Original Article

Cytochrome P450 2C9 Gene Polymorphism and Losartan Response in Essential Hypertensive Patients. A Pharmacogenetic Association Study in Iraq

Ali Hassan Ijam[1], Bahir Abdul-Razzaq Mshimesh[1], Ahmed Sahib Abdulamir[2], Shokry Faaz Alsaad[3]

[1]Department of Pharmacology and Toxicology, College of Pharmacy, Mustansiriyah University, Baghdad, [2]Department of Microbiology, College of Medicine, Al-Nahrain University, Baghdad, [3]Department of Internal Medicine, College of Medicine, University of Babylon, Hilla, Iraq

Abstract

Background: In today's clinical practice, drug research, and drug regulation, one of the most significant challenges is interindividual diversity in therapeutic efficacy and safety. Pharmacogenetics is now in its early phase of development in Iraq. Limited pharmacogenetic data exist about the prevalence and impact of *CYP2C9* gene polymorphism within the Iraqi population. **Objectives:** This study examines the potential impact of *CYP2C9* gene polymorphisms (namely, rs1799853 and rs1057910) on the therapeutic response to losartan in a cohort of Iraqi patients diagnosed with essential hypertension. **Material and Methods:** This prospective interventional clinical study was conducted on a sample of hypertension patients from Babylon governorate in Iraq. For all selected patients, blood pressure was measured. Then they received 100 mg of losartan once daily, after 4 weeks of losartan therapy, blood pressure was reassessed and compared with its initial values, and the changes were recorded. Blood samples were obtained from all patients for genetic analysis, employing established methodologies. The genotyping of *CYP2C9* rs1799853 and rs1057910 variant alleles was conducted using the Sanger sequencing method. Subsequently, the treatment responses of patients with polymorphic genotypes were compared to those of patients bearing the wild-type of genotype. **Results:** According to the findings of the present study, 28% of patients showed a positive response to losartan based on the predetermined criteria (a decrease in systolic blood pressure of at least 15% and diastolic blood pressure of at least 10%). No statistically significant differences P value < 0.05) were seen in the distribution of genotypes of both single nucleotide polymorphisms between the responder and nonresponder groups. Furthermore, a comparative study was conducted to examine the wild-type and heterozygous mutant genotype groups for both single nucleotide polymorphisms in terms of changes in systolic or diastolic blood pressure reduction. The results revealed that there was no statistically significant variation found between these two groups. **Conclusion:** The *CYP2C9* gene polymorphism has no impact on the antihypertensive efficacy of losartan.

Keywords: CYP2C9 polymorphism, hypertension, losartan, pharmacogenetics

Introduction

Interindividual variability in drug response is a major challenge in current clinical practice. Studies of clinical pharmacogenetics have been proposed as a means to improve the efficacy of pharmacological therapy tailored to individual patients.[1]

Pharmacogenetics is the study of the interindividual variability in response to prescribed medications due to genetic origins. It is based on the concept that the genetic makeup of an individual, as manifested in the phenotypic characteristics of protein structure, configuration, and concentration, might potentially influence pharmacological effects through several mechanisms.[2] Significantly, it has been estimated that approximately 20%–30% of the

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_1648_23

Address for correspondence: Dr. Ali Hassan Ijam, Department of Pharmacology and Toxicology, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.
E-mail: ahzajam84@gmail.com

Submission: 05-Nov-2023 **Accepted:** 10-Dec-2023 **Published:** 23-Jan-2026

How to cite this article: Ijam AH, Mshimesh BA-R, Abdulamir AS, Alsaad SF. Cytochrome P450 2C9 gene polymorphism and losartan response in essential hypertensive patients. A pharmacogenetic association study in Iraq. Med J Babylon 2025;22:1487-94.

variation in drug response can be attributed to genetic polymorphisms, which are predominantly found in genes associated with drug absorption, distribution, metabolism, and excretion. Additionally, these polymorphisms are also present in genes related to drug targets and immune responses.[3] Recent evidence suggests that mutations in the gene encoding the cytochrome P450 (CYP) enzyme may contribute to the variable responses to some medications in clinical trials.[4,5] One of the most crucial members of the cytochrome P450 superfamily, is the CYP2C9, it hydroxylating a wide range of medications and it is thought to be involved in the metabolic processes of approximately 16% of pharmaceutical compounds, including the antihypertensive losartan, the anticoagulant warfarin, the analgesic ibuprofen, and the antidiabetic drugs tolbutamide and glimepiride.[6]

The *CYP2C9* gene is situated on chromosome 10 and consists of 51,434 base pairs with nine exons. This gene is highly polymorphic, and, to date, approximately 85 *CYP2C9* alleles have been identified in the regulatory and coding regions of *CYP2C9*.[7] The most prevalent variants among these alleles are *CYP2C9*2* (R144C rs1799853) and *CYP2C9*3* (I359L rs1057910), which have much lower CYP2C9 enzyme activity than the wild-type allele (*CYP2C9*1*).[8]

Losartan potassium is the first selective angiotensin receptor blocker approved for clinical use in treating hypertension. It binds selectively and competitively with high affinity to the AT1 receptor, resulting in blocking AII-induced physiological effects. The process of oxidation of losartan leads to the formation of a biologically active metabolite known as E-3174. The potency of this metabolite exceeds that of losartan, and it has a prolonged half-life. The primary mechanism by which losartan exerts its antihypertensive effect is through the action of its metabolite, E-3174.[9]

To date, up to knowledge, there is a limited number of clinical research investigating the relationship between *CYP2C9* gene polymorphisms and the efficacy of antihypertensive medications, such as angiotensin receptor blockers.[5,10-13] The therapeutic implications of different *CYP2C9* genotypes, including variations in the response of blood pressure (BP) reduction in patients using losartan, remain incompletely understood.[5] The objective of the current study was to investigate the potential impact of *CYP2C9* gene polymorphism, specifically rs1799853 and rs1057910, on the therapeutic response of losartan in some hypertensive Iraqi patients. Additionally, the study aimed to add valuable insights into the variability of antihypertensive drug responses. These findings would be beneficial for healthcare professionals in making well-informed decisions regarding personalized hypertension medication.

Materials and Methods

Study design

The present study is a prospective interventional clinical trial designed to examine the potential impact of *CYP2C9* gene polymorphisms (namely, rs1799853 and rs1057910) on the therapeutic response of losartan in a cohort of patients diagnosed with essential hypertension.

Patients selection

The participants (males and females) were recruited from the private clinic of an interventional cardiologist according to the inclusion and exclusion criteria of the study listed below and diagnosed as hypertensive patients at stages I or II according to the ESH (2018) guideline.[14] These patients were selected during the period from the first of June 2022 to the end of February 2023.

Of a total of 272 hypertensive patients, 172 were excluded due to incompliance, loss of contact, severe hypotension, use of other antihypertensive drugs, and missing the date of sampling. Only 100 patients completed the study.

Inclusion criteria

Patients (males and females) diagnosed with essential hypertension with mean systolic BP (SBP) ≥140 and <180 mm Hg, whereas mean diastolic BP (DBP) ≥90 and <110 mm Hg, age between ≥25 and ≤80 years.

Exclusion criteria

Any condition that may interfere with the study protocol or aim was excluded, including patients with known or suspected secondary hypertension, those whose BP measurements are <180/110 mm Hg, and patients with other cardiovascular diseases such as myocardial infarction, atrial fibrillation, heart failure, and stroke. Also patients with metabolic or endocrine disorders (like diabetes and thyroid disease), autoimmune disease, malignant tumors, psychiatric disorders, renal or liver dysfunction, in addition to pregnant and breast-feeding women, alcoholic patients, and those who require other antihypertensive drugs rather than losartan.

Study protocol

During the process of patient screening for essential hypertension, the selected individuals were interviewed using a specialized data sheet that was particularly developed for the purpose of this study. The BP was measured using a mercury sphygmomanometer following a minimum resting period of 10 min in a seated position. Additional variables such as age, gender, height, weight, and body mass index (BMI) were assessed for each individual and documented with other information, including their name, smoking status, dietary habits, level of physical activity, and family history of hypertension.

For all patients enrolled BP was measured. Then they received 100 mg of losartan once daily, after 4 weeks of losartan therapy, BP was reassessed and compared with its initial values, and the changes were recorded. Also, during the follow-up, each participant was interviewed to determine if they had used any medications other than losartan, with the purpose of ensuring that all participants were only taking losartan since the aim of the study was to determine the therapeutic efficacy of losartan.

Samples collection

Venous blood samples (2 mL) were collected from all patients using a disposable plastic syringe and placed in an EDTA tube to be used as whole blood for genetic analysis of *CYP2C9*.

Evaluation of losartan therapeutic efficiency

Evaluation of losartan efficiency in patients with essential hypertension was made by using the following criteria: Responder if there is a reduction of SBP by at least 15% and DBP by at least 10% and nonresponder if there is a reduction of SBP less than 15% and DBP less than 10%.[15]

The percentage of changes was calculated as the BP reduction (mmHg) from the baseline to the 4 weeks of treatment and was further divided by the initial BP value preceding the initiation of losartan treatment, while the percentage of therapeutic efficiency was calculated by dividing the number of responders by the total number of responder and nonresponder individuals.

Molecular biological studies

DNA extraction and primer optimization

The DNA extraction was carried from a blood sample using the ReliaPrep Blood gDNA Miniprep System, a procedure developed by Promega.[16] The Quantus Fluorometer was employed to assess the concentration of extracted DNA, enabling the evaluation of both the quantity and quality of the samples for subsequent applications. The primers utilized in this study were specifically developed for the purpose of polymerase chain reaction (PCR) amplification and subsequent DNA sequencing. These primers were made to target two distinct regions within the *CYP2C9* gene, region 1 that involves (intron 1, exon 2, intron 2, exon 3, and some of intron 3) and region 2 that involves (intron 6, exon 7, and some of intron 7), and their sequences [Table 1]. Prior to conducting PCR, primer optimization was performed to determine the optimal annealing temperature at which the primer would effectively bind to the DNA template.

PCR and program protocol

The DNA samples were subjected to amplification using the PCR technique.[17] Each reaction consisted of 12.5 µL of master mix (Promega, Wisconsin, USA), 1 µL of each primer (10 Pmol), 3 µL of DNA template, and the remaining volume was made up of 25 µL using nuclease-free water. The PCR settings utilized for the amplification of the CYP2C9 gene involved a single cycle of initial denaturation at a temperature of 95°C for a duration of 5 min. This was followed by denaturation (30 cycles) at 95°C for 30 s, annealing at 63°C for 30 s, and extension at 72°C for 1 min. The final extension step was performed at 72°C for a period of 7 min. The PCR products were ultimately seen using a UV transilluminator on a 1.5% gel of agarose that had been treated with ethidium bromide to validate their purity and assess their mobility.

Standard DNA sequencing and post-sequencing analysis

Sanger sequencing[18] was performed on PCR products using a Macrogen Corporation, Seoul, South Korea, ABI3730XL automated DNA sequencer to identify SNPs (rs1799853 and rs1057910). Genius software was used for the analysis of the data.

Statistical analysis

The data was saved and processed via IBM SPSS 26.0. Numerical data were expressed as mean ± SD, whereas categorical variables were expressed as percentages and frequencies. Patients are considered responders if there is a reduction of SBP by at least 15% and DBP by at least 10%. A paired *t* test was used to test the significance of SBP and DBP reductions before and after losartan treatment. The independent *t* test was used to test the significance of SBP and DBP reductions across responder and nonresponder groups. A one-way ANOVA test was used as a statistical test for the numerical variables SBP and DBP changes across different genotypes. Chi square (χ^2) test was used to compare responder and nonresponder proportions in genotype groups and to test the deviation from the Hardy–Weinberg equilibrium (HWE). P value > 0.05 was considered significant.

Ethical approval

This research began after getting approval from the scientific committee in the University of Mustansiriyah/ College of Pharmacy. Also, the agreement of the Babylon Health Directorate was achieved according to the Ministry

Table 1: Primer sequences

Primer	Sequence 5′–3′	Annealing temperature (°C)	Product size (bp)
CYP2C9-F1	GCCTGTGTGGCTGAATAAA	63	990
CYP2C9-R1	CTGGTGACATGTTCTGGAATAG		
CYP2C9-F2	TTCAGCCTATGTGTGTCTTTAT		942
CYP2C9-R2	CTAAGAGTAGCCAAACCAATCT		

F1: forward primer for region one, F2: forward primer for region two, R1: reverse primer for region one, R2: reverse primer for region two

of Health's Ethical Committee. All participants in this study signed a written consent.

Results

Patients' demographic and clinical characteristics

In this study, only 100 patients out of 272 hypertensive screened patients completed the study. Their age range was between 18 and 80 years, with a mean ± SD of 50.58 ± 11.28 years. The distribution of gender was 48 males (48%) and 52 females (52%). More than half of the patients were obese, with a mean BMI of 32.21 ± 6.42 kg/m^2 [Table 2].

Antihypertensive efficiency of losartan

Systolic and diastolic BP changes and response status and the percentage of losartan antihypertensive efficiency

Before starting the losartan treatment, mean (± SD) SBP and DBP were 154 ± 10.31 mm Hg and 93.85 ± 5.02 mm Hg, respectively. Four weeks after treatment, average SBP and DBP were 136.16 ± 12.55 and 86.07 ± 7.59 mm Hg, respectively [Table 3]. Regarding the response status and therapeutic efficiency of losartan as an antihypertensive agent, the result showed that it reduced the SBP by at least 15% and DBP by at least 10% in 28% of studied patients [Table 4].

Table 2: Patients demographic and clinical characteristics

Patients characteristics (*N* = 100)	Values
Age (years)	50.58 ± 11.28
Gender	
Male	48 (48%)
Female	52 (52%)
BMI (kg/m^2)	32.21 ± 6.42

Data existing as mean ± (SD) for numerical variable, *N*: number, and percentage (%) for categorical data. SBP: systolic blood pressure, DBP: diastolic blood pressure

Table 3: Changes in blood pressure level before and after losartan treatment

Blood pressure	Before treatment	After treatment	Changes of BP (%)
SBP (mmHg)	154 ± 10.31**	136.16 ± 12.55	−11.27 ± 9.28
DBP (mmHg)	93.85 ± 5.02**	86.07 ± 7.59	−8.10 ± 8.65

Data existing as mean ± (SD). SBP: systolic blood pressure, DBP: diastolic blood pressure, (−) mean a reduction in blood pressure. Paired sample *t* test is used for statistical analysis. **Statistically highly significant ($P > 0.01$)

Table 4: Response status and the percentage of losartan antihypertensive efficiency

Response status	Value, *N* (%)	Efficiency, %
Responder	28 (28)	28%
Not responder	72 (72)	

Data (categorical) existing as a number (*N*), and percentage (%)

Systolic and diastolic BP changes among losartan responder and nonresponder hypertensive patients

After losartan treatment, the percentage of SBP changes in the responder group was (−21.55 ± 4.84) versus the nonresponder group (−7.26 ± 7.29), and the percentage of DBP changes in the responder group was (−14.92 ± 3.62) versus the nonresponder group (−5.45 ± 8.59). All of these differences were found to be statistically significant at a significance level of $P < 0.05$, as shown in Table 5.

Genetic variants of *CYP2C9* gene

Along with the analysis of two specific regions of the *CYP2C9* gene, the two major allelic polymorphisms *CYP2C9* rs1799853 on exon 3 and rs1057910 on exon 7 have been identified among the 100 hypertensive patients [Table 6].

Association of CYP2C9 rs1799853 and rs1057910 single nucleotide polymorphism genotypes with baseline patients' demographic and clinical characteristics

There were no statistically significant differences ($P > 0.05$) in demographic and clinical characteristics between the rs1799853 and rs1057910 SNP genotypes of the hypertensive patients enrolled in this study [Tables 7 and 8].

Table 5: Changes in systolic and diastolic blood pressure in responder versus nonresponder hypertensive patients

Variables	Responder *N* (28)	Nonresponder *N* (72)	*P* value
% SBP changes	−21.55 ± 4.84	−7.26 ± 7.29	<0.05
% DBP changes	−14.92 ± 3.62	−5.45 ± 8.59	<0.05

Data existing as mean ± SD, independent sample *t* test used for statistical analysis, SBP: systolic blood pressure, DBP: diastolic blood pressure. $P > 0.05$was statistically considered significance

Table 6: Genotype and allele frequency of the identified single nucleotide polymorphisms

SNPs			
No.	**Genotype frequency**	**Allele frequency**	**HWE *P* value**
1	**rs1799853**		
	CC—73(73%)	C—169(84.5%)	0.67
	CT—23(23%)	T—31 (15.5%)	
	TT—4 (4%)		
2	**rs1057910**		
	AA—86(86%)	A—183 (91.5%)	0.06
	AC—11(11%)	C—17 (8.5%)	
	CC—3 (3%)		

Data existing as number (N) and percentage (%), HWE: Hardy-Weinberg Equilibrium. SNPs: single nucleotide polymorphism, C: cytosine, T: thymine, A: adenine

Table 7: Association of *CYP2C9* rs1799853 single nucleotide polymorphism genotype with demographic and clinical characteristics

patient's characteristic	rs1799853 SNP genotypes ($N = 100$)			*P* value
	CC ($N = 73$)	CT ($N = 23$)	TT ($N = 4$)	
Age (years)	49.7 8 ± 11.28	53.39 ± 11.21	49.00 ± 11.91	0.396
BMI (kg/m2)	31.53 ± 6.20	33.78 ± 7.28	35.52 ± 1.44	0.197
Gender				
Male	37 (50.7%)	10 (43.5%)	1 (25%)	0.536
Female	36 (49.3%)	13 (56.5%)	3 (75%)	
Pre SBP (mm Hg)	154.38 ± 10.45	152.93 ± 9.99	153.12 ± 11.79	0.832
Pre DBP (mm Hg)	94.28 ± 5.27	92.93 ± 4.30	91.25 ± 2.20	0.308

Data exist as mean ± SD for numerical data, a number (*N*), and percentage (%) for categorical data, one-way ANOVA test used as statistical test for numerical variable and Chi square test used for categorical variable, $P < 0.05$ was statistically considered significant

Table 8: Association of *CYP2C9* rs1057910 single nucleotide polymorphism genotype with demographic and clinical characteristics

Patient's characteristic	rs1057910 SNP genotype ($N = 100$)			*P* value
	AA ($N = 86$)	AC ($N = 11$)	CC ($N = 3$)	
Age (years)	50.03 ± 11.18	53.45 ± 9.33	55.67 ± 21.22	0.471
BMI (kg/m^2)	31.86 ± 6.06	35.86 ± 8.36	28.65 ± 5.40	0.093
Gender				
Male	42 (50.7%)	3 (43.5%)	3 (25%)	0.075
Female	44 (49.3%)	8 (56.5%)	0 (75%)	
Pre-SBP (mm Hg)	154.30 ± 10.55	151.81 ± 9.88	153.33 ± 2.88	0.752
Pre-DBP (mm Hg)	93.54 ± 5.02	94.53 ± 4.71	100.00 ± 0.00	0.080

Data exist as mean ± SD for numerical data, a number (*N*), and percentage (%) for categorical data, one-way ANOVA test used as a statistical test for numerical variable and Chi square test used for categorical variable, $P < 0.05$ was the statistically considered significant. BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure. *N*: number of patients, AA: wild type genotype, AC: heterozygous mutant genotype, CC: homozygous mutant genotype

Table 9: Association of losartan antihypertensive response with *CYP2C9* rs1799853 and rs1057910 single nucleotide polymorphism genotypes

	Genotype	Responder (28)	Nonresponder (72)	Total (100)	*P* value
1	**rs1799853 C<T**				
	CC	22 (30.14%)	51 (69.86%)	73 (100%)	0.730
	CT	5 (21.74%)	18 (78.26%)	23 (100%)	
	TT	1 (25%)	3 (75%)	4 (100%)	
2	**rs1057910 A <C**				
	AA	26 (30.23%)	60 (69.77%)	86 (100%)	0.386
	AC	2 (18.18%)	9 (81.82%)	11 (100%)	
	CC	0 (0%)	3 (100%)	3 (100%)	

Data existing as number (*N*) and percentage (%), Chi square (χ^2) used as a statistical test for categorical variables, $P < 0.05$ was statistically considered significant. CC, AA: wild type genotype. CT, AC: heterozygous mutant genotype. TT, CC: homozygous mutant genotype. C: cytosine, T: thymine, A: adenine

Association of losartan antihypertensive response with *CYP2C9* rs1799853 and rs1057910 single nucleotide polymorphisms genotypes

No significant differences ($P > 0.05$) were found in the genotype distribution of identified SNPs between responder and nonresponder groups of hypertensive patients, so the BP response to losartan treatment was not significantly associated with coding rs1799853 and rs1057910 SNP genotypes of the *CYP2C9* gene [Table 9].

Differences in systolic and diastolic BP reduction and percentage of losartan antihypertensive efficiency with respect to single nucleotide polymorphisms genotypes

Regarding the differences in SBP and DBP reductions, although the decrease in SBP was higher in the rs1799853 CC genotype group than in the CT and TT genotype groups (12.28 + 9.51% vs. 8.01 + 8.26% and 11.41 + 7.81%) respectively, also the reduction in SBP was higher in the rs1057910 AA genotype group than in the AC and

Table 10: Blood pressure changes and losartan efficiency with respect to CYP2C9 rs1799853 and rs1057910 single nucleotide polymorphism genotypes

	Genotypes	SBP changes, %	DBP changes, %	Efficiency, %
1	rs1799853 C<T			
	CC wild type	−12.28 ± 9.51%	−8.98 ± 8.55%	30.1%
	CT heterozygous mutant	−8.01 ± 8.26%	−5.79 ± 8.28%	21.7%
	TT homozygous mutant	−11.41 ± 7.81%	−5.33 ± 11.73%	25.0%
	P value	0.157	0.247	0.730
2	rs1057910 A<C			
	AA wild type	−11.86 ± 9.12%	−7.80 ± 8.86%	30.2%
	AC heterozygous mutant	−9.09 ± 10.34%	−10.37 ± 8.08%	18.2%
	CC homozygous mutant	−2.22 ± 5.02%	−8.33 ± 2.88%	0.0%
	P value	0.149	0.655	0.386

Data existing as mean ± (SD), one-way ANOVA test used as statistical analysis. SBP: systolic blood pressure, DBP: diastolic blood pressure. *P* value < 0.05was statistically considered significant

CC genotype group (11.86 + 9.12% vs. 9.09 + 10.34% and 2.22 + 5.02%) respectively significant differences were not found ($P > 0.05$).

No significant differences ($P > 0.05$)were found regarding the changes in the DBP which were 8.98 ± 8.55%, 5.79 + 8.28%, and 5.33 ± 11.73% among the rs1799853 CC, CT, and TT genotype groups, respectively ($P = 0.247$). Also, no significant differences ($P > 0.05$) were found regarding the changes in the DBP which were 7.80 + 8.86%, 10.37 + 8.08%, and 8.33 + 2.88% among the rs1057910 AA, AC, and CC genotype groups, respectively ($P = 0.655$).

Regarding losartan, the percentage of its efficiency was lower in heterozygous mutant CT and AC genotypes of rs1799853 and rs1057910 (21.7% and 18.2%), respectively, when compared to the wild-type genotypes of both SNPs [Table 10].

Discussion

Drug therapy is an important method for lowering the prevalence of hypertension, which is a global health concern. Currently, hypertension is treated pharmacologically with a "one-size-fits-all" or empirical trial-and-error strategy. This method, however, falls short of meeting the treatment requirements of many patients; pharmacogenetics has been proposed as a means of improving patient-specific medication therapy.[1] Pharmacogenetics in hypertension aims to enhance treatment efficacy and decrease toxicity by using genetic determinants of treatment response.[19]

Many factors, including age, race, and gene–gene interactions, might influence hypertension, resulting in a multigenetic and multifactorial antihypertensive response to angiotensin receptor blockers.[20]

The primary objective of this study was to investigate the influence of genetic polymorphisms in the *CYP 450 2C9* gene on the variability in BP response to losartan among hypertensive Iraqi patients. Up to our knowledge, this is the first study in which the clinical significance of genetic polymorphisms of *CYP2C9* gene has been investigated in purely hypertensive patients treated with losartan in an Iraqi population.

Losartan therapeutic efficiency

The low losartan therapeutic efficiency reported by the present study (28%) despite significant differences in SBP and DBP values before and after losartan treatment may be the result of the BP response criteria used in this study, which is the patient's regard responder if there is a reduction of SBP by at least 15% and DBP by at least 10%, and this level of therapeutic efficiency may be changed when other criteria reflect the BP response to losartan.

Impact of *CYP2C9* gene polymorphism on percentage of systolic and diastolic BP reduction

The presence of genetic polymorphisms in the CYP2C9 enzyme has been linked to the variability in BP responses to various pharmaceutical agents. There are many studies that have examined the differences in the response of drugs and therapies used in various diseases regarding *CYP2C9* genetic polymorphism in the literature.[21]

The present study examined the BP response to losartan in hypertensive patients with different *CYP2C9* genotypes. At baseline, there were no significant differences ($P > 0.05$) between genotypes of the rs1799853 and rs1057910 SNP variants regarding clinical and demographic features (age, gender, BMI, and baseline SBP and DBP. This lack of significant differences may be attributed to the fact that all individuals enrolled in this study met the predetermined criteria for participation. The value of this finding in the current study is important as it aligns with the study's objective of investigating the impact of *CYP2C9* genetic polymorphism on the therapeutic response to losartan. Any observed variations in the reduction of SBP and DBP, based on SNP genotypes, can be attributed to

genetic variations rather than differences in demographic characteristics among the groups.

There were no statistically significant variations observed in the percentage of changes in SBP and DBP among different genotypes of CYP2C9 rs1799853 and rs1057910 SNP variants. Similarly, no statistically significant changes were identified in the therapeutic effectiveness of losartan between individuals with heterozygous or homozygous *CYP2C9* rs1799853 and rs1057910 SNP genotypes and those with the wild-type of genotype. There are conflicting findings from earlier research about the relationship between *CYP2C9* polymorphism and the antihypertensive effect of angiotensin receptor blockers.[13] In the present study, the response to losartan treatment is not significantly associated with coding SNP variants of the CYP2C9 gene, this result is in line with some studies which indicated that there was no evidence of significant differences in BP responses to several antihypertensive drugs among different genotypes of CYP2C9 polymorphism. Also, this result is in line with a recent study found that CYP2C9 rs1799853 and rs1057910 SNP genotypes do not significantly affect SBP and DBP reduction in newly diagnosed 74 hypertensive patients.[5] A further study demonstrated the influence of *CYP2C9* genetic polymorphisms on the antihypertensive efficacy of losartan in 39 Japanese patients with hypertension which showed insignificant differences regarding changes in SBP and DBP between the rs1057910 mutant variant genotype and wild-type genotype carriers, which was comparable to our finding but provided better evidence because of our larger sample size.[12] Moreover, our results agree with those of Qayyum *et al.*[10] who found that two *CYP2C9* SNP variants, rs1799853 and rs1057910, exhibited no association with the Losartan BP response. Liu *et al.*[13] found that the rs1057910 SNP variant was not associated with the response of antihypertensive treatment with valsartan. Similarly, the rs1057910 SNP variant and irbesartan's therapeutic impact on essential hypertension were not observed to be significantly associated.[11]

Contrary to our result, the SBP increased significantly with the rs1057910 SNP variant in a Danish prospective study of optimum monotherapy in patients with type 1 diabetes and nephropathy; nevertheless, the total number of patients involved was limited ($n = 60$).[22] Another study performed by Joy *et al.*[23] showed that the response to losartan considering antihypertensive effects was diminished in genetically polymorphic individuals., it found that the BP was decreased in patients with the wild-type genotype while increased in patients carrying the rs1799853 SNP and rs1057910 SNP variants. This study only comprised a small number of participants ($n = 59$).[23] Our research is unique in the field since it specifically examines a cohort of pure hypertensive patients who only received a 100 mg dosage of losartan as a pharmacological intervention for essential hypertension. The majority of previously published trials on losartan, as previously mentioned in detail, either focused on medications other than losartan in patients with primary hypertension[11,13] or included hypertensive patients with concurrent disorders including diabetes or renal issues.[22,23] In addition, our study had a sample size that was comparatively bigger when compared to the clinical research mentioned before. Nevertheless, the main limitation of our investigation remains the sample size, as the allocation of patients to each distinct genotype group is limited. This limitation may partially account for the reduced statistical significance observed in relation to clinically relevant outcomes.

Conclusion

The presence of polymorphisms in the *CYP2C9* gene among our hypertension patients did not exhibit any association with the effectiveness of losartan as antihypertensive agent. Nevertheless, it is anticipated that the lack of association in this study would not discourage subsequent, more extensive investigations aimed to confirm or refute the findings of the current study.

Acknowledgments

The authors would like to thank Mustansiriyah University (www.uomustansiriyah.edu.iq), Baghdad, Iraq, for its support in the present work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Arnett DK, Claas SA. Pharmacogenetics of antihypertensive treatment: Detailing disciplinary dissonance. Pharmacogenomics 2009;10:1295-307.
2. Padmanabhan S, editor. Handbook of Pharmacogenomics and Stratified Medicine. Cambridge, USA: Academic Press; 2014.
3. Lauschke VM, Ingelman-Sundberg M. Prediction of drug response and adverse drug reactions: From twin studies to next generation sequencing. Eur J Pharm Sci 2019;130:65-77.
4. Ali Saleh M, Kadhim HM, Sahib AS, Abdulamir AS, Altawil R. The effect of CYP2C9 and VKORC1 genetic polymorphism on warfarin dose requirements in a sample of Iraqi patients. J Kerman Univ Med Sci 2021;28:139-49.
5. Tanrikulu FP, Babaoglu MO, Cakir B, Bozkurt A, Güven GS. The effect of CYP2C9 gene polymorphisms on blood pressure lowering response to losartan in patients with essential hypertension. Cukurova Med J 2022;47:1015-23.
6. Parikh SJ, Evans CM, Obi JO, Zhang Q, Maekawa K, Glass KC, *et al.* Structure of cytochrome P450 2C9* 2 in complex with losartan: Insights into the effect of genetic polymorphism. Mol Pharmacol 2020;98:529-39.
7. PharmVar Standards. Available from: https://www.pharmvar.org/genes. [Last accessed on 20 Mar 2023].
8. Wei L, Locuson CW, Tracy TS. Polymorphic variants of CYP2C9: mechanisms involved in reduced catalytic activity. Mol Pharmacol 2007;72:1280-8.

9. Song JC, White CM. Pharmacologic, pharmacokinetic, and therapeutic differences among angiotensin II receptor antagonists. Pharmacotherapy 2000;20:130-9.
10. Qayyum A, Ashraf W, Javaid S, Imran I, Kaukab I. Association between cytochrome P450 2C9 gene polymorphisms and blood pressure in response to losartan. Prec Med Commun 2022;2:19-26.
11. Hong X, Zhang S, Mao G, Jiang S, Zhang Y, Yu Y, *et al*. CYP2C9* 3 allelic variant is associated with metabolism of irbesartan in Chinese population. Eur J Clin Pharmacol 2005;61:627-34.
12. Yin T, Maekawa K, Kamide K, Saito Y, Hanada H, Miyashita K, *et al*. Genetic variations of CYP2C9 in 724 Japanese individuals and their impact on the antihypertensive effects of losartan. Hypertens Res 2008;31:1549-57.
13. Liu Y, Kong X, Jiang Y, Zhao M, Gao P, Cong X, *et al*. Association of AGTR1 A1166C and CYP2C9* 3 gene polymorphisms with the antihypertensive effect of valsartan. Int J Hypertens 2022;2022:7677252.
14. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, *et al*. ESC/ESH guidelines for the management of arterial hypertension. Kardiol Pol 2018;77:71-159.
15. Dobovisek J, Spinar J, Niegowska J, Soucek M, Kanic V, Rekic S. Efficacy and tolerability of losartan in patients with essential hypertension: A multicentre, double-blind comparison of losartan with metoprolol. J Clin Basic Cardiol 2005;8:43.
16. http://www.promega.com/resources/pubhub/reliaprepblood-gdnaminiprep-system-low-elution-volume-with-high-yield/ Updated. Promega Corporation Website.
17. Abdullah AM, Merza NS, Merza AS. Detection of Toxoplasma gondii oocysts in contaminated soils using polymerase chain reaction analysis in Duhok City Iraq. Med J Babylon 2022; 19:271.
18. Al-Kaim HW, Al-Dahmoshi HO. Prevalence of AcrAB-TolC efflux pump among Proteus mirabilis isolated from cystitis patients in Hilla City, Iraq. Med J Babylon 2023;20:503-10.
19. Ashiq K, Ashiq S, Mustafa N. Pharmacogenomics and the concept of personalized medicine for the management of hypertension. Pak Heart J 2023;56:188-90.
20. Chen K, Xiao P, Li G, Wang C, Yang C. Distributive characteristics of the CYP2C9 and AGTR1 genetic polymorphisms in Han Chinese hypertensive patients: A retrospective study. BMC Cardiovasc Disord 2021;21:1-6.
21. Park YA, Song YB, Yee J, Yoon HY, Gwak HS. Influence of CYP2C9 genetic polymorphisms on the pharmacokinetics of losartan and its active metabolite E-3174: A systematic review and meta-analysis. J Pers Med 2021;11:617.
22. Lajer M, Tarnow L, Andersen S, Parving HH. CYP2C9 variant modifies blood pressure-lowering response to losartan in type 1 diabetic patients with nephropathy. Diabet Med 2007;24: 323-5.
23. Joy MS, Dornbrook-Lavender K, Blaisdell J, Hilliard T, Boyette T, Hu Y, *et al*. CYP2C9 genotype and pharmacodynamic responses to losartan in patients with primary and secondary kidney diseases. Eur J Clin Pharmacol 2009;65:947-53.