенного субстрата данного изофермента и его метаболита, уровнем плазменной концентрации препарата, эффективностью и безопасностью тамсулозина не подтверждена. Вопрос о вкладе генетических полиморфизмов CYP3A4 и CYP3A5 на клинические параметры терапии тамсулозином требует дальнейшего изучения.

Ключевые слова: тамсулозин; фармакогенетика; CYP3A4; CYP3A5; концентрация тамсулозина

Список сокращений: СНМП – симптомы нижних мочевых путей; ДГПЖ – доброкачественная гиперплазия предстательной железы; ВЭЖХ – высокоэффективная жидкостная хроматография; НПР – нежелательные побочные реакции; ОАМ – общий анализ мочи; ОАК – общий анализ крови; БХ – биохимический анализ крови; ПСА – анализ на простат-специфический антиген; ТРУЗИ ПЖ – трансректальное ультразвуковое исследование предстательной железы; ООМ – объем остаточной мочи; УФМ – урофлоуметрия; IPSS – Международная система суммарной оценки симптомов болезней предстательной железы (International Prostate Symptom Score); QoL – шкала IPSS по оценке качества жизни (Quality of Life); ЕМ – «быстрые» метаболизаторы; ІМ – «промежуточные метаболизаторы; РМ – «медленные» метаболизаторы; СОЭ – скорость оседания эритроцитов; НПВП – нестероидные противоовоспалительные препараты; иАПФ – ингибиторы ангиотензинпревращающего фермента; ОС – субшкала IPSS по оценке тяжести обструктивных симптомов; ИС – субшкала IPSS по оценке тяжести ирритативных симптомов.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common urologic diseases among men [1]. The classic clinical manifestations of BPH are lower urinary tract symptoms (LUTS), such as pollakiuria, urgency, nocturia and a feeling of an incomplete bladder emptying [2].

According to the European Association of Urology guidelines[1] α1-adrenoblockers are the first-line treatment for LUTS in BPH, and tamsulosin is one of the most commonly used drugs in this group. When using tamsulosin, some patients may experience undesirable adverse reactions (ARs) with vascular reactions being the most dangerous [3]. In addition, the efficacy of the conservative tamsulosin therapy in patients with LUTS for BPH is heterogeneous, and up to one third of patients may claim its ineffectiveness [4]. Thus, the problem of improving the efficacy and safety of the tamsulosin treatment for LUTS in BPH remains relevant.

Tamsulosin is metabolized by cytochrome P450 superfamily enzymes, mainly by CYP3A4 and CYP2D6, with a minor involvement of other CYP isoenzymes [5]. The activity of CYP enzymes is genetically determined and may vary between individuals. Currently, the contribution of carriage of different genetic variants of the cytochrome P450 superfamily enzymes, involved in the metabolism of a huge number of drugs to their efficacy and tolerability, is being actively studied.

The CYP3A subfamily consists of four enzyme isoforms CYP3A4, CYP3A5, CYP3A7, and CYP3A43 [6]. Among human CYP3A enzymes, CYP3A4 and CYP3A5 are considered the most important in the drug metabolism [7]. Both enzymes are abundantly represented in the liver and intestine [8, 9]. The studies have previously characterized the CYP3A4 gene as highly polymorphic. However, most of the variant alleles of the gene cannot explain 10-100-fold differences in the enzyme activity in different populations [10, 11]. The latter may be due to either the limited effect of the CYP3A4 gene polymorphism phenomenon on the enzyme activity or their very low frequency in the population (<0.1%). Another case is with the CYP3A4*22 variant (rs35599367), which encodes an enzyme with a reduced functional activity and for which significant associations with a decreased clearance of a number of drugs (clopidogrel, tacrolimus, cyclosporine, tricyclic antipsychotics, simvastatin, etc.) have been shown, which requires an adjustment of their dosing regimen [12]. The Dutch Pharmacogenetics Working Group (DPWG) has developed recommendations on the prescription and dosing of quetiapine depending on the type of CYP3A4 metabolizers [13].

Another variant of interest to researchers is the CYP3A4*1B variant (rs2740574). Thus, in pharmacokinetic studies, the CYP3A4*1B carriage required increased doses of tacrolimus and cyclosporine in patients after the transplantation because this variant was associated with a decrease in dose-adjusted drug concentrations [14]. In contrast, in patients taking simvastatin, the carriage of the CYP3A4*1B variant was associated with a lower incidence of a drug dose reduction or a need for drug switching [14]. However, controversy remains regarding the encoded effect (a functional activity) of the enzyme in marker carriers [12–14].

CYP3A4 is the major isoform expressed in most humans. However, another CYP3A5 isoform may contribute to the overall CYP3A activity, as these two isoforms have an overlapping substrate specificity. The CYP3A5*3 variant (rs776756, 6986 A >G) carriage is associated with a reduced expression of the enzyme, which is reflected by a decrease in its functional activity [15]. The carriage frequency of this allelic variant is up to 90% in European populations and varies widely in other populations: from 67 to 75% in Asian groups and from 24 to 32% in African groups [16, 17]. The other two alleles, CYP3A5*6 and CYP3A5*7, encoding a non-functional variant of the enzyme, are less common in European and Asian populations with an incidence of <0.5% and are more characteristic of African groups [15]. The scientific literature widely presents the data on the influence of CYP3A5 allelic variants on changes in pharmacokinetics, metabolism, safety and efficacy of drugs of different groups: tamoxifen, atorvastatin, simvastatin, apixaban, dabigatran, and others [18]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has developed professional recommendations on CYP3A5 for tacrolimus dosing [19].

Despite the widespread use and popularity of tamsulosin preparations in practice, there is currently no accurate information on the effect of CYP3A genetic polymorphisms on the efficacy and safety of the tamsulosin therapy. Based on the evidence that CYP3A enzymes are involved in the excretion of tamsulosin, it was hypothesized that polymorphisms of these enzymes may influence the drug response to the preparation administration.

Therefore, **THE AIM** of this study was to evaluate the contribution of CYP3A4 and CYP3A5 gene marker carriage to the efficacy and safety of the tamsulosin therapy in patients with LUTS for BPH.

[1] EAU Guidelines. Edn. presented at the EAU Annual Congress Paris April 2024. Available from: https://uroweb.org/guidelines/management-of-non-neurogenic-male-luts

ОРИГИНАЛЬНАЯ СТАТЬЯ
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MATERIALS AND METHODS

The study was conducted from December 2021 to May 2023 on the basis of the endoscopic urology department of Municipal Polyclinic No. 7 (Naberezhnye Chelny, Republic of Tatarstan, Russia) and the Research Institute of Molecular and Personalized Medicine of the Russian Medical Academy of Continuing Professional Education (RMA CPE).

Ethical approval

The study was approved by the Ethical Committee of Scientific Research of RMA CPE (Protocol No. 13 dated 27 Dec 2021) and was conducted in accordance with the legislation of the Russian Federation and international regulatory documents (Helsinki Declaration of the World Medical Association, 2013; National Standard of the Russian Federation, GOST R 52379-2005).

Study Design

The authors conducted a single-center prospective observational open-label non-randomized study. A total of 148 male patients (mean age, 65.4) with complaints of LUTS and an established diagnosis of BPH (ICD-10 N40) were included in the study. All patients were followed up for at least 8 weeks and were examined 4 times (day 0, week 2, week 4 and week 8) in dynamics according to the study design (Fig. 1).

All patients were taking tamsulosin (Omnic®, 0.4 mg capsules, Netherlands) 0.4 mg/day. The patients did not receive any other medications for LUTS in BPH during the tamsulosin therapy.

The main part of the study included an 8-week treatment and follow-up, including visit 1 (screening and inclusion) and three follow-up visits after 2, 4 and 8 weeks. At visit 1 (the 1st day), at the inclusion moment of the patient in the study at the initial visit, a patient's medical history was collected, and the patient was examined using a set of clinical assessment of the LUTS manifestation according to the international system IPSS and QoL; instrumental methods (the study of urodynamic parameters: a maximum urine flow velocity (Q_{max}), the determination of residual urine and prostate volumes, according to the ultrasound testing). The routine tests were performed: a general blood analysis, a biochemical blood analysis (creatinine, urea), prostate-specific antigen test (PSA), a general urine analysis, the tamsulosin therapy prescription at a dose of 0.4 mg/day, taking a blood test for genotyping. Not earlier than on the 6th day of the study, after reaching 5 drug half-lives and reaching the equilibrium residual concentration (Css_{min}), the patient was referred for blood plasma before the tamsulosin administration to determine Css_{min} and for a morning urine sample to determine the CYP3A4 activity. At visit 2 (on the 14th day) and 3 (on the 28th day), the dynamics of the prescribed therapy was evaluated using the validated IPSS and QoL questionnaire. At the final visit 4 (on the 56th day), the dynamics of the therapy was evaluated according to the IPSS and QoL questionnaire and instrumental methods (a repeated Q_{max} estimation, the determination of the postvoid residual urine volume and prostate volume according to the ultrasound). The data from 142 patients were included in the outcome analysis, only those who had undergone all the 4 visits. The data from 6 patients were excluded because they had refused to participate in the study.

Eligibility criteria

The inclusion criteria for the study were: a male gender; the age over 18 years; a written informed consent to participate in the study; a confirmed diagnosis of "benign prostatic hyperplasia (N40 ICD10)"; complaints of LUTS moderately or severely pronounced, assessed by the IPSS scale by more than 7 points; a residual urine volume (RUV) less than 100 ml, according to the ultrasound (USG) of the bladder; a prostate volume from 25 to 100 cm^3 according to the transrectal ultrasound (TRUS) of the prostate gland; the absence of prostate cancer, including clinically insignificant (in cases of PSA) increase of more than 4 ng/ml. In accordance with the clinical recommendations of the Ministry of Health of the Russian Federation on the management of patients with benign prostatic hyperplasia (approved by the Ministry of Health of the Russian Federation in 2020)[2], a multifocal prostate biopsy was performed).

The non-inclusion criteria were: complicated BPH; any causes other than BPH that may, in the opinion of the investigator, lead to dysuria or an altered urine flow velocity (e.g., the neurogenic bladder, a bladder neck stricture, the urethral stricture, acute or chronic prostatitis, acute or chronic urinary tract infections); concomitant cancer; concomitant severe cardiovascular (e.g., unstable angina, a recent myocardial infarction, or poorly controlled arterial hypertension) and a cerebrovascular disease (a recent stroke or spinal cord injury); renal and hepatic insufficiency.

The exclusion criteria were: a drug intolerance

[2] Clinical recommendations of the Ministry of Health of the Russian Federation. Benign prostatic hyperplasia, 2020. Available from: https://cr.minzdrav.gov.ru/schema/6_1. Russian

detection; a patient's refusal to take the prescribed therapy; a patient's refusal to participate in the study.

Genotyping

The material for the determination of gene polymorphisms was 4 ml of blood from the veins of the elbow bend, collected using a vacuum system for a venous blood collection VACUETTE (Greiner Bio-One, Austria) into tubes with K3-ethylenediaminetetetraacetate (EDTA). The DNA isolation was performed using the reagent kit "DNA-Extran-1" for a genomic DNA isolation from whole blood (CJSC Syntol, Moscow, Russia).

Genotyping of patients was performed at the Research Institute of Molecular and Personalized Medicine of RMA CPE.

The carriage of CYP3A4*1B (c.-392G >A, rs2740574), CYP3A4*22 (c.522-191C >T, rs35599367) and CYP3A5*3 (c.6986A >G, rs776746) polymorphic markers was determined for all 142 patients.

For genotyping by CYP3A4*1B and CYP3A5*3 allelic variants, SNP-Screen reagent kits (CJSC Syntol, Moscow, Russia) were used according to the manufacturer's instructions. Genotyping by a CYP3A4*22 allelic variant was performed using reagent kits "TaqMan® SNP Genotyping Assays" and TaqMan Universal Master Mix II, without UNG (Applied Biosystems, Foster City, USA) according to the manufacturer's instructions.

The carriage of polymorphic markers was determined by a real-time polymerase chain reaction on a Real-Time CFX96 Touch device (Bio-Rad Laboratories, Inc., USA).

After the inclusion in the study, the blood was collected from all patients for a genetic testing. Depending on the genotyping results, the patients were divided into groups according to the phenotypes of "extensive metabolizers" (EM), "intermediate metabolizers" (IM) and "poor metabolizers" (PM) depending on the carriage of CYP3A4*22 and CYP3A5*3 variants [12, 16].

CYP3A phenotyping

A CYP3A4 activity was determined by estimating the ratio of 6-beta-hydroxycortisol (6b-HC) to cortisol concentrations in the patient urine collected in the morning.

Cortisol is a specific CYP3A4 substrate. By calculating the metabolic ratio of the concentrations of cortisol and its metabolite 6b-HC, the activity of CYP3A4 is determined: high values of the ratio indicate a high activity of the isoenzyme, while low values indicate a low activity. The methodology for determining a CYP3A4 activity is generally accepted [20].

Cortisol and its metabolite were determined by high-performance liquid chromatography (HPLC) with a mass spectrometric detection. Agilent 1200 liquid chromatograph (Agilent Technologies Inc., USA, 2008) and AgilentTripleQuad LC/MS 6410 mass spectrometer were used. The results were processed using Agilient MassHunter Workstation Software LC/MS Data Acquisition for 6400 Series Triple Quadrupole (version B.08.02). To perform a chromatographic determination, the sample preparation technique and conditions of chromatographic analysis presented in the work by Smirnov V.V. et al., were used [20].

Determination of tamsulosin plasma concentration

The tamsulosin plasma concentration was determined by HPLC on an Agilent 1200 liquid chromatograph (Agilent Technologies Inc., USA, 2008). Agilent Polaris 3 C18-A column (length 50 mm; inner diameter 3.0 mm; grain size 3.0 µm) was used. The separation was performed at a column temperature of 40°C. The mobile phase consisted of two components: solution "A" (1 mL of concentrated formic acid was diluted with deionized water to a total volume of 1 L) and solution "B" (1 mL of concentrated formic acid was diluted with acetonitrile to the total volume of 1 L). A chromatographic separation was carried out in a gradient elution mode.

The sample preparation was carried out by the method of blood plasma protein precipitation. The plasma samples were thawed at room temperature. Then 100 µl of plasma was transferred into Eppendorf-type plastic tubes, 250 µl of a methanol mixture with 0.1% hydrochloric acid (in the ratio of components 9:1) was added, mixed on a Vortex shaker (Elmi Ltd., Latvia) and left for 10 min. Then the samples were mixed once again. Next, the obtained samples were centrifuged at 10 000 rpm for 10 min. The supernatant was transferred to chromatographic vials and placed on the autosampler of the chromatograph for the analysis.

For the tamsulosin spectra detection, an AgilentTripleQuad LC/MS 6410 mass spectrometer with an electrospray ionization in the positive ionization mode was used. The tamsulosin spectra were recorded in the multiple molecular reaction mode. The atomizer gas pressure was 35 *psi.* The volume velocity of the drying gas was 10 L/min, and the temperature of the ion source was 350°C. The fragmentation voltage value was

ОРИГИНАЛЬНАЯ СТАТЬЯ
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135 V, and the voltage on the collision cell was –30 V. Under these conditions, the tamsulosin quantification limit was 1 ng/ml.

The results were processed using Agilient MassHunter Workstation Software LC/MS Data Acquisition for 6400 Series Triple Quadrupole (Version B.08.02).

Group analysis

As part of the analysis, comparison groups were formed from the total study sample of 142 patients regarding (1) CYP3A phenotype as determined by CYP3A4*22 and CYP3A5*3 genotype and (2) the carriage of individual allelic variants of CYP3A4*1B, CYP3A4*22 and CYP3A5*3.

Comparisons in (1) were made between the groups of "fast" (Extensive Metabolizers, EM) (n=17), "intermediate" (Intermediate Metabolizers, IM) (n=117) and "slow" (Poor Metabolizers, PM) (n=8) metabolizers (EM *vs* IM *vs* PM).

Comparisons in (2) were made between the groups according to the carriage of genotypes for CYP3A4*1B (AA (n=128) *vs* AG (n=14)), CYP3A4*22 (CC (n=133) *vs* CT (n=9)) and CYP3A5*3 (AA+AG (n=18) *vs* GG (n=124)). For CYP3A5*3, pooling of the AA+AG group was done given a low frequency for the AA genotype (n=1).

Statistical processing

For a statistical processing of the study data, methods of parametric and nonparametric statistics with the help of STATISTICA v10.0 (StatSoft Inc., USA) and Microsoft Excel 2010 program for Windows were used. When selecting the method, the normality of a sample distribution had been taken into account and evaluated using the Shapiro-Wilk's *W*-test and the Kolmogorov-Smirnov criterion.

A sample description for non-normally distributed parameters was performed by calculating the median (Me) and interquartile range as 25th and 75th percentiles (Q1 and Q3), for normally distributed parameters - by determining the mean (M) with a standard deviation (Standart Deviation, SD).

The Student's t-test or Mann-Whitney test (depending on the nature of the distribution of quantitative indicators) was used to compare quantitative indicators.

Depending on the distribution nature, multiple samples of continuous data were compared using either single- or multivariate analysis of variance (for normally distributed data) or the Kruskal–Wallis H-test (for data that do not follow a normal distribution). Correction for multiple comparisons was performed using the Bonferroni.

Frequency characteristics of qualitative indicators were compared using Pearson's χ^2 tests.

To establish the nature and strength of the relationship between the signs, the correlation analysis was used, preliminarily checking the normality of the variables distribution using the Shapiro-Wilk criterion. In case of quantitative variables and their conformity to the law of normal distribution, the Pearson's linear correlation coefficient (r) was calculated; otherwise, the Spearman's rank correlation coefficients (ρ) or the Kendall's correlation coefficients (τ) were used. The critical level of significance was taken as p <0.05. The correlation coefficient r from 0.3 to 0.7 at p <0.05 meant a positive moderate but reliable correlation between the traits; r >0.7 at p <0.05 meant a strong and reliable relationship; a negative value of r corresponded to an inverse correlation.

RESULTS

Study participants

Clinical and epidemiologic characteristics of the patients, who have been included and undergone all phases of the study, are presented in Table 1.

The following information is important with regard to the comorbidities in the study patients. The study group included 108 patients, or 76.1%, who had been diagnosed with at least one comorbidity in addition to BPH. In turn, among these patients, 51 individuals (35.9% of the cohort) had multiple comorbidities in different classes of diseases. Finally, with no comorbidities (other than BPH), 32 individuals were included in the sample, representing 23.9% of the total sample.

The list of drug groups taken by the patients for the comorbid nosology is presented in Table 2.

It should be noted that only 1 patient in the sample was taking a CYP3A inhibitor drug as concomitant pharmacotherapy in the treatment of LUTS associated with BPH.

Primary outcome of the study

Efficacy assessment

In the study sample of 142 patients with LUTS for BPH taking tamsulosin, the distribution of genotypes for the allelic variants studied was as expected and agreed with the Hardy-Weinberg law distribution (p >0.05). This indicated that the frequency distribution of genotypes in this sample of patients reflects their distribution in the population as a whole (Table 3).

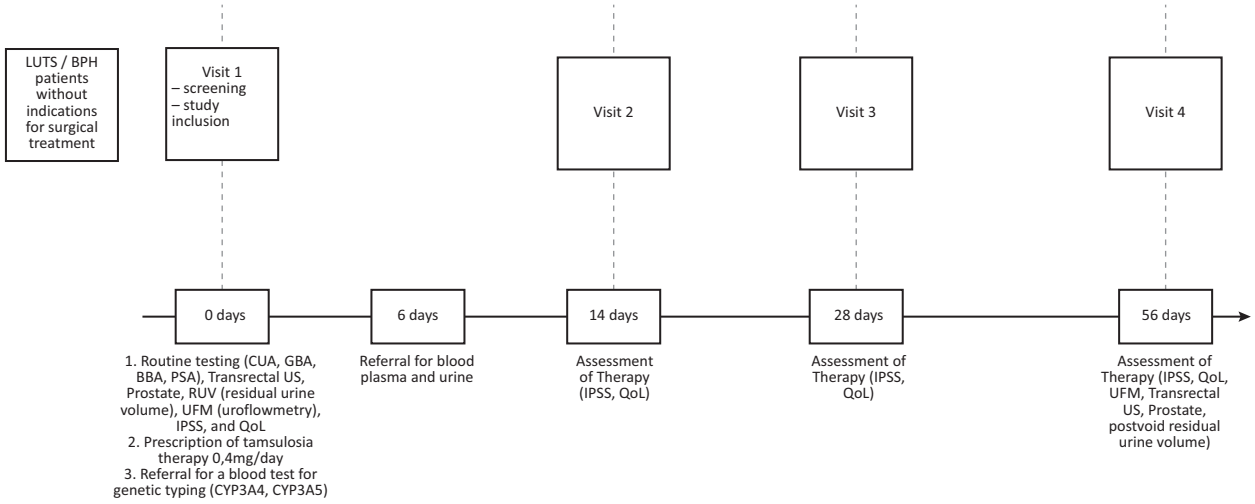

Figure 1 – Study design

Notes: LUTS – lower urinary tract symptoms; BPH – benign prostatic hyperplasia; CUA – common urine analysis; GBA – general blood analysis; BBA – biochemical blood analysis; PSA – prostate-specific antigen test; TRUS – transrectal ultrasound; RUV – residual urine volume; UFM – uroflowmetry; IPSS – International Prostate Symptom Score; QoLS – Quality of Life scale.

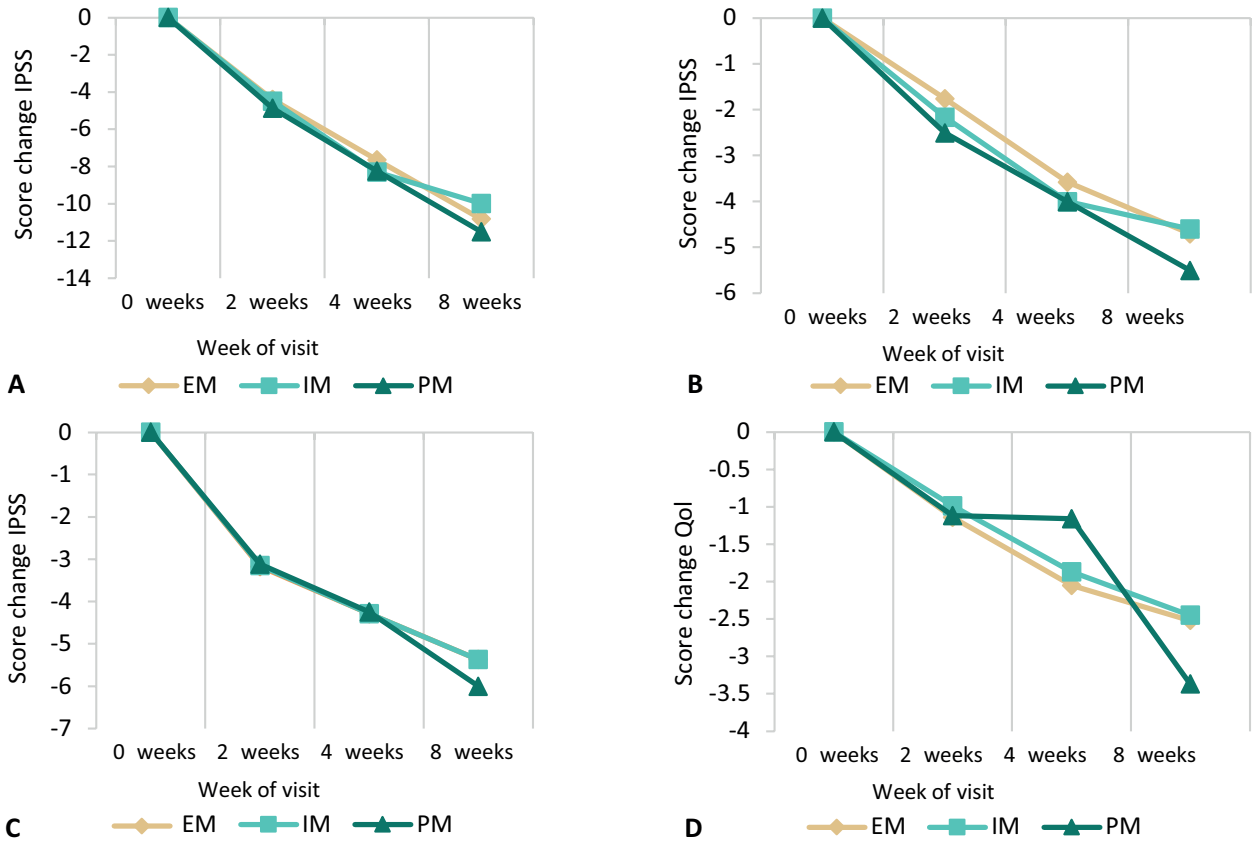

Figure 2 – Dynamics of changes in the sum of IPSS scores

Note: A – total IPSS score; B – obstructive symptoms subscale; C – irritative symptoms subscale; D – IPSS quality of life scale. EM – extensive metabolizers; IM – intermediate metabolizers; PM – poor metabolizers.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2024-12-1-32-48

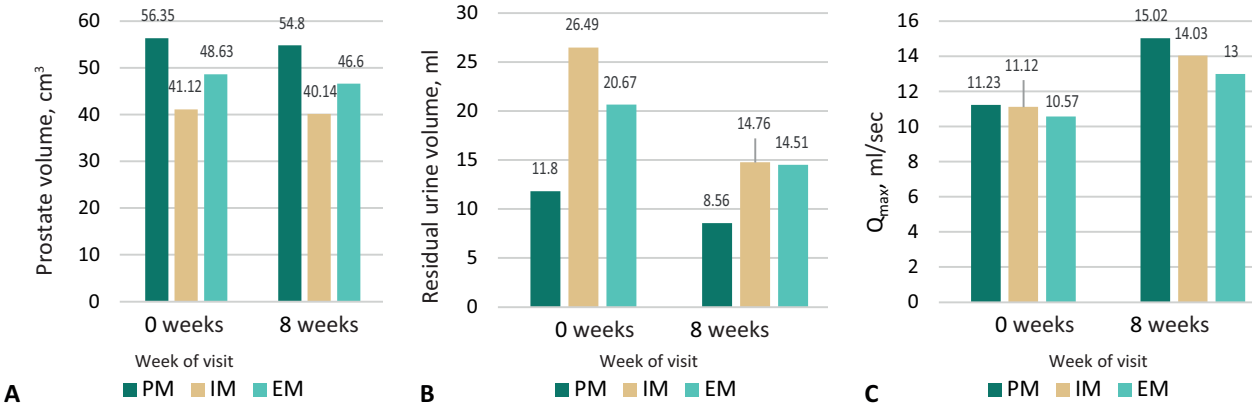

Figure 3 – Data comparison of instrumental assessment of therapy efficacy

Note: A – prostate volume; B – residual urine volume; C – maximum urine stream velocity; EM – extensive metabolizers; IM – intermediate metabolizers; PM – poor metabolizers.

Table 1 – Clinical and epidemiologic characteristics of patients

Indicator	Value	*n*
Mean age (Me [Min; Max]), years	68 [37; 86]	142
Body mass index, kg/m² (M±SD)	26.83±4.31	142
Smoking, *n* (%)	25 (17.6)	142
Alcohol, *n* (%)	77 (54.22)	142
Creatinine, mmol/L (M±SD)	85.4±13.78	142
Urea, mmol/l (M±SD)	5.8±1.41	142
Relative density, g/l (M±SD)	1015.5±8.58	142
Urine pH	5.72±0.7	142
Hemoglobin, g/L (M±SD)	148.5±13.46	142
Erythrocytes, 10^9/L (M±SD)	5.34±3.63	142
Leukocytes, 10^9/l (M±SD)	7.8±2.32	142
Platelets, 10^9/l (M±SD)	258.1±69.88	142
ESR, mm/hour (M±SD)	12.02±10.42	142
PSA, ng/mL (M±SD)	2.59±1.73	142
Comorbidities, *n* (%):		
1. Cardiovascular:	98 (69.0)	
– Hypertensive disease	68 (47.8)	
– Ischemic heart disease	21 (14.7)	
– Others	9 (6.3)	
2. Endocrinologic (type 2 diabetes mellitus – insulin-independent)	6 (4.2)	
3. Pulmonologic (chronic obstructive pulmonary disease, bronchial asthma)	6 (2.4)	
4. Gastroenterological	8 (5.6)	
5. Urologic (urolithiasis, kidney cysts, erectile dysfunction)	7 (4.9)	
6. Neurological (degenerative and dystrophic diseases of the spine, intervertebral hernias)	7 (4.9)	
Total, *n* (%):	108 (76.0)	
Comorbid patients	51 (35.9)	
Without concomitant pathology	34 (23.9)	

Note: ESR – erythrocyte sedimentation rate; PSA – prostate specific antigen test.

Table 2 – Concomitant drug therapy in patients during the follow-up period

Drug group	*n*	Drugs	CYP3A Inhibitors	CYP3A inductors	CYP3A Substrates
Diuretics	10	indapamide spironolactone	–	–	–
Calcium channel blockers	10	amlodipine lercanidipine	nifedipine (*n*=1)	–	–
Angiotensin receptor antagonist	3	candesartan telmisartan valsartan	–	–	–
Diabetics	6	metformin gliclazide empagliflozin manninil insulin	–	–	–
iACEIs	14	perindopril lisinopril enalapril	–	–	enalapril (*n*=4)
Anticoagulants	1	apixaban	–	–	apixaban
β-adrenoblockers	15	bisoprolol nebivolol metoprolol	–	–	–
Statins	11	atorvostatin rosuvostatin simvostatin	–	–	atorvostatin rosuvostatin simvostatin
NSAIDs	1	paracetamol	–	–	–
Antiaggregants	23	acetylsalicylic acid clopidogrel ticagrelor	–	–	–
Others	10	mesalazine isosorbitol dinitrite terbinafine formoterol methotrexate tofizopam phenibut phosphoglyph rebagit	–	–	symbecord inhaled glucocorticosteroids (*n*=3)
Without concomitant drug therapy, *n* (%)	73 (51.4)	–	–	–	–

Notes: NSAIDs – non-steroidal anti-inflammatory drugs; iACEs – angiotensin-converting enzyme inhibitors.

Table 3 – Distribution of genotypes for studied polymorphisms by frequency, conformity of distribution to Hardy-Weinberg law

Allelic variant	Alleles	*n* (%)	Genotypes	*n* (%)	χ^2	*p*–value
CYP3A4*1B (c.-392G >A, rs2740574)	A	270 (95.1)	AA	128 (90.1)	0.3817	0.8262
	G	14 (4.9)	AG	14 (9.9)		
			GG	0 (0)		
CYP3A4*22 (c.522-191C >T, rs35599367)	C	275 (96.8)	CC	133 (93.7)	0.1520	0.9267
	T	9 (3.2)	CT	9 (6.3)		
			TT	0 (0)		
CYP3A5*3 (c.6986A >G, rs776746)	A	19 (6.7)	AA	1 (0.7)	0.2400	0.8869
			AG	17 (11.9)		
	G	265 (93.3)	GG	124 (87.4)		

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2024-12-1-32-48

Table 4 – Distribution of CYP3A phenotypic variants in study sample

Enzyme	Phenotype	Frequency, *n* (%)	Genotypes
CYP3A	Poor metabolizers (PM)	8 (5,6)	CYP3A4*22/*22 и CYP3A5*3*3
	Intermediate metabolizers (IM)	117 (82,4)	CYP3A4*1/*1 и CYP3A5*3/*3, CYP3A4*1/*22 и CYP3A5*1/*3
	(Extensive Metabolizers, (EM)	17 (12,0)	CYP3A4*1/*1 и CYP3A5*1/*3, CYP3A4*1/*1 и CYP3A5*1/*1

Table 5 – Data of indicators for assessing tamsulosin pharmacotherapy effectiveness in patients under study

Visit	Parameter	CYP3A4*1B genotype p		*p*	CYP3A4*22 genotype		*p*	CYP3A5*3 genotype		*p*
		AA (*n*=128)	AG (*n*=14)		CC (*n*=133)	CT (*n*=9)		AA+AG (*n*=18)	GG (*n*=124)	
1 (day 0)	IPSS, score	19.06±7.22	20.71±6.04	0.41	19.18±7.06	19.77±8.25	0.81	20.05±7.22	19.10±7.12	0.59
	Irritative symptoms subscale	10.54±4.7	10.78 ±4.02	0.83	10.51±4.65	11.33 ±4.44	0.61	10.94 ±4.41	10.51±4.67	0.71
	Obstructive symptoms subscale	8.0 [5.5; 11.0]	9.0 [7.0; 13.0]	0.30	8.0 [6.0; 11.0]	8.0 [5.0; 13.0]	0.78	8.0 [6.0; 14.0]	8.0 [6.0; 11.0]	0.7
	QoL	5.12 ±0.80	5.5 ±0.75	0.09	5.15 ±0.80	5.33 ±0.86	0.51	5.16 ±0.78	5.16 ±0.81	0.97
	Prostate volume, cm^3	35.25 [29.69; 47.3]	48.5 [30.32; 70.0]	0.10	35.66 [30.0; 48.5]	40.0 [33.2; 63.6]	0.92	42.6 [29.08; 63.5]	35.25 [30.0; 48.05]	0.43
	RUV, ml	15.0 [2.5; 31.75]	18.5 [5.0; 40.0]	0.46	15.0 [2.0; 35.79]	9.0 [5.0; 20.14]	0.87	12.5 [0.0; 38.07]	15.0 [3.5; 33.75]	0.65
	Q_{max}, ml/sec	10.9 [8.1; 13.8]	9.45 [7.7; 12.3]	0.30	11.0 [8.5; 13.3]	10.9 [8.8; 14.0]	0.78	10.8 [8.3; 12.7]	10.95 [8.65; 13.45]	0.83
2 (2 weeks)	IPSS, score	–4.42±4.57	–5.28±5.29	0.51	–4.48±4.62	–4.88±5.03	0.79	–4.44±4.0	–4.51±4.73	0.95
	Irritative symptoms subscale	–3.17±3.35	–2.92 ±3.12	0.84	–3.14±3.36	–3.33 ±2.73	0.86	–3.27±3.12	–3.13±3.36	0.86
	Obstructive symptoms subscale	–2.0 [–3.0; 0.0]	–2.5 [–4.0; 0.0]	0.92	–2.0 [–3.0; 0.0]	–2.0 [–4.0; –1.0]	0.80	–1.0 [–3.0; 0.0]	–2.0 [–3.0; –0.5]	0.37
	QoL	–1.03 ±1.11	–1.21 ±0.97	0.55	–1.04 ±1.11	–1.11 ±0.92	0.86	–1.38 ±1.37	–1.0 ±1.05	0.16
3 (4 weeks)	IPSS, балл	–8.10±6.21	–9.35±5.56	0.47	–8.20±6.13	–8.55±6.69	0.86	–7.83±4.21	–8.28±6.39	0.77
	Irritative symptoms subscale	–4.25±3.83	–4.35 ±2.89	0.94	–4.24±3.80	–4.55 ±2.83	0.81	–4.22±2.34	–4.27±3.91	0.95
	Obstructive symptoms subscale	–4.0 [–6.0; –2.0]	–4.0 [–9.0; –2.0]	0.44	–4.0 [–6.0; –2.0]	–3.0 [–6.0; –1.0]	0.76	–3.5 [–5.0; –2.0]	–4.0 [–6.0; –2.5]	0.69
	QoL	–1.84 ±1.25	–2.21 ±1.36	0.29	–1.66 ±1.11	–1.89 ±1.27	0.60	–2.05 ±1.55	–1.85 ±1.22	0.53
4 (8 weeks)	IPSS, score	–9.93±7.14	–12.28±6.26	0.24	–10.08±7.11	–11.44±6.87	0.57	–10.83±5.42	–10.07±7.30	0.67
	Irritative symptoms subscale	–5.40±4.35	–6.35 ±2.70	0.49	–5.45±4.30	–6.11 ±2.80	0.65	–6.16±2.74	–5.40±4.39	0.47
	Obstructive symptoms subscale	–4.0 [–7.0; –2.0]	–6.0 [–10.0; –3.0]	0.29	–4.0 [–7.0; –2.0]	–4.0 [–8.0; –2.0]	0.71	–4.0 [–8.0; –2.0]	–4.0 [–7.0; –2.0]	0.88
	QoL	–2.47 ±1.38	–2.85 ±1.74	0.34	–3.22 ±1.64	–2.46 ±1.39	0.12	–2.5 ±1.65	–2.51 ±1.38	0.96
	Prostate volume, cm^3	36.1 [29.12; 46.9]	37.75 [31.2; 64.0]	0.31	36.5 [29.0; 47.21]	37.9 [32.0; 62.05]	0.48	37.75 [28.09; 59.0]	36.1 [29.62; 47.6]	0.77
	RUV, ml	7.0 [2.5; 19.0]	9.0 [5.0; 20.0]	0.33	7.0 [3.0; 20.0]	7.0 [5.0; 10.0]	0.86	8.0 [3.0; 15.0]	7.0 [2.5; 19.35]	0.77
	ΔRUV	–5.0 [–17.37; 1.0]	–8.39 [–23.0; 0.0]	0.61	–6.0 [–18.0; 1.0]	–2.76 [–17.14; 1.0]	0.53	–7.5 [–14.0; 3.0]	–5.0 [–19.0; 1.0]	0.55
	Q_{max}, ml/sec	13.8 [9.1; 17.2]	12.75 [7.8; 16.7]	0.52	14.0 [10.3; 17.2]	14.7 [13.2; 16.7]	0.45	14.05 [8.7; 16.2]	14.0 [11.0; 17.2]	0.42
	ΔQ_{max}	2.3 [–0.1; 5.0]	2.6 [0.9; 4.4]	0.74	2.8 [0.8; 5.0]	4.3 [2.4; 5.4]	0.40	2.65 [0.9; 3.9]	2.8 [0.8; 5.3]	0.60

Note: IPSS – International Prostate Symptom Score; QoL – IPSS quality of life scale; RUV – residual urine volume; Q_{max} – maximum urine stream velocity according to uroflowmetry results.

Table 6 – ARs distribution in study sample

AR type	*n* (%)
Retrograde ejaculation	8 (22.2)
Orthostatic hypotension	7 (19.5)
Epigastric burning	4 (11.1)
Dizziness	4 (11.1)
Hypertension	3 (8.4)
Dyspepsia	2 (5.5)
Headaches	2 (5.5)
Blurred vision	2 (5.5)
Erectile dysfunction	1 (2.8)
Diarrhea	1 (2.8)
Back pain	1 (2.8)
Rhinitis	1 (2.8)
Total	36

Note: AR – adverse reaction.

Table 7 – Frequency of AR patients with regard to CYP3A metabolic activity classification

Enzyme	Phenotype	*n* (%)	*p*
CYP3A	IM	5 (20,8%)	0,168
	EM	19 (79,2%)	
	PM	0 (0%)	

Note: Pearson's χ^2 test was used for p-value calculations. EM – extensive metabolizers; IM – intermediate metabolizers; PM – poor metabolizers.

Table 8 – Data of descriptive statistics of tamsulosin Css_{min} values in the studied samples

Parameter	Value
Number of samples	75
Mean (M), ng/ml	8,2
SD	7,78
Median (Me), ng/ml	5,9
Q1	2,13
Q3	11,6
Maximum, ng/ml	26,5
Minimum, ng/ml	0,0

Table 9 – Comparison of Css_{min} tamsulosin values in EM, IM and PM groups by CYP3A

Indicator	CYP3A phenotype						*p*
	EM (*n*=11)	min–max	IM (*n*=61)	min–max	PM (*n*=3)	min–max	
Css_{min} (Me [25.75]). ng/ml	7.26[0.0;15.05]	0–23.4	5.88[2.4;11.6]	0–26.5	8.4[0.18;10.19]	0.18–10.19	0.9539

Note: Kruskal–Wallis *H*-test was used to calculate the *p*-value. EM – extensive metabolizers; IM – intermediate metabolizers; PM – poor metabolizers.

Table 10 – Comparison of tamsulosin Css_{min} values between patients regarding carriage of CYP3A4*1B, CYP3A4*22 and CYP3A5*3 variants

Allele	Genotype	*n*	Css_{min} (Me [25,75]), ng/ml	min–max	*p*
CYP3A4*1B	AG	8	7.21[2.25;19.22]	0–26.5	0.57
	AA	67	5.88[2.13;11.3]	0–26.3	
CYP3A4*22	CT	4	9.29[4.29;18.34]	0.18–26.5	0.37
	CC	71	5.88[2.13;11.6]	0–26.3	
CYP3A5*3	AG	11	7.26[0.0;15.05	0.0–23.4	0.76
	GG	64	5.89[2.36;11.45]	0–26.5	

Note: Mann–Whitney test was used for *p*-value calculations.

ОРИГИНАЛЬНАЯ СТАТЬЯ
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Table 11 – Results of HPLC-MS/MS performed for the determination of cortisol and 6b-HC concentrations in urine

Groups (*n*=131)	Values	Cortisol concentration, ng/ml	6b-HC concentration, ng/ml	6b-HC / cortisol (relative units)
EM (*n*=16)	Me	60.6	129.05	1.9
	Q1	43.3	106.2	1.55
	Q3	97.65	217.25	3.85
	max	175.2	325.4.	5.8
	min	18.4	19.2	0.8
IM (*n*=108)	Me	51.65	104.75	2.4
	Q1	28.65	64.45	1.3
	Q3	84.5	178.6	4.1
	max	273.9	1075.5	8.8
	min	1.6	6.1	0.2
PM (*n*=7)	Me	43.12	132.72	2.97
	Q1	36.08	105.25	5.31
	Q3	50.92	289.54	2.55
	max	129.78	80.45	7.97
	min	28.09	344.02	2.23

Note: EM – extensive metabolizers; IM – intermediate metabolizers; PM – poor metabolizers.

Table 12 – Differences in 6-hydroxycortisol / cortisol metabolic ratio in patients with different CYP3A phenotypes

Group of patients by CYP3A phenotypes	Comparison (*p*-value)
EM *vs* IM *vs* PM	0.235
EM *vs* IM	0.902
IM *vs* PM	0.106467
EM *vs* PM	0.076627

Notes: Kruskal–Wallis *H*–test and Mann–Whitney paired *U*–test were used for *p*-value calculations.
EM – extensive metabolizers; IM – intermediate metabolizers; PM – poor metabolizers.

Table 13 – Spearman correlation coefficient values (r_s) reflecting relationship between cortisol concentration, 6b-HC and 6b-HC/cortisol ratio of patients and difference in values of studied clinical parameters before and after therapy

Indicator	Cortisol concentration	*p*	6b-HC concentration	*p*	6b-HC / cortisol	*p*
IPSS	-0.047027	>0.05	0.073377	>0.05	-0.105449	>0.05
OS	-0.004519	>0.05	0.045193	>0.05	-0.059237	>0.05
IS	-0.058387	>0.05	0.084310	>0.05	-0.114064	>0.05
QoL	-0.057905	>0.05	-0.048397	>0.05	-0.019504	>0.05
ΔRUV	-0.098710	>0.05	0.098710	>0.05	0.163890	>0.05
ΔQ_{max}	-0.103879	>0.05	-0.103879	>0.05	0.035049	>0.05

Note: OS – IPSS subscale to assess the severity of obstructive symptoms; IS – IPSS subscale to assess the severity of irritative symptoms; QoL – IPSS scale to assess the quality of life (QoL); RUV – residual urine volume; Q_{max} – maximum urine flow rate according to the results of uroflowmetry.

According to the results of genotyping, depending on the genotype and the encoded phenotypic activity of CYP3A, all patients were divided into groups according to the level of the enzyme activity [16]. The distribution of phenotypic variants of the CYP3A activity is presented in Table 4.

The dynamics of changes in the subjective assessment of LUTS symptomatology by the IPSS scale, subscale and Qol among the patients belonging to different types of CYP3A metabolizers is presented in Fig. 2.

Thus, the obtained data demonstrate the absence of statistically significant (using ANOVA-test) association between the CYP3A phenotype and clinical parameters of the tamsulosin therapy efficacy assessment in the sample of the examined patients with LUTS in BPH (p >0.05).

Figure 3 shows the comparison of the prostate volume, RUV and Q_{max} in patients from PM, IM and EM groups at visits1 and 4.

The analysis shows that there is no statistically significant association between the phenotype determined by the CYP3A4 and CYP3A5 genotype and clinical parameters of the tamsulosin therapy efficacy assessment in the studied sample of patients (p >0.05 by the Mann–Whitney U-test).

Further correlations between the clinical parameters of the therapy efficacy evaluation in patients with LUTS in BPH and the carriage of certain polymorphic markers of the genes CYP3A4*1B, CYP3A4*22, CYP3A5*3, were searched for (Table 5).

When comparing the results of the patients' treatment in the study between the combined group of CYP3A5*3 polymorphism (AA+AG) carriers and non-carriers (GG) during the observation period, no statistically significant data were revealed. Similar results were obtained when analyzing the influence of the CYP3A4*1B and CYP3A4*22 polymorphisms carriage on clinical parameters of the tamsulosin LUTS therapy for BPH.

The analysis of the calculation results showed that in the group of 142 patients no statistically significant associations were found for any of the considered clinical parameters and carriage of CYP3A4 and CYP3A5 variants in the patients.

Safety assessment

Throughout the follow-up of the patients taking tamsulosin for the indication of LUTS for BPH, a total of 36 cases of the adverse reactions (ARs) development were identified in 30 patients (Table 6).

However, 24 patients reported developing 1 AR, and 6 patients developed more than 1 AR. Among all the patients who had developed ARs, none of them was the reason for withdrawal of the prescribed therapy. The distribution of ARs according to CYP3A phenotypes is presented in Table 7.

Evaluation of relationship of tamsulosin equilibrium residual concentration with CYP3A phenotype and CYP3A4 and CYP3A5 allelic variants

Among 142 patients with LUTS for BPH receiving the tamsulosin therapy, plasma was collected from 88 patients to determine the equilibrium residual concentration (Css_{min}) of the drug. Of the 88 samples, 75 sample results were selected for the analysis, and 13 were excluded due to the overestimated absolute Css_{min} values, which might have been due to the patients taking another dose of the drug before their medical prescriptions and before the plasma sample had been collected. The descriptive statistics of the results of the samples included for the analysis are presented in Table 8.

The effect of CYP3A phenotypes on Css_{min} of tamsulosin in patients with LUTS for BPH was evaluated. A statistical calculation was performed for EM (n=11), IM (n=61) and PM (n=3) groups (Table 9).

According to the results of the group comparison, no significant associations between tamsulosin Css_{min} values and CYP3A phenotype type (EM, IM and PM) of patients were revealed (p >0.05).

The comparison of tamsulosin Css_{min} in patients under study regarding the carriage of CYP3A4 and CYP3A5 gene variants revealed no significant differences between carriers and non-carriers of CYP3A4*1B (p=0.57), CYP3A4*22 (p=0.37) and CYP3A5*3 (p=0.76) alleles (Table 10).

Evaluation of the effect of CYP3A isoenzyme activity on efficacy and safety

The metabolic ratio of 6b-HC/cortisol in urine was determined in 131 patients. The results of CYP3A phenotyping of 6b-HC / cortisol in urine from patients with LUTS for BPH genotyped for CYP3A4 and CYP3A5, allelic variants and their descriptive statistics are presented in Table 11 and Fig. 4.

No association was found between the metabolic ratio of 6b-HC / cortisol in urine and the CYP3A phenotype encoded by the combined genotypes of CYP3A4 and CYP3A5 gene variants (Table 12).

The Spearman correlation analysis showed that there was no statistically significant relationship between the concentrations of cortisol, 6b-HC, their ratio and all the studied parameters (Table 13).

DISCUSSION

The biotransformation of tamsulosin in the body occurs under the action of CYP3A4 and CYP2D6 enzymes. In the instructions of tamsulosin preparations in the precautions section, there is information that the drug should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole) and CYP2D6 (e.g., paroxetine); used with caution with moderate inhibitors of CYP3A4 (e.g., erythromycin) and CYP2D6 (e.g., terbinafine). Clearly, the functional activity of

ОРИГИНАЛЬНАЯ СТАТЬЯ
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metabolizing enzymes plays a key role in the drug response.

Previously, a number of authors have investigated a potential role of genetic markers encoding changes in the activity of CYP3A4, CYP3A5 and CYP2D6 enzymes on the variability of drug pharmacokinetics parameters in healthy volunteers. Thus, Kim K.A. et al. (2018) investigated the effect of allelic variants of CYP2D6 (*2, *4, *5, *10, *14, *21, *41 and *xN) and CYP3A5 (*3) genes on the peak concentration (C_{max}) and area under curve (AUC) of the drug in plasma in 29 volunteers. The authors concluded that a significant effect on C_{max} and AUC values was produced by carriage of CYP2D6*4 and *10 markers, whereas genotypes for CYP3A5*3 had no effect on the studied parameters [21]. In another study by Villapalos-García G. et al. (2021), in a group of 79 healthy subjects, it was shown that the subjects which were slow metabolizers by CYP3A5, had lower clearance rates (Cl/F) of tamsulosin than normal and fast metabolizers, but the associations leveled off after the correction by a multiple comparison correction. Significant correlations were found for CYP2D6 variants: poor (*4/*4 and *4/*5) and intermediate (*1/*4, *1/*5, *4/*15) CYP2D6 metabolizers had higher AUC values (p=0.004), higher T1/2 (*p*=0.008) and lower Cl/F values (*p*=0.006) compared to normal (*1/*1) and extensive(*1/*1×2) metabolizers [22].

It should be noted that the absolute majority of works on tamsulosin pharmacogenetics investigate the effect of CYP2D6 markers on the pharmacokinetics of the drug. In all cases, the studies were conducted on healthy volunteers of a relatively young age [21–24].

The present study was the first attempt to evaluate the carriage contribution of allelic variants of CYP3A4 and CYP3A5 genes to the efficacy and safety of the tamsulosin therapy in patients with LUTS for BPH. The Association for Molecular Pathology (AMP) joint consensus recommendation lists CYP3A4*22 (rs35599367) and CYP3A5*3 (rs776746) variants as tier 1 markers, a minimum sets of alleles to test, if the drug is metabolized by these enzymes. Other alleles, CYP3A5*6 and CYP3A5*7, also belonging to the first level, have not been studied, due to their low prevalence in the European population [13]. This was the reason for the choice of markers for this study.

The analysis of the obtained results shows that the CYP3A phenotype of patients, determined by CYP3A4 and CYP3A5 genotypes, has not played a significant role in modulating IPSS scores used for a subjective assessment of the therapy efficacy and has not affected on the frequency of the ADR. Despite the fact that CYP3A4*22 (rs35599367) and CYP3A5*3 (rs776746) variants encode alternative splicing, lead to the protein shortening and expression of a non-functional protein. In this study, the analysis of their contribution separately did not reveal associations with the parameters of the tamsulosin therapy efficacy assessment (IPSS, QoL, RUV and Q_{max}).

There is increasing evidence that genetic variations in CYP3A4 and CYP3A5 contribute significantly to the interindividual variability of the CYP3A metabolic activity [15, 16]. In particular, the authors have focused their attention on CYP3A4*22 (rs35599367) and CYP3A5*3 (rs776746), for which many studies have identified their effects on the CYP3A activity. In the present study, the joint contribution of these polymorphic markers to the phenotypic activity of CYP3A was investigated and, in turn, was assessed by the level of an endogenous cortisol metabolism. The essence of the method of determining a CYP3A activity is that the ratio of the 6b-HC metabolite to the initial cortisol can be used to judge the enzyme activity. No relationship between CYP3A phenotypes and the difference in 6b-HC/cortisol ratios between the poor, intermediate, and extensive metabolizer groups were found. CYP3A phenotyping by 6b-HC / cortisol is not always a convenient and reliable way to determine the enzyme activity, which had been confirmed by a number of studies [25, 26]. In this case, the results also show that there is no correlation between the metabolic activity of CYP3A, determined by the ratio of endogenous cortisol and its metabolite, and the carriage of alleles encoding a decrease in the functional activity of CYP3A. The analysis also revealed no correlation between 6b-HC / cortisol and the tamsulosin therapy efficacy in patients with LUTS in BPH.

In vitro studies show that the formation of tamsulosin metabolites, AM-1, M-1 and M-2, is catalyzed by CYP3A4, while the formation of M-3 and M-4 is catalyzed by CYP2D6 [27], and the main pharmacological action is due to the parent compound. Considering the metabolic pathway and the fact of potential adverse effects when CYP3A4 inhibitors are co-administered, the influence of CYP3A on the pharmacokinetic parameters of the tamsulosin therapy is undeniable. However, assuming that CYP2D6 variants play a predominant role in the drug metabolism, the effect of CYP3A variants may be masked by the CYP2D6 activity. This may also explain the results obtained in this study.

Study limitations

The study limitation was a relatively small sample size, so some possible clinically significant associations between factors could not be proved by statistical methods. A limited follow-up period, a limited number of candidate genes and allelic variants of CYP3A4 and CYP3A5 in the analysis are also worth mentioning. The contribution of candidate genes and allelic variants of CYP2D6, which is also involved in tamsulosin metabolism, was not analyzed in this work. The study was conducted within outpatient reception hours in a polyclinic, which does not allow minimizing the influence of the daily regimen, lifestyle, diet, possible concomitant pharmacotherapy and other factors on the variability of clinical parameters of efficacy and safety,

values of a measured equilibrium residual concentration of the drug, variability of concentrations of cortisol and its metabolite used to assess the activity of CYP3A enzymes.

CONCLUSION

A possible association between the carriage of CYP3A4*1B, CYP3A4*22, CYP3A5*3 allelic variants, a CYP3A activity estimated by the urine content of the endogenous substrate of this isoenzyme and its metabolite, a plasma concentration, and the tamsulosin efficacy and safety, has not been confirmed.

The issue of the contribution of CYP3A4 and CYP3A5 genetic polymorphisms to clinical parameters of the tamsulosin therapy requires a further study with increasing the sample of patients, with the inclusion of CYP2D6 gene markers in the analysis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

All the authors confirm that their authorship meets the ICMJE international criteria (all the authors have made a substantial contribution to the conceptualization, conduct of the study and preparation of the article, read and approved the final version before publication. Shokhrukh P. Abdullaev – idea and concept of the study, conducting the study, systematizing literature data, writing and editing the text of the manuscript, formulating conclusions; Maksim N. Shatokhin – idea and development of the concept of the manuscript, systematization of literary data, text editing, formulation of conclusions, approval of the final version of the manuscript for publication; Oleg L. Sigailo – analysis and interpretation of literature data, participation in the research, analysis and discussion of the results obtained; Sherzod P. Abdullaev – idea and concept of the study, statistical data processing, writing and editing the manuscript, formulation of conclusions; Pavel O. Bochkov – development of methods and quantitative determination of drug concentration in blood plasma, formulation of phenotyping methods in samples, statistical data processing, text editing, formulation of conclusions; Svetlana N. Tuchkova – carrying out genotyping of samples, editing the text of the manuscript; Oleg V. Teodorovich – participation in the development of the concept of the manuscript, editing of individual sections of the manuscript; Oleg B. Loran – critical revision of the manuscript, approval of the final version of sections of the manuscript for publication; Dmitry A. Sychev – development of the research concept, critical analysis of the results obtained, approval of the final version of the manuscript for publication.

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