Nat. Volatiles & Essent. Oils, 2021; 8(4): 15968-15979

NVEO
Natural Volatiles &
Essential Oils

Indicators Of The Course Of Benign Prostatic Hyperplasia Depending On The Genotypes Of G2677t Mdr1 And T3435c Mdr1 Genes

I.R.Mavlyanov[1] , M.K. Gulyamova[2] , Z.I. Mavlyanov[3] , A.T. Rakhmatov[4]

1 Doctor of Medical Sciences, Professor, Head of the Department of Clinical Pharmacology

2Candidate of medical sciences, Associate Professor of the Department of Neurological disorders in children

3Doctor of Medical Sciences, Associate Professor of the Department of Clinical Pharmacology

4Aspirant of the Department of Clinical Pharmacology

Abstract

This paper presents the research results on the study of the features of clinical manifestations of benign prostatic hyperplasia and the effectiveness of its drug treatment, depending on the genotypes of the G2677T MDR1 and T3435C MDR1 genes. It was shown that there is a definite relationship between individual signs of the course of the disease and the carriage of genotypes of the studied genes. The effect of the treatment of the disease is also interrelated with the genotypes of the G2677T MDR1 and T3435C MDR1 genes.

Keywords: benign prostatic hyperplasia, IPSS, QOL, V_{max}urineflow, Vprostate, Vresidual urine, bloodPSA, G2677TMDR1 and T3435CMDR1 genes.

Today, there is no doubt that the nature of the individual pharmacological response to drug effects largely depends on the genetic characteristics of the patient's body causing changes in the pharmacokinetics and / or pharmacodynamics of the drug [1]. This makes it possible to adjust the dose, frequency and route of administration of drugs, to replace them with another drug, which contributes to an increase in the effectiveness and safety of pharmacotherapy [2,3]. Consequently, the use of advances in the field of pharmacogenetics and pharmacogenomics creates a real condition for achieving the personification of pharmacotherapy.

It is known that polymorphism of the genes of the cytochrome P-450 family involved in the biotransformation of drugs is widely used to form personal pharmacotherapy regimens [4,5]. Along with this, it has recently begun to study the role and significance of genes involved in the processes of absorption, distribution and elimination of drugs [6,7,8]. Among them is the MDR1 gene, which controls the transport protein - Glycoprotein - P. These genes determine the individual genetic potential of the organism to ensure the protection of cells of organs and systems from excessive intake of xenobiotics.At the same time, these genes are insufficiently studied both in relation to certain groups of drugs and diseases. Among the studied numerous polymorphisms of the latter, the most significant is the C3435T

polymorphism MDR1 [9, 10]. In connection with the above, in this work, we studied the role of two polymorphisms of the specified gene MDR1 (G2677T) and MDR1 (T3435C) in the effectiveness of the medical treatment of benign prostatic hyperplasia.

Materials and methods.

The study was carried out in 101 patients with benign prostatic hyperplasia (BPH), aged 50 to 89 years (mean age 69.75 ± 1.04 years), who received treatment at the urology department at the Republican Clinical Hospital No. 1. The control group consisted of 20 practically healthy volunteers.

Patients, depending on the drugs used for drug treatment, were divided into two groups:1) patients who received the drug Prostamed (n = 47); 2) patients who received the drug Permikson (n = 47). The diagnosis of BPH was verified by conventional methods.

In the examined patients, along with traditional studies, special studies for BPH were carried out, such as IPSS, QOL, Vmax of urine flow, Vprostate, Vresidual urine, as well as blood PSA.

The collection of biological material for DNA extraction was carried out taking into account the established procedure for human rights, which was carried out with the written consent of the studied persons.

Blood samples were collected from patients and healthy volunteers in an amount of 1.5 ml and taken in 3 ml of EDTA solution and stored at -20̊C.

Isolation of DNA from whole blood was carried out using a Ribot-prep reagent kit (manufactured by Interlabservice, Russia).

Detection of MDR1 gene polymorphism was determined by the Real-Time PCR method (the kit was manufactured by OOO NPF Litekh, Moscow, Russia).

Statistical processing of results. The digital material was statistically processed on a personal computer using a package of applied programs for statistical analysis. The arithmetic mean (M), standard deviation (σ), relative values (frequency, percent), Student's test (t) with calculating the error probability (P) were calculated.

Results and discussion

In this work, we have studied some indicators of the course of BPH in the dynamics of its treatment, depending on the genotypes of the studied MDR1 gene polymorphisms.

As can be seen from the data presented in Figure 1, in the dynamics of treatment, the value of the IPSS indicator decreases comparatively more among patients with the heterozygous GT genotype of the G2677T MDR1 gene, and among patients with the TT genotype, on the contrary, there are comparatively less pronounced shifts. At the same time, the difference between patients with TT and GT genotypes in this regard is 16.2%.

Analysis of the dynamics of changes in another QOL indicator (Fig. 1) indicates that the smallest shifts take place among patients with the GG genotype of the G2677T MDR1 gene, the value of which is 10% lower than that among patients with the GT genotype. Consequently, a relatively pronounced decrease in the value of both the IPSS index and the QOL is observed with the heterozygous GT genotype of the G2677T MDR1 gene.

Figure 2 presents the results of a study of the dynamics of indicators of prostate volume and residual urine volume.

The conducted research, as can be seen from the data presented in Figure 2, show that the value of prostate volume in the dynamics of treatment in all genotypic variants of the G2677T MDR1 gene decreases almost the same. However, a relatively more pronounced decrease in the volume of the

prostate gland is observed among carrierswith the TT and GT genotypes, in comparison with those of the GG genotype.In contrast to the prostate gland volume values, the residual urine volume value is markedly reduced by more than 2 times among the carrierswith GG genotype, both in comparison with the TT genotype and the GT genotype. At the same time, the value of the latter decreases by 39.1% more than that in patients with the TT genotype. Consequently, the volume of the prostate gland in the dynamics of treatment, regardless of the drug used, if it decreases more in TT genotype carriers, then the volume of residual urine is among GG genotype carriers of the MDR1 polymorphism under study.

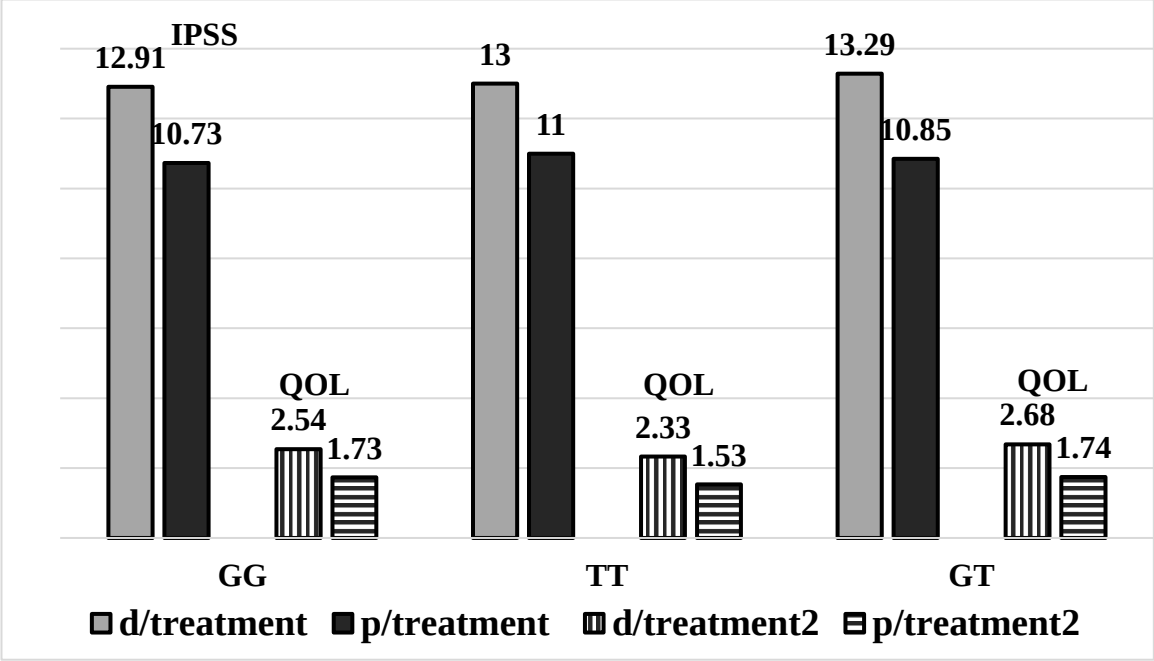

Fig.1. The value of IPSS and QOL indices in patients with BPH in the dynamics of treatment, depending on the genotypes of the G2677T MDR1 gene.

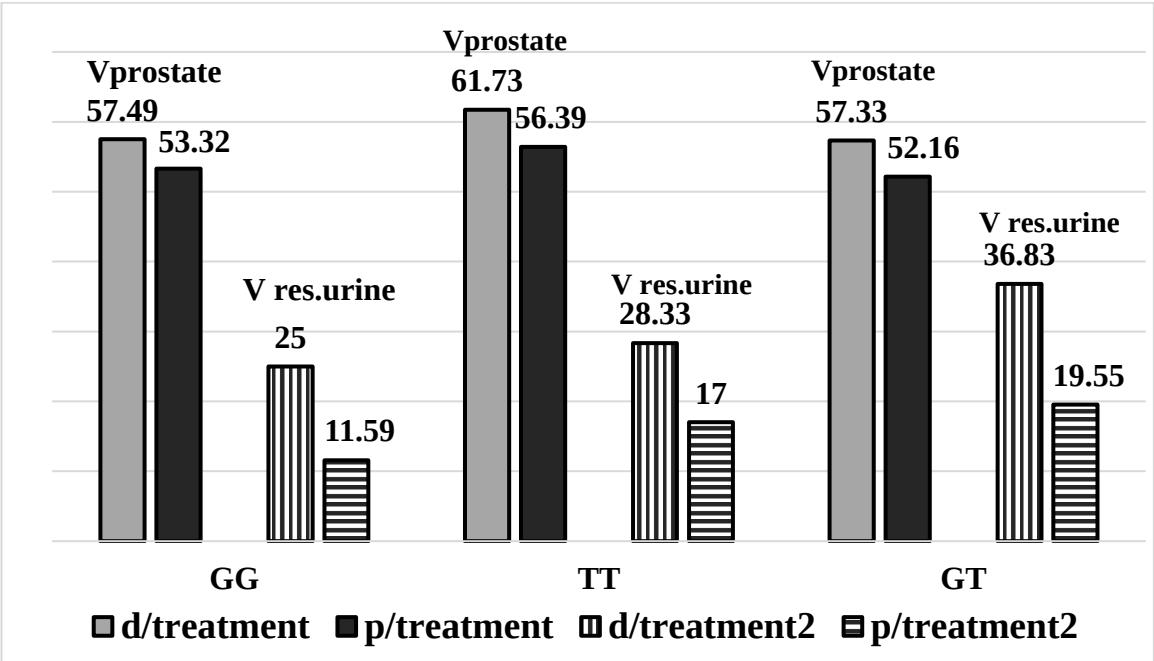

Fig.2. The value of indicators of the volume of the prostate gland (V prostate) and the volume of residual urine (V residual urine) in patients with BPH in the dynamics of treatment, depending on the genotypes of the G2677T MDR1 gene.

The study results of the volume of the maximum urine flow rate (V urine flow rate) and PSA are presented in Figure 3.

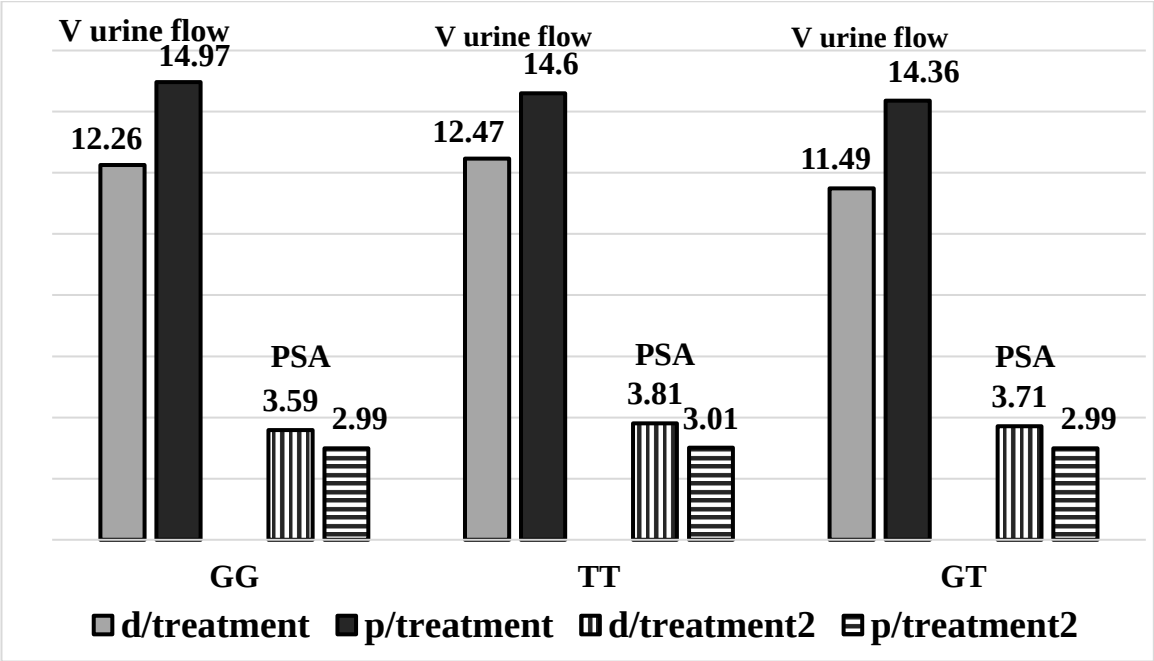

Fig.5.9. The value of the maximum urine flow rate (V urine flow) volume indicators and PSA in patients with BPH in the dynamics of treatment, depending on the genotypes of the G2677T MDR1 gene.

As can be seen from the data presented, the value of the volume of the maximum urine flow in the dynamics of the treatment is relatively more increased among carrierswith the GG and GT genotypes, compared with those of the TT genotype. At the same time, the value of this indicator in the group of carrierswith GG and GT genotypes becomes higher compared to before the treatment by 22.1% and 25.0%, respectively. At the same time, among thosewith the TT genotype, the value of this indicator increases comparatively less pronouncedly.

The value of the PSA indicator, in the dynamics of treatment, decreases almost equally, however, there is a certain tendency for the predominance of the effect of treatment among patients with TT genotype of the G2677T MDR1 gene. At the same time, the value of the studied indicator in the dynamics of treatment decreases by 21% compared to the value before treatment. Consequently, if the value of the indicator of the volume of the maximum urine flow in the dynamics of treatment increases more among patients with the GT genotype of the G2677T MDR1 gene, then the value of the PSA indicator - among the patients with the GT genotype.

Thus, the analysis of the results of the treatment of BPH, depending on the genotypes of the G2677T MDR1 gene, indicates that the effectiveness of treatment without taking into account the drug used is in a certain connection with the indicators of evaluating the effectiveness of treatment. So, if the best results in relation to indicators of IPSS, QOL, V urine flow were found among patients with carriers of the GT genotype, then in relation to indicators of V prostate and PSA - among patients carriers of the

TT genotype. At the same time, a more pronounced effect of treatment in relation to the indicator V residual urine was observed among the patients who were carriers of the GG genotype of the G2677T MDR1 gene.

We carried out a similar analysis in relation to another polymorphism of the studied gene - the T3435C MDR1 gene.

The results of the study of the IPSS and QOL values in the examined patients in the dynamics of treatment, depending on the genotypes of the T3435C MDR1 gene, are presented in Figure 4.

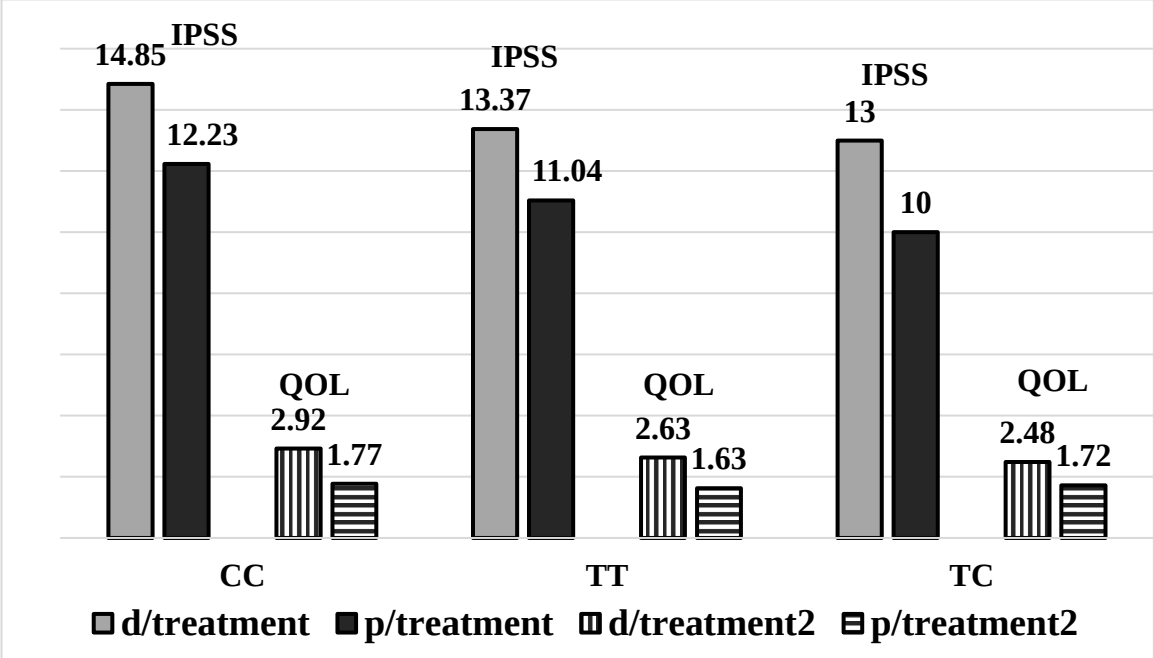

Fig.4. The value of IPSS and QOL in patients with BPH in the dynamics of treatment depending on the genotypes of the T3435C MDR1 gene.

As can be seen from the data presented in Figure 4, in the dynamics of treatment, the value of the IPSS indicator decreases comparatively more, as in the study of the G2677T gene. Among patients with the carriage of the heterozygous TC genotype of the T3435C MDR1 gene, and among patients with the carriage of the CC and TT genotypes, on the contrary, there is relatively less pronounced shifts. At the same time, the difference between patients with TT and TS genotypes is 24.5%.

The analysis of the dynamics of changes in the QOL indicator, as can be seen from Fig. 5.10., indicates that the greatest shifts take place among patients with the CC genotype of the T3435C MDR1 gene, the value of which is 28.5% higher than that among patients with the TC genotype. Consequently, a relatively pronounced decrease in the value of the IPSS indicator, if it occurs in patients with the heterozygous TC genotype, then the QOL indicator is in patients with the CC genotype of the T3435C MDR1 gene.

A similar analysis carried out in relation to the ratio of the volume of the prostate gland and the volume of residual urine in patients with BPH in the dynamics of treatment, depending on the genotypes of the MDR1 T3435C gene, are presented in Figure 5.

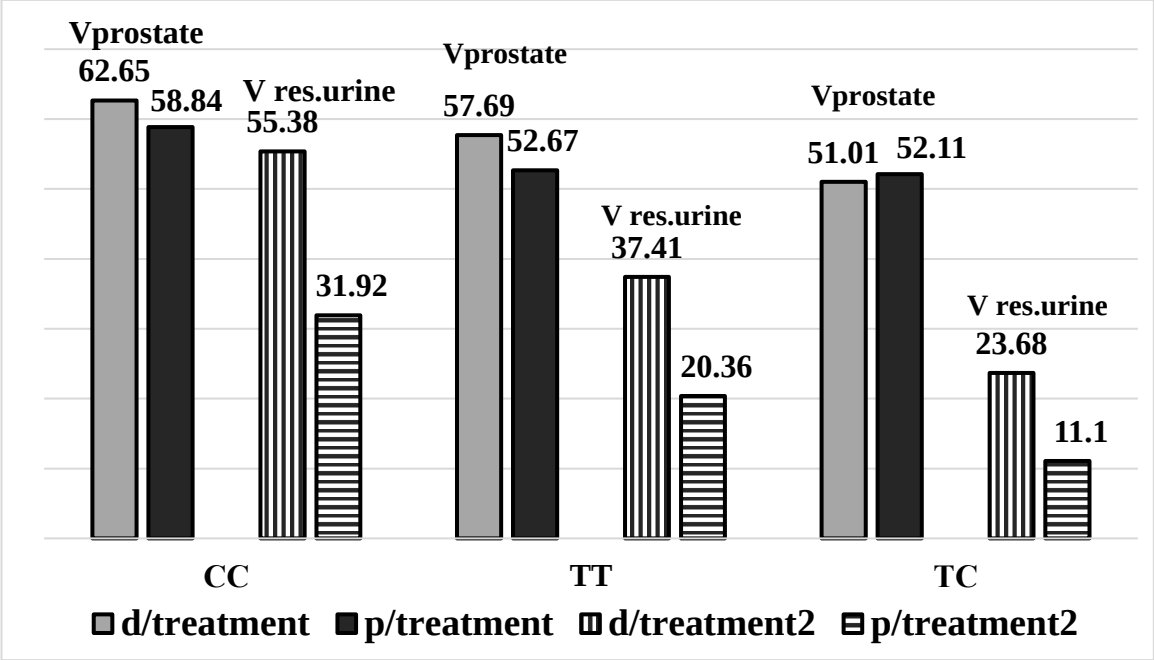

Fig.5. The value of indicators of the volume of the prostate gland (V prostate) and the volume of residual urine (V residual urine) in patients with BPH in the dynamics of treatment, depending on the genotypes of the T3435C MDR1 gene.

The conducted research, as can be seen from the data presented in Figure 5, shows that the value of the prostate volume in the dynamics of treatment, in contrast to the MDR1 G2677T gene polymorphism, undergoes small shifts, even in carriers of the heterozygous TC genotype it practically does not change significantly. In contrast to the values of the volume of the prostate gland, the value of the volume of residual urine, as in the case of the MDR1 G2677T gene polymorphism, undergoes more pronounced shifts in the dynamics of treatment. This is especially clearly seen in patients with the heterozygous TS genotype.At the same time, the value of the volume of residual urine in them decreases by 53.13% in comparison with the initial one. Somewhat less pronounced shifts were found among carriers of CC and TT genotypes of the studied gene. Consequently, the volume of the prostate gland in the dynamics of treatment, regardless of the drug used, if it decreases more in carriers of the TT genotype, then the volume of residual urine is among the carriers of the TS genotype of the MDR1 polymorphism under study.

The study results of the maximum urine flow rate volume(Vurine flow rate) and PSA are presented in Figure 6.

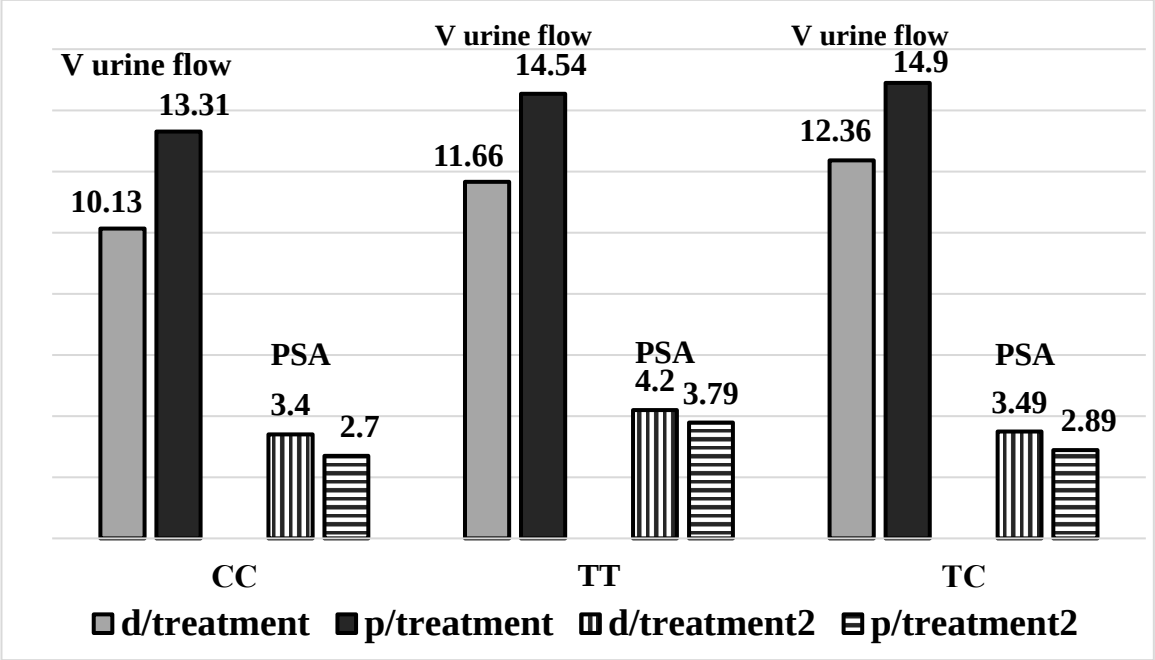

Fig.6. The value of the maximum urine flow rate (V urine flow) and PSA in patients with BPH in the dynamics of treatment, depending on the genotypes of the T3435C MDR1 gene.

As can be seen from the data presented, the value of the maximum urine flow volume in the dynamics of the treatment, without taking into account the drug used, increases comparatively more among carriers of the CC genotypes, in comparison with carriers of the TT and TC genotypes. At the same time, the value of this indicator in the group of carriers of the CC genotype becomes 31.4% higher than before the treatment.At the same time, among carriers of the TT genotype, the value of this indicator, although it also increases, is less pronounced. Consequently, the most pronounced effect of treatment in relation to the indicator of the volume of the maximum urine flow is observed among patients with the carriage of the CC genotype of the T3435C MDR1 gene.

The value of the PSA indicator, as can be seen from the data presented in Fig. 6, is also markedly reduced among patients with the carriage of the CC genotype, which is reduced by 21% compared to the initial one. The least pronounced effect of treatment in relation to the PSA indicator in dynamics was found among patients with TT carriage of the genotype of the MDR1 polymorphism under study. Consequently, even here, better results are observed among patients with the carriage of the CC genotype of the T3435C MDR1 gene.

Thus, the analysis of the results of the treatment of BPH, depending on the genotypes of the T3435C MDR1 gene, indicates that the effectiveness of treatment without taking into account the drug used.As in the case of the G2677T MDR1 gene polymorphism, it is in a certain connection with the "indicators" of the effectiveness of the medication of the disease we are studying. Thus, at the same time, a relatively pronounced effect of treatment in relation to the IPSS indices and the residual urine volume is traced among patients with carriage of the TS genotype. While in relation to the QOL indices, the volume of the maximum urine flow and PSA is traced among patients with the carriage of the CC genotype of the T3435C MDR1 gene.

The obtained data allows one to orientate to a certain extent when assessing the effectiveness of the ongoing drug treatment of BPH and takes the "first steps" for a differentiated choice of drug therapy. It should be noted that the use of the results of the analysis of the association of the genotypes

of two genes, in contrast to the genotypes of one gene, increases the predictive value of the approach to the selection of drugs for the treatment of the studied pathology.

To assess the significance of the polymorphism of the genes of drug transporters, in particular the MDR1 G2677T and T3435C gene polymorphisms studied, we have examined the dependence of the severity of the effect of the drugs used on the genotypes of the studied genes. As "indicators" for assessing the effectiveness of drug treatment, we selected the indicators of the maximum urine flow and the volume of residual urine.The severity of the effect of the drugs used was conditionally divided into 3 categories: for the indicator of the volume of the maximum urine flow - an increase in the value of the latter by 0-25% - a minimally expressed or moderate effect; 2-50% - moderately pronounced effect and over 50% - pronounced effect; for the indicator of the volume of residual urine - a decrease in the value of the latter by 0-25% - a minimal or moderate effect, by 25-50% - a moderately pronounced effect and by 50% or more - a pronounced effect.

The study results on the severity of the effect of BPH drug treatment in relation to the ratio of the maximum urine flow volume depending on the genotypes of the G2677T MDR1 gene are presented in Figure 7.

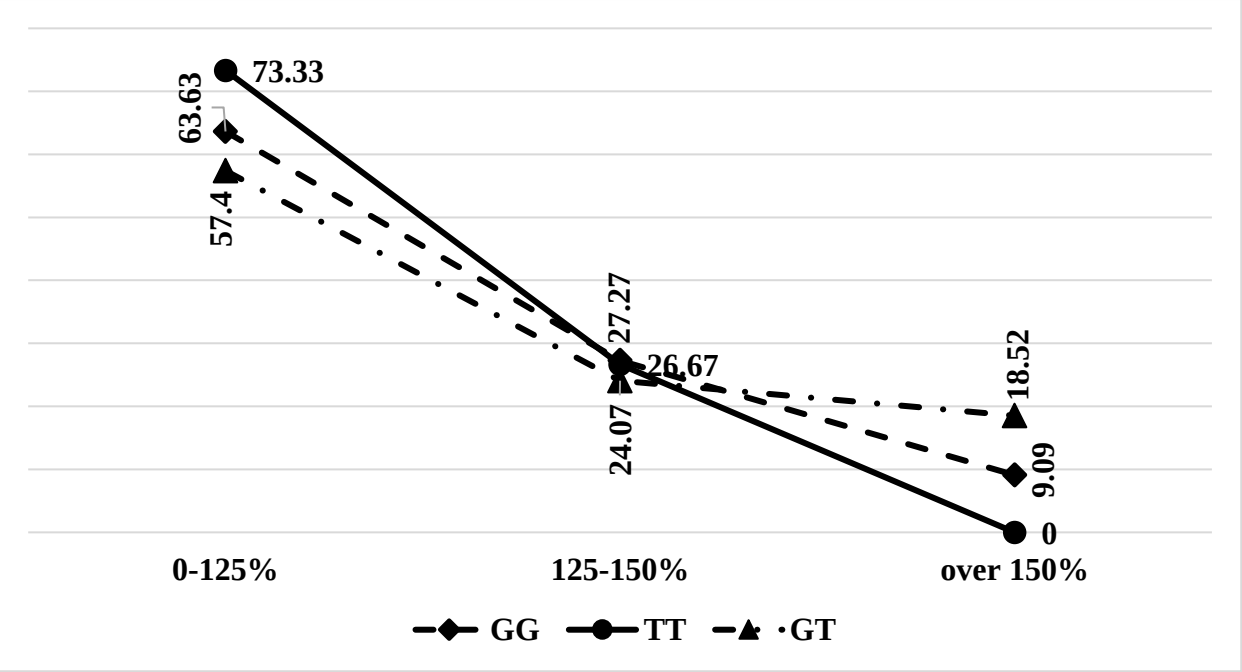

Fig.7.Specific ratio of the BPH drug treatment effect occurrencein terms of the severity of the increase in the volume of the maximum urine flow, depending on the genotypes of the G2677T MDR1 gene.

As can be seen from the presented data, the pronounced effect is most often found among patients with the GT genotype of the G2677T MDR1 gene, in comparison with its other genotypes. At the same time, the proportion of patients with a pronounced effect in relation to the studied indicator was almost 2 times higher than those with the GG genotype. And among patients with the TT genotype, there were practically no patients with a pronounced effect in relation to the studied indicator. The proportion of patients with a moderately pronounced effect was found equally often in all genotypes of the studied gene. Consequently, the best results in relation to the indicator of the volume of the maximum urine flow in the dynamics of treatment are among carriers of the GT genotype of the G2677T MDR1 gene.

The results of a similar study in relation to another gene T3435C MDR1 are presented in Figure 8.

As can be seen from the presented data, the pronounced effect on the ratio of the volume of the maximum urine flow is most often found among patients with BPH who carry the TT genotype of the T3435C gene, in comparison with the CC and TC genotypes. At the same time, the proportion of patients with a pronounced effect in relation to the studied indicator was 20.5% higher than those with the carriage of the TS genotype and relatively close to the CC genotype. The proportion of patients with a moderately pronounced effect was found noticeably often among patients with the carriage of the CC genotype.At the same time, the proportion of patients with a moderately pronounced effect was 3.9 times higher than that among carriers of the TT genotype and 1.8 times higher than among patients with the TS genotype of the studied gene. Consequently, the best results of treatment in relation to the indicators of the maximum urine flow volume are among patients with the the CC genotype of the T3435C MDR1 gene.

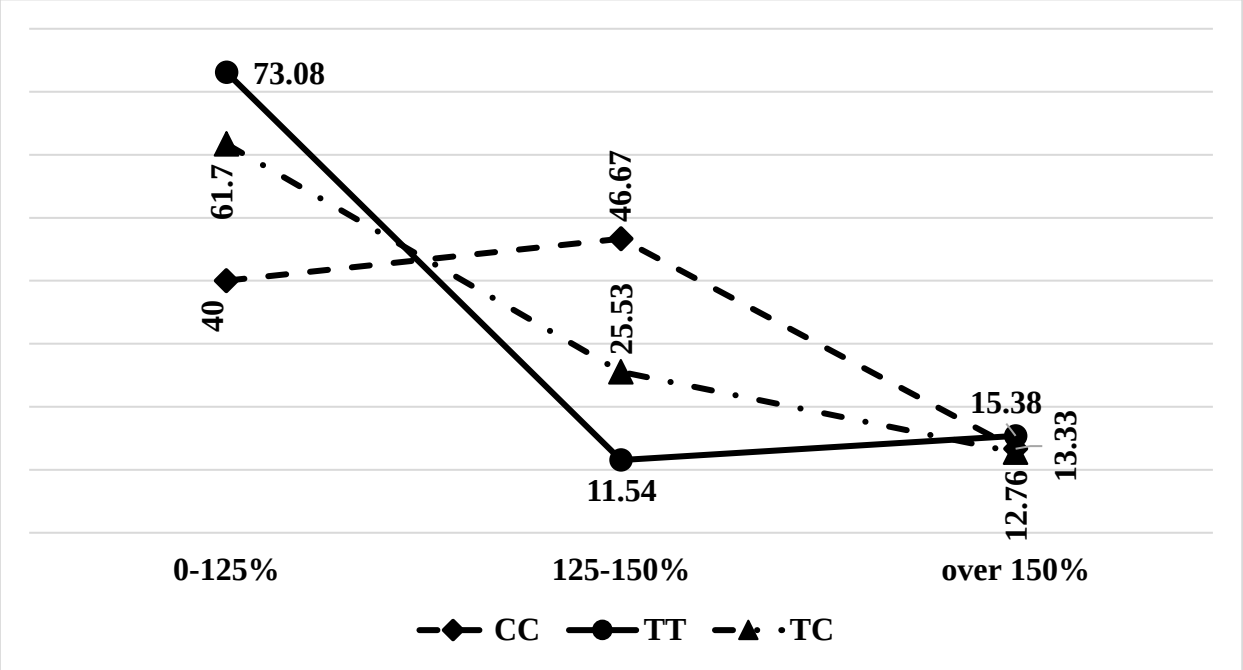

Fig.8. Specific ratio of the BPH drug treatment effect occurrencein terms of the severity of the increase in the volume of the maximum urine flow, depending on the genotypes of the T3435C MDR1 gene.

Нами в настоящей работе представлены результаты анализа динамики сдвигов в значениях показателяобъема остаточной мочи в зависимости от генотипов изучаемых генов.

As can be seen from the data presented in Figure 9, the value of the residual urine volume is markedly reduced among patients with BPH and the GT genotype of the G2677T MDR1 gene. At the same time, a pronounced effect of treatment among carriers of this genotype, if it occurs in ¾ of the examined patients, among patients with TT genotypes - in 3/5 of the examined people, and among patients with the GG genotype - in ½ of the examined people.At the same time, the moderately pronounced effect was most often found among patients with the GG genotype, in comparison with others. Consequently, the indicator of residual urine volume in terms of severity is more efficiently reduced among patients with BPH who carry the GT genotype of the MDR1 gene polymorphism under study.

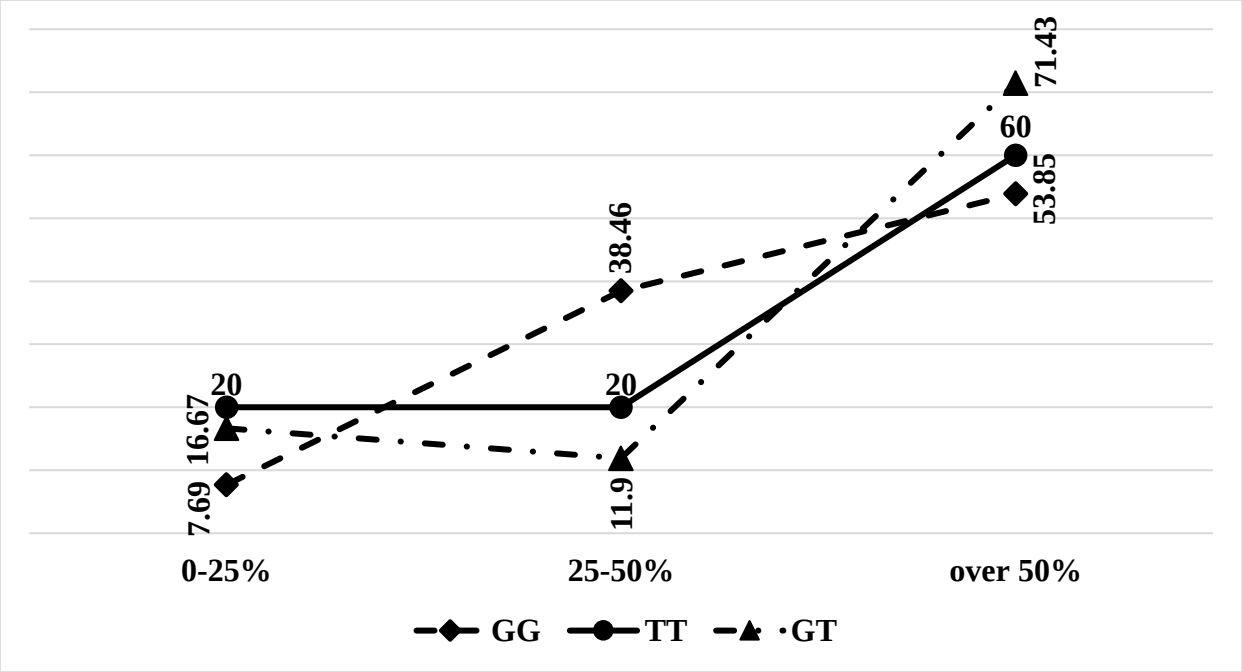

Fig.9. Specific ratio of BPH drug treatment effect occurrence in terms of the severity of the decrease in residual urine volume, depending on the genotypes of the G2677T MDR1 gene.

A similar analysis of the shifts dynamics in the indicator of residual urine volume through the prism of another polymorphism of the MDR1 gene, the T3435C MDR1 gene, also shows the presence of certain differences in the effect in terms of severity from the genotypes of the studied gene.

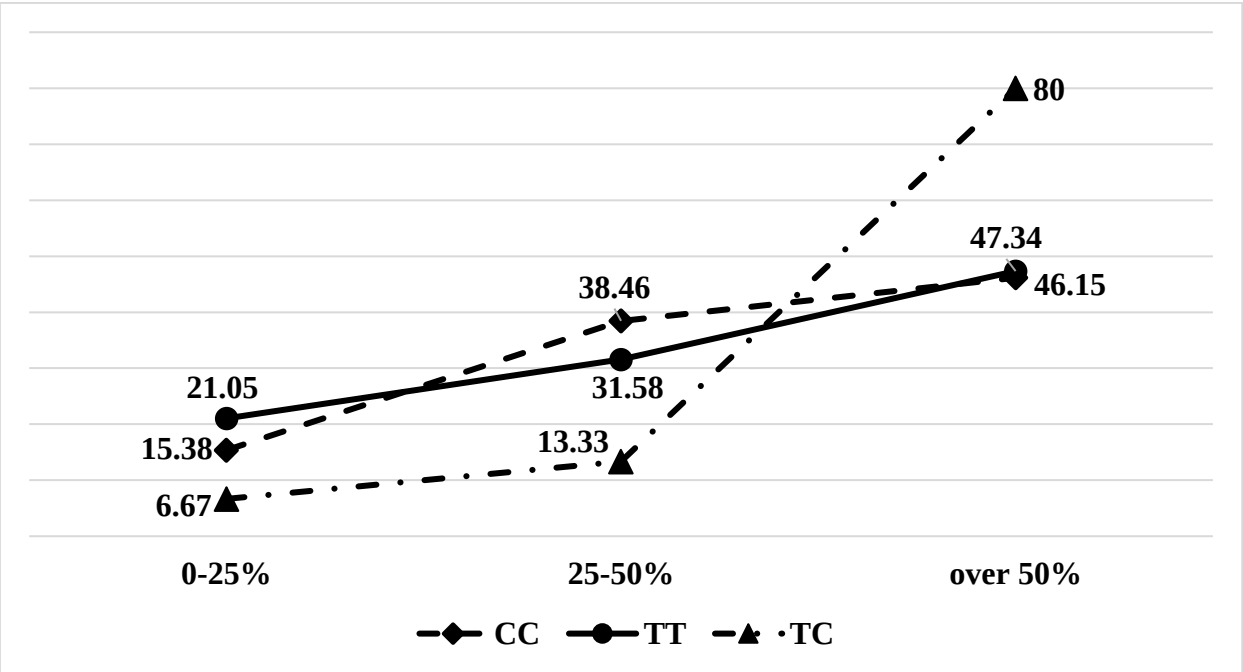

Fig.10. Specific ratio of the BPH drug treatment effect occurrence in terms of the severity of the decrease in residual urine volume, depending on the genotypes of the T3435C MDR1 gene.

In terms of severity, a pronounced effect of treatment in relation to the indicator of residual urine volume is observed among patients with the TC genotype of the T3435C MDR1 gene. As can be seen from Fig. 10, a pronounced effect of treatment among patients with this genotype took place in the vast majority of patients — in 4/5. At the same time, patients with a similarly pronounced effect of treatment among patients with CC and TT genotypes accounted for almost half of the examined patients, respectively. Consequently, the indicator of residual urine volume is markedly reduced among patients with heterozygous TS genotype of the studied MDR1 gene polymorphism.

Thus, the results of the studies carried out indicate that the nature and severity of changes in the indicators of BPH course is in a certain relationship with the genotypes of the studied MDR1 gene polymorphisms. The identified features in this regard may well serve to develop differentiated approaches for the drug treatment of BPH, taking into account the nature of changes in the "indicators" of assessing the course of this pathology.

Conclusion

1.The severity of the effect of drug treatment for BPH in relation to individual indicators of the course of the disease depends to a certain extent on the carriage of genotypes of the G2677T MDR1 gene. The best results in relation to IPSS, QOL, V urine flow rates were found among patients with GT genotype, and in relation to prostate V and PSA indicators - among patients with TT genotype carriers. At the same time, a more pronounced effect of treatment in relation to the indicator V residual urine took place among the patients with the GG genotype of the G2677T MDR1 gene.

2. When studying the T3435C MDR1 gene, a pronounced effect of treatment in relation to the IPSS indices and the residual urine volume is among patients with the TS genotype.And, in relation to the QOL, the volume of the maximum urine flow and PSA, it is among patients with the CC genotype of the studied gene. There is a certain relationship between the genotypes of the studied genes and the indicators of the course of BPH, and this can be clearly seen in relation to the indicators of the volume of residual urine, the volume of the prostate gland, and the volume of the maximum flow of urine.

3. The relationship between the genotypes of the G2677T MDR1 and T3435C MDR1 genes with the indicators of BPH course is clearly seen in relation to the indicators of residual urine volume, prostate gland volume, and maximum urine flow volume.

References:

1.Sychev D.A., Ignatiev I.V., Ramenskaya G.V., Kolkhir S.V., Kukes V.G. Significance of polymorphism of the MDR1 gene encoding glycoprotein-P for individualization of pharmacotherapy. Clinical Pharmacology and Therapy, 2005, 14 (1), pp. 1-5;

2.Seredenin S.B. Lectures on pharmacogenetics. M.: MIA, 2004, p.303;

3.Pharmacogenomics. Ed. M.Rothstein Willy-liss, New Jersey, 2003, p.368;

4.McLeod H., Evans W. Pharmacogenomics: unlocking the human genome for better drug therapy. Annu. Rev. Pharmacol. Toxicol., 2001, 41, 101-121;

5.Meyer U. Pharmacogenomics and adverse drug reactions. Lancet,2000, 356, 1667-1671;

6.Rokhlina F.V., Novik G.A., Kalinina N.M., Bychkova N.V., FilippovaYu.N., Zaraisky M.I. Influence of C3435T polymorphism of the MDR1 gene on the effectiveness of therapy for juvenile idiopathic arthritis. Pediatric Pharmacology, 2013, volume 10, No. 5, p. 46-51;

7.MironovaJ. A., Trofimov V.I., Simakova M.A. et al. Multidrug resistance gene (MDR1) - a marker of therapeutic resistance and severity of diseases. Russian Allergological Journal. 2010; 3: 9-13;

8. AnneseV., ValvanoM. R., PalmieriO. etal. World Multidrug resistance 1 gene in inflammatory bowel disease: A Meta-analysis. J Gastroenterol. 2006 June 21; 12 (23): 3636–3644;

9.Lazarowski A., Czornyj L., Lubienieki F., Girardi E., Vazquez S., D'Giano C. ABC Transporters during Epilepsy and Mechanisms Underlying Multidrug Resistance in Refractory Epilepsy – Epilepsia 2007, Vol. 48, pp. 40–9 (10);

10. Woodahl E.L., Yang Z., Bui T., Shen D.D., Ho R.J.Multidrug resistance gene G1199A polymorphism alters efflux transport activity of Pglycoprotein. J PharmacolExpTher 2004; 310: 1199–207;