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ARAŞTIRMA / RESEARCH

The effect of CYP2C9 gene polymorphisms on blood pressure lowering response to losartan in patients with essential hypertension

CYP2C9 gen polimorfizmlerinin losartan kullanan esansiyel hipertansif hastalarda tedavi yanıtı üzerine etkisi

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Abstract

Purpose: In this study, the possible effects of *CYP2C9* polymorphisms on the clinical response to losartan were investigated in a group of hypertensive patients.
Materials and Methods: Seventy-four patients, newly diagnosed to have essential hypertension, and were subsequently prescribed losartan by attending physicians, were prospectively recruited for the study. Blood pressure measurements at the initiation of losartan treatment and six weeks after were completed for all participants. Genetic analysis for *CYP2C9* polymorphisms was performed in blood samples collected at baseline. *CYP2C9 *2* and **3* variant alleles were genotyped, and polymorphic patients' treatment responses were compared with the patients' who were carrying the wild type genotype.
Results: Analysis comparing the wild type genotype and *CYP2C9*1*2* genotype revealed a trend toward more systolic blood pressure reduction in favor of wild-type genotype. However, there was no statistically significant difference between these two groups considering the change in diastolic blood pressure levels. Regarding the *CYP2C9*1*3* genotype, there were no significant differences in systolic or diastolic blood pressure changes.
Conclusion: *CYP2C9*1*2* polymorphism affects the systolic blood pressure response to losartan in hypertensive patients, while the *CYP2C9*1*3* genotype was not shown in associated with systolic or diastolic blood pressure responses.

Öz

Amaç: Bu çalışmada, anti-hipertansif olarak losartan kullanan hastalarda *CYP2C9* polimorfizmlerinin tedavi yanıtı üzerine etkileri incelenmiştir.
Yöntemler: Araştırmaya yeni tanı almış, evre 1 esansiyel hipertansiyonu olan 74 hasta dahil edildi. Bu hastalara tedavi öncesi ve losartan başlandıktan altı hafta sonra kan basıncı ölçümleri yapılarak elde edilen kan basıncı düşüşleri kaydedildi. Hastalardan ilk tanı sırasında alınmış olan kan örneklerinden DNA izolasyonu yapılarak *CYP2C9 *2* ve **3* polimorfik alelleri için genetik analizler yapıldı. Polimorfik alelleri taşıyan bireyler ile yabanıl tip (wild-type) genotip taşıyıcılarının anti-hipertansif tedavi yanıtları karşılaştırıldı.
Bulgular: *CYP2C9*1*2* genotipine sahip hastalar, yabanıl tip genotipe sahip hastalar ile kıyaslandığında diyastolik kan basıncı için gruplar arasında istatistiksel açıdan anlamlı fark saptanmazken, sistolik kan basıncındaki düşüşün yabanıl tip genotipe sahip hastalarda daha belirgin olma eğiliminde olduğu görüldü. *CYP2C9*1*3* genotipi ise tedavi sonuçlarında anlamlı bir değişikliğe neden olmadı.
Sonuç: Bulgularımız, *CYP2C9*1*2* polimorfizminin hipertansif hastaların losartan ile tedavisinde sistolik kan basıncı yanıtını etkileyebileceğini düşündürmektedir. Öte yandan, *CYP2C9*1*3* genotipinin sistolik veya diyastolik kan basıncı yanıtlarıyla ilişkisi gösterilememiştir.

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Anahtar kelimeler: Hipertansiyon, losartan, CYP2C9, genetik polimorfizm, farmakogenetik

INTRODUCTION

Individualized, or personalized medicine, has been a popular model over the last decade that separates people into different groups, with medical decisions, practices and/or interventions, including drug treatments. This is based on the fact that patients with the same disease are different from each other and may respond differently to the same drug, prescribed for the same diagnosis[1,2]. Recently, it has been suggested that genetic polymorphisms in the cytochrome P450 (CYP) enzyme system may be a reason for the difference in treatment responses of some drugs[3-5].

Cytochrome P450 enzyme system is located in the liver microsomes and is essential for human drug metabolism. An enzyme sub-grouped in this system is CYP2C9[6]. This enzyme is responsible for the oxidative metabolism of many drugs like warfarin, phenytoin, non-steroidal anti-inflammatory drugs, glipizide, irbesartan and losartan[7]. Losartan is an anti-hypertensive drug oxidized by CYP2C9 and is the first selective angiotensin II receptor antagonist, reported to significantly reduce the risk of cardiovascular end-points in hypertensive patients[8]. Oxidation of losartan results in the production of an active metabolite called E-3174. This metabolite is more potent than losartan and has a longer half-life[9]. Thus, the main anti-hypertensive effect of losartan comes from its metabolite, E-3174.

More than one hundred single-nucleotide polymorphisms have been identified for the CYP2C9 gene and CYP2C9 enzyme activity may change with these genetic polymorphisms[10,11]. The clinical reflection of alterations in enzyme activity is expected to be altered the corresponding drug responses[7,11]. As an example, the dose requirement of a given patient for warfarin is shown to be determined by the *CYP2C9* genotype of the patient[12]. Similar clinical results have also been demonstrated for phenytoin, which is another substrate[13].

To date, there are only a few clinical studies on *CYP2C9* gene polymorphisms and their association with the response to antihypertensive drugs, including irbesartan and losartan, which are other substrates of the same enzyme[14-16]. A priori knowledge based on published in vitro and pre-clinical in vivo studies has revealed the effects of *CYP2C9* polymorphisms on losartan oxidation, and the most studied two polymorphisms are *CYP2C9*2* and *CYP2C9*3*[9,17].

It is well known that these polymorphisms result in variant enzymes of CYP2C9, and particularly the variant allele CYP2C9*3 is found to be associated with decreased activity of losartan oxidation[18]. The clinical consequences of different *CYP2C9* genotypes, such as variability in blood pressure lowering response and/or the risk of cardiovascular end-points in patients taking losartan have not been fully clarified yet.

This study was designed to evaluate the possible effect of *CYP2C9* gene polymorphisms on the blood pressure lowering response to losartan in patients with newly-diagnosed essential hypertension. It was hypothesized that the blood pressure declines will be different in patients carrying the wild type genotype compared to patients carrying *CYP2C9* variant genes (**2* and/or **3*).

MATERIALS AND METHODS

This study was approved by the Research Ethics Committee of 'Hacettepe University School of Medicine' (Approval number: 08/06-3, Date: 06/06/2008) and it was conducted in accordance with the Declaration of Helsinki Guidelines. During the initiation and conduct of the study, all approvals requested by the ethics committee and written informed patient consent was obtained from all included participants.

Study design

Between July 01, 2008 and July 31, 2009, we prospectively reached patients with newly diagnosed hypertension among those admitted to the General Internal Medicine outpatient clinics of Hacettepe University Hospital, and prescribed losartan by attending physicians. After the initial evaluations and blood pressure measurements, the same research physician followed all patients who accepted to participate in the study for 6 weeks while on losartan treatment, with initial serum collection for further genotyping (Figure 1). Only those who attended a control visit at the sixth week of losartan therapy

were included for genetic testing and further analyses. Genetic tests were performed in collected sera at the laboratories of the Pharmacology Department and genotyping was performed at one session after completion of all patients, upon the control visit of the last participant.

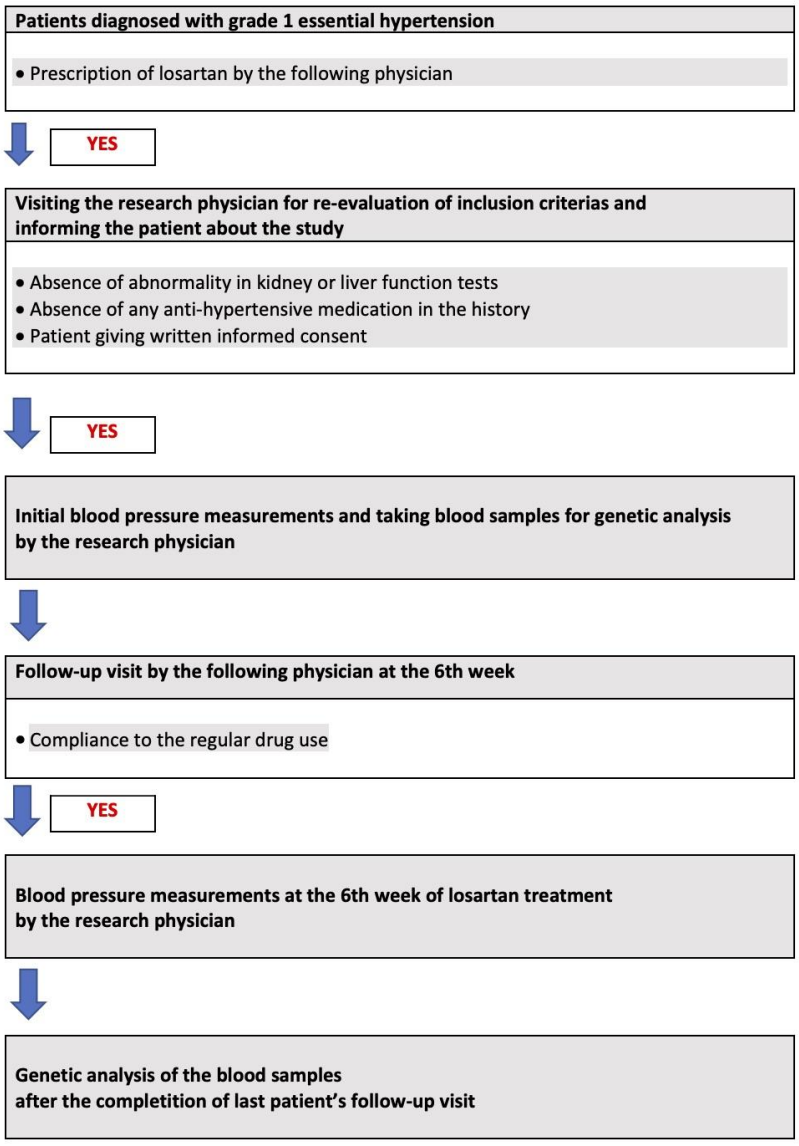

Figure 1. The schematic representation of study flow

Patients

Inclusion criteria were adult patients aged over 18-years, with newly diagnosed hypertension, prescribed losartan as the sole treatment by the attending physician; and given informed consent for the prospective follow-up and serum sample drawing for *CYP2C9* polymorphisms. The diagnosis and classification of hypertension were made according to the guidelines produced by the European Society of

Hypertension (ESH) and the European Society of Cardiology (ESC) (19). Only the patients with grade 1 hypertension, which means having a systolic blood pressure (SBP) of 140–159 mmHg and/or a diastolic blood pressure (DBP) of 90–99 mmHg were included. The exclusion criteria were as follows: taking any drugs with anti-hypertensive effect, BP higher than grade 1 (BP ≥ 160/100 mmHg); secondary hypertension by using physical examination and routine laboratory tests, with abnormal liver- (>2 times increase in transaminases) or kidney- (>1.5 times increase in creatinine value) function tests; current pregnancy; and history of any allergy to losartan or its active metabolite or other ingredients of drug tablets.

Measurements of blood pressure

Blood pressures were measured at the start of the protocol and at the sixth week by the same research physician using a mercury sphygmomanometer. During the measurement, subjects were in a seated position after a minimum of 10-minute resting. The final blood pressure value was determined by taking the average of two successive measurements, taken one minute apart. For patients with blood pressures above 140/90 mmHg, the measurements were repeated one week later, to confirm any elevation in blood pressure.

Data collection

Data were collected on any comorbidities, medication history, cigarette and alcohol use, grape-fruit drink (if any). All routine laboratory evaluations pertinent with a newly diagnosed hypertension case, ie. fasting blood sugar, serum lipid profile, liver and kidney function tests, albumin measurement in 24-hour urine, electrocardiography, echocardiography and ophthalmic examination for retinopathy were searched in the patient files for each patient. During the control visit at the sixth week, in addition to the blood pressure measurements, all patient files were re-searched again for renal function tests and Na excretion in 24-hour urine that were presumed to be done at the control.

All of the study measurements and data gathering were done by the same researching physician. The main source for study data was the patient files which were routinely used in our university hospital. These hard-copy files were routinely used for patient follow-up and are securely saved in the hospital archives.

Pharmacogenetic analysis

Blood samples from patients taken into tubes with ethylene diamine tetraaceticacid (EDTA) were preserved at -20°C until DNA isolation. Genomic DNA was extracted from peripheral blood leukocytes using the QIAamp DNA Blood Kit (Qiagen, Hilden, Germany). Genotyping of *CYP2C9 *2* and **3* variants were done by using polymerase chain reaction (PCR) based endonuclease digestion, as described previously [17]. The forward and reverse primers were 5-ACA AAT ACA ATG AAA ATA TCA TG-3 and 5-CTA ACA ACC AGA CTC ATA ATG-3 for *CYP2C9*2* and 5-TGC ACG AGG TCC AGA GAT GC-3 and 5-GAT ACT ATG AAT TTG GGA CTT C-3 for *CYP2C9*3* determination. PCR was performed in a 25 μL mixture containing 0.5 unit Taq polymerase enzyme, 200 ng purified DNA, 250 μM of each deoxynucleotide, 1.25 μM of each primer and 2 mM $MgSO_4$. Amplification was conducted by using a 'PTC-200 thermal cycler' (MJ Research Inc., Waltham, MA, USA) and the PCR conditions were as follows: initial denaturation at 94 °C for 5 min., followed by 35 cycles of 60 sec. at 94 °C, 90 sec. at 60 °C, 30 sec. at 72 °C, and a final extension at 72 °C for 7 min. The PCR products were allowed overnight incubation at 37 °C with endonucleases to be digested and restriction fragments were separated by agarose gel (%3) electrophoresis. AvaII and NsiI endonucleases (New England Biolabs, GmbH, Frankfurt, Germany) were used as restriction enzymes for *CYP2C9 *2* and **3*, respectively. The primers used for genotyping, restriction enzymes and the cleavage products generated after PCR-restriction fragment length polymorphism (RFLP) procedure are shown in Table 1.

Statistical analysis

Blood pressure values were expressed as median and interquartile differences (IQR 25–75). The amount of decline in blood pressure was calculated for each patient to be used in comparative analyses and expressed as a percentage. The absolute reduction percentage was calculated as the blood pressure reduction (mmHg) from the baseline to the sixth week of treatment and was further divided by the initial blood pressure value preceding the initiation of losartan treatment. The percentages of decline in systolic and diastolic blood pressures between groups were compared by Mann-Withney U test.

Table 1. Primers and restriction enzymes used for genotyping *CYP2C9 *2* and **3* variants (17)

Variant	Primer	Enzyme	PCR product	Cleavage products
*CYP2C9 *2*	5-ACA AAT ACA ATG AAA ATA TCA TG-3	AvaII	691 bp	527 bp + 164 bp
	5-CTA ACA ACC AGA CTC ATA ATG-3			
*CYP2C9 *3*	5-TGC ACG AGG TCC AGA GAT GC-3	NsiI	131 bp	110 bp + 21 bp
	5-GAT ACT ATG AAT TTG GGA CTT C-3			

PCR: polymerase chain reaction

Table 2. Distribution of baseline biochemical measures of study participants (n=74)

Parameter	Value*
Creatinine (mg/dL)	0.53 ± 0.15
Creatine clearance (ml/min)	113 ± 23
Fasting blood sugar (mg/dL)	94 ± 18
Triglyseride (mg/dL)	145 ± 79
LDL (mg/dL)	118 ± 29

*****Values are reported as mean ± standard deviation.
LDL: low-density lipoprotein; HDL: high-density lipoprotein

Non-parametric tests were used for statistical analyses because the participant number was low after allocation to groups regarding variant genotypes; the decline in blood pressure values was expressed, as percentages did not fit a normal distribution. Calculations for 95% confidence interval of allele and genotype frequencies were performed using the following formulation: Allele frequency ± 1.96x√fx (1-f)/(allele or individual number). The distribution of genotype frequencies was evaluated for fitness to Hardy-Weinberg equation.

RESULTS

Initially, 101 patients agreed to participate in the study. Of these, 37 were excluded from analyses due to poor compliance with regular medication use and/or lack of attendance to the sixth week control visit. Final analysis was completed for 74 patients; of whom 54 (73%) were females and 20 (27%) were males. The mean age of the study population was 48.3 ± 7.4 years. The mean body mass index of patients was calculated as 29.4 ± 3.9 kg/m^2. The baseline biochemical parameters are summarized in Table 2. Before initiating losartan, median systolic and diastolic blood pressures were 150 (150–159) mmHg and 99 (90–99) mmHg, respectively. The important comorbidities accompanying hypertension were diabetes mellitus type 2 in four patients and impaired fasting glucose in the other three patients. Twenty-four hour urine samples were examined for 55 patients and microalbuminuria was detected in five of them. Among the 70 patients evaluated by echocardiography, left ventricular hypertrophy and diastolic dysfunction were demonstrated in two and six patients, respectively. Out of 70 patients who underwent an ophthalmic examination, 17 had stage 1 hypertensive retinopathy at baseline, whereas there were no other pathological findings in the remaining 53 patients.

Apart from wild type *CYP2C9 *1*1* (n=43, 58%), the most frequent polymorphisms were *CYP2C9 *1*2* (n=16, 22%) and *CYP2C9 *1*3* (n=12, %16). No patients with *CYP2C9 *2*2* were detected, while the study population contained limited subjects with *CYP2C9 *3*3* (n=1, 1%) and *CYP2C9 *2*3* (n=2, 3%). The fitness of genotype frequencies to Hardy-Weinberg equation was checked; and the proposed frequencies for *CYP2C9 *1*2* and *CYP2C9 *1*3* were 21% and 18%, respectively. These values were both within the limits of 95% confidence interval computed in our study. The allele and genotype frequencies of *CYP2C9* found in the study population are listed in Table 3 and the appearance of different genotypes on agarose gel after electrophoresis is shown in Figure 2, below.

Table 3. Distribution of allele and genotype frequencies of *CYP2C9* among study participants

		Frequency, n (%)	95% CI
Allele (n=148)	*CYP2C9 *1*	114 (77)	70-84
	*CYP2C9 *2*	18 (12)	7-17
	*CYP2C9 *3*	16 (11)	5-15
Genotype (n=74)	*CYP2C9 *1*1*	43 (58)	50-66
	*CYP2C9 *1*2*	16 (22)	15-28
	*CYP2C9 *2*2*	0 (0)	
	*CYP2C9 *1*3*	12 (16)	10-22
	*CYP2C9 *3*3*	1 (1)	0-3
	*CYP2C9 *2*3*	2 (3)	0-5

CI: confidence interval

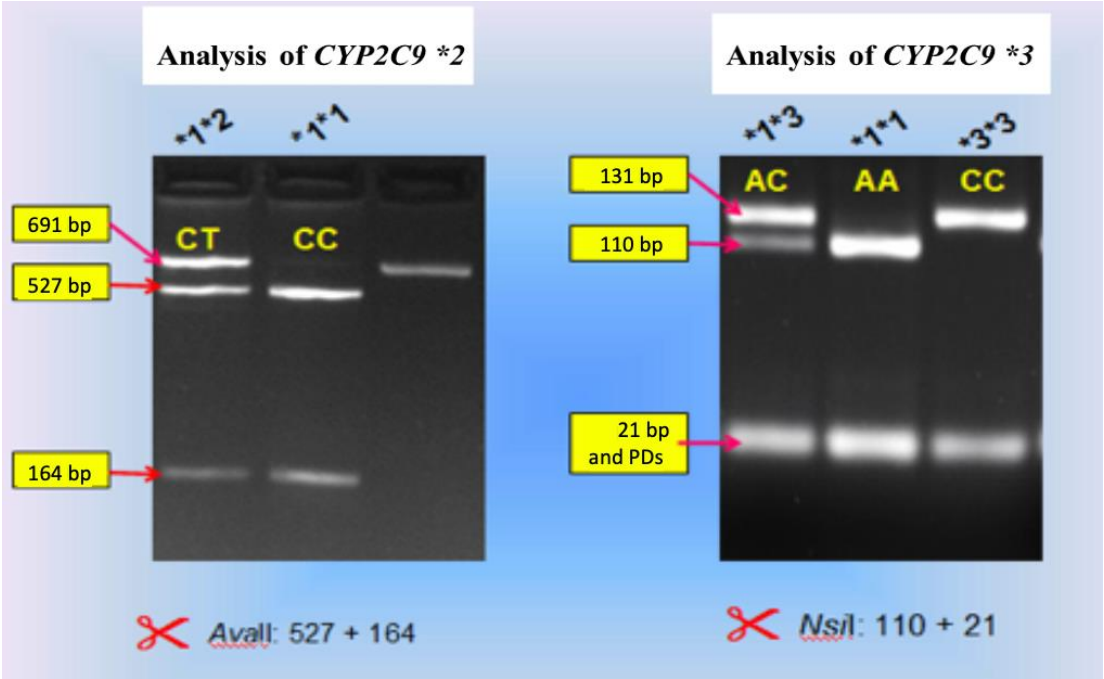

Figure 2. The view of products of PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) procedure on agarose gel (%3), after 3 hours of electrophoresis. CYP2C9*2 and CYP2C9*3 allele primers cleaved with restriction enzymes AvaII and NsiI, respectively.

Six weeks after losartan treatment, the median systolic and diastolic blood pressures were 130 (120–150) mmHg and 82 (80–90) mmHg, respectively. The median rates of decline were 13% (0–19) for SBP and 10% (0–20) for DBP. Comparisons were made across the wild type (*CYP2C9*1*1*) and other variant genotypes. When all patients with variant genotypes (*CYP2C9*1*2, *1*3, *3*3 and *2*3*) were evaluated together as a single group, the result was statistically non-significant, but there was a trend toward a significant decline in SBP, favoring the wild type (p=0.07). Considering 24-hour urine Na excretion as a marker for salt intake, there was no statistically significant difference between the two groups (p=0.70).

Comparisons of wild type with each variant genotype one-by-one was also performed for *CYP2C9*1*2* and *CYP2C9*1*3*. The decline in SBP was higher, but statistically not significant in the wild subjects compared to subjects with *CYP2C9*1*2* (p=0.06).

Analyses did not reveal any significant difference with regard to a change in DBP. The median amount of sodium excretion in 24-hour urine was also similar between the groups. However, analysis comparing the wild type genotype and *CYP2C9*1*3* genotype did not reveal any significant differences between the two groups, neither for systolic nor for diastolic blood pressures (Table 4).

Table 4. Decline in blood pressure levels in response to losartan by different *CYP2C9* genotypes

Genotype	***CYP2C9 *1*1*** **(n=43)**	***CYP2C9 *1*2*** **(n=16)**	***CYP2C9 *1*3*** **(n=12)**
SBP decline (%) , median (IQR)	13 (7-19)	7 (0-13)	16 (0-20)
† p value		**0.06**	**0.67**
DBP decline (%), median (IQR)	11 (0-20)	10 (0-20)	11 (0-19)
† p value		**0.26**	**0.96**

† p values were obtained by comparing the given genotype with the wild type (*1*1);
SBP: systolic blood pressure; DBP: diastolic blood pressure; IQR: interquartile range

DISCUSSION

Genetic polymorphisms often play a role in the pharmacokinetic and pharmacodynamic responses to drugs[11,17]. In case of losartan treatment among hypertensives, the predicted effect of the *CYP2C9* gene related **2* and **3* polymorphisms is evident at the pharmacokinetic level, as the enzyme is responsible for losartan metabolism, by converting it to a more potent active metabolite called E3174[18]. There are several preclinical studies reporting decreased levels of E3174 in polymorphic individuals[9,17]. However, data about the clinical outcomes of these polymorphisms in hypertensive patients treated with losartan are scarce, and our study is unique in evaluating clinical endpoints at the sixth week of treatment in a real patient setting.

The results of our analysis support the hypothesis suggesting a variation in blood pressure lowering response to losartan in polymorphic individuals. We found that the change in SBP was less in patients carrying the *CYP2C9*1*2* variant genotype compared with the *CYP2C9*1*1* wild type genotype. While this change was statistically non-significant, there was a trend for a higher SBP change in the wild-type genotype group and this was close to statistical significance at alfa=0.05 (p=0.06). However, analysis failed to find a difference in clinical blood pressure reductions across the groups with *CYP2C9*1*3* variant genotype and *CYP2C9*1*1* wild type genotype both for SBP or DBP changes.

Another similar research is published by Hallberg et al. (2002)[14]. In this study, results from 49 patients treated with irbesartan (another angiotensin II receptor blocker metabolized by CYP2C9 enzyme) were reported. Although, the metabolism of irbesartan is different from that of losartan (i.e., via the conversion of the drug to its inactive metabolite), Hallberg et al. studied the same variant genotypes of *CYP2C9* (**2 and/or *3 alleles*) and concluded that *CYP2C9* genotype predicts the blood pressure response to irbesartan in patients with essential hypertension. The authors could not analyze results about *CYP2C9*3* allele, because of an inadequate number of patients. Our results are in parallel with those of Hallberg et al., but provide better evidence for individuals having *the CYP2C9*3* variant allele, because of our larger sample size.

In a recent study by Joy et al. (2009), losartan was the drug of choice in patients with chronic renal failure [20]. It was shown that the response to losartan considering anti-proteinuric and anti-hypertensive effects was diminished in genetically polymorphic individuals. In that study, the blood pressure was decreased in patients with wild type genotype while it was increased in patients carrying *CYP2C9*2* and/or *CYP2C9*3* variant alleles. The number of cases included in this study was relatively small (n=59) [20].

The clinical effects of CYP2C9 variant alleles were also studied by Lajer et al. (2007) in a group of patients with type 1 diabetes and nephropathy. In this research, the blood pressure lowering response to losartan was reported to be modulated by *CYP2C9*3* polymorphism, however the total number of cases included here was again relatively small (n=60) [15].

In another publication by Yin et al. (2008), the impact of genetic variations of *CYP2C9* on the anti-hypertensive effect of losartan was reported in 39 hypertensive Japanese patients. In this study, no difference was observed between *CYP2C9*1*3*

variant genotype and *CYP2C9*1*1* wild type genotype, which was similar to our findings[16].

Allelic frequencies observed in our study were 0.12 and 0.10 for *CYP2C9*2* and *CYP2C9*3* respectively, and they were within the range previously defined for other Caucasian populations. The *CYP2C9*2* and *CYP2C9*3* alleles were reported to be the most common variants in various Caucasian populations with allelic frequencies ranging between 0.08–0.14 and 0.04–0.16, respectively[21,22]. Our findings were also in line with those reported in other Turkish samples[17,23].

As mentioned before, in our study *CYP2C9*2* variant allele was found to cause an apparent difference in the clinical response to losartan, whereas the difference was not significant for *CYP2C9*3*. This was in contrast to the previous preclinical studies with losartan in which the effect of the *CYP2C9*3* variant allele was found to be stronger than that of the *CYP2C9*2* allele[9,17]. This discrepancy may be linked to a single dose of losartan use in those studies. The effects which cannot be shown by a single dose drug can become clear when the drug is used for a longer period. Indeed, this issue was previously described for warfarin, which is another substrate of *CYP2C9*[24].

Our study is unique in the literature, since we focused on the patients 'prescribed losartan for essential hypertension'. As given in detail above, most of the previously published studies on losartan mainly included patients with renal problems[15,20] or they focused on different drugs other than losartan in patients with essential hypertension[14]. Additionally, comparing with other clinical studies reported up to now, our work included a relatively larger sample size. However, sample size is still the main limitation of our study, since the number of cases allocated to each different genotype group is low and this could, at least partially, explain the decreased statistical significance for clinically significant results. However, 73% of our study population was male, whereas only % 27 was female and we could not conduct sub-group analysis separately for different genders, since the number of cases allocated to each group would be low. Therefore, questioning the possible effect of gender on the results remains unanswered.

In conclusion, *CYP2C9*1*2* genotype seems to have the potential to predict the systolic blood pressure response to losartan, in humans with mild essential hypertension. However, there is a need for larger studies in heterogeneous populations to confirm our results. *CYP2C9* gene has many identified variants and we studied two of them, namely, the **2* and **3* alleles. We hope to motivate future research on this issue; as the evidence gets stronger, the more individualized treatments for hypertension could be possible. *CYP2C9* appears to be a good candidate to be included in genetic analysis for personalized medicine in hypertensive patients.

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