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Role of ABCC2 Gene Polymorphism on Deferasirox Hepatic Toxicity in Thalassemia Patients

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Abstract
Objectives: To investigate the relationship between ABCC2 gene polymorphism (G>A, rs 8187710) and (C>T, rs 717620) and hepatotoxicity in thalassemia patient treated deferasirox.
Methods: The present work included a cross sectional study, 100 patients suffering iron overload and thalassemia out of 650 patients in (thalassemia center) and 100 healthy patients to compare the parameters of liver function tests of thalassemia patients with healthy group. The allele specific polymerase chain reaction technique (pcr) was used to detect the (G>A, rs 8187710) and (C>T, rs 717620 single nucleotide polymorphism (SNP).
Results: 58 Patients with rs 8187710 who are wild (GG) and 32 patients hetero (GA) and 56 patients with rs 717620 who wild (CC) and 31 hetero (CT) are exposed to hepatotoxicity than patients with homo groups.
Conclusion: According to the results of the currents study, the (G>A, rs 8187710) and (C>T, rs 717620) single nucleotide polymorphism (SNP) was associated with hepatotoxicity in patients treated deferasirox.
Keywords: Thalassemia, ABCC2 gene polymorphism, deferasorox, hepatotoxicity.

Introduction

A homozygous mutation in the gene of beta-globin causes thalassemia major, which leads in a complete absence of beta chains. The frequency of thalassemia has historically been high in the Middle East, in part because of the elevated carrier rate and a proclivity for marriages between relatives in the region.[1] One of the most important complications of thalassemia is tissue iron overload.Without chelating medication, iron overload eventually results in failure of the heart, liver, and endocrine systems.[2] Lifelong treatment is necessary for patients with severe beta-thalassemia in order to avoid and manage the clinical side effects of the condition.[3] Blood transfusion, iron chelation, and splenectomy are the current therapy options for transfusion dependent thalassemia TDT and for a specific group of patients, hematopoietic stem cell transplantation (HSCT).[3] In order to cure iron excess, various iron chelators can be used. Important iron chelators include deferiprone (DFP), deferasirox (DFX), and deferroxamine (DFO), each of which has benefits and drawbacks.[4] Cytosolic labile iron is chelated by deferasirox. Deferasirox can increase the levels of hepcidin that results in the degradation of ferroportin. TFR, transferrin receptor.[5] The European Medicines Agency (EMA) and the FDA both approved the medication as a first-line treatment for iron excess brought on by blood transfusions in 2005 and 2006, respectively. According to the EMA, treatment should only begin if there is evidence of chronic iron overload, which can occur after a packed red blood cell transfusion of 100 ml/kg (for example, 20 units for a person weighing 40 kg) or when serum ferritin levels are >1,000 g/l.[5] Deferasirox is metabolized primarily by the enzyme uridine diphosphate glucuronosyltransferase (UGT). Only 8% of DFX and its metabolites are excreted in the urine, while MRP2, also referred to as ABCC2, and breast cancer resistance protein clear 84% of DFX and its metabolites through the bile.[6] For ABCC2, a number of SNPs have also been reported, some of which influence transporter expression and/or function. Due to their high allele frequency in humans, two of these SNPs, –24C>T (rs717620) and 4544G>A (rs8187710), which are situated in the 5'-UTR and exon 32, respectively, have undergone substantial research.[7] MRP2 appears to have a role in the Deferasirox anion's elimination from the liver into the bile. Due to this, people who have genetic variation in the ABCC2 gene may be more likely to have hepatotoxicity. MRP2 may reduce the DFR of biliary elimination due to ABCC2 polymorphisms.

Patients and Methods

The present work included a cross sectional study, 100 patients suffering iron overload and thalassemia out of 650 patients in (thalassemia center) and 100 healthy patients to compare the parameters of liver function tests of thalassemia patients with healthy group. Thalassemia patients taken deferasirox as monotherapy at least three months, medical history, physical examinations, and complete investigations were recorded on a standardized pro form by respective ward physicians' patients during their visiting to Kerbala teaching hospital of children (thalassemia center). This study performed from October 2022 to January 2023. All patients were diagnosed by consultant pediatrician. The patients age range were from 14 to 57 year. Available clinical data were gender, age, weight and height, ferritin, ALP, TBIL, ALT, AST.

Exclusion Criteria

- Patient with liver disease.

Blood Sampling

A disposable syringe was used to draw five milliliters of blood from each individual, which was then separated into two sections as follows: After allowing the first portion (3 ml) to clot at room temperature for approximately 30 minutes, samples were placed in a centrifuge at a speed of 4000 x g to

get serum that was used to measure the levels of biomarkers. The remaining of blood was saved in EDTA tube and stored freezing at –40°C until using for DNA extraction and molecular analysis.

The Dose of Deferasirox Depends on the Level of Serum Ferritin

- If S. Ferritin = 3000 Dose = 40mg
- If S. Ferritin = 1500 – 3000 Dose = 30mg
- If S. Ferritin = 500 – 1500 Dose = 20mg

If S. Ferritin less than 500 The drug will be stopped for three month and we repeat the liver function tests and S.Ferritin.[8]

Genetic Analysis

DNA was extracted from blood using DNA isolation kit (AddPrep Genomic DNA Extraction Kit). Genotyping was carried out by allele-specific PCR for two types of SNPs (rs717620 CT Rs8187710 GA) Gene ABCC2. Primers and a green master mix kit (Promega/USA) were used, PCR products were separated on a 1.5% agarose gel.

The ABCC2 gene rs 8187710 and rs 717620 were amplified using Polymerase Chain Reaction (PCR) using specified primers. The study's primers were created by current study (Table 1).

Statistical Analysis

All participants' questionnaire responses were put on a data sheet and given a serial identity number. Errors were prevented by using multiple entries. The Statistical Package for the Social Sciences, version 28.0 (IBM, SPSS, Chicago, Illinois, USA), as well as the Real Statistics Resource Pack for Mac (Release 7.2) of the resource pack for Excel 2016, were used to create the data analysis for this project. 2013 through 2020 for copyright (1).

Results

Hardy–Weinberg Equilibrium for G>A, rs 8187710) in Patients

The result of comparison between observed and anticipated value for ABCC2 (G>A, rs 8187710) tested population were shown in (Table 2). illustrated the distribution and percentage of individuals having rs 8187710 differ from those expected under Hardy–Weinberg equilibrium {number of observed vs expected were: GG (58, 54.76); AA (10, 6.67); GA (32, 38.48) (goodness-of-fit $\chi 2$ for rs 8187710; 2.836, $P<0.0922$ (NS)} and therefore it was statistically non significant.

Hardy–Weinberg Equilibrium for (C>T, rs 717620) in Patients

The result of comparison between observed and anticipated values for ABCC2 (C>T, rs 717620) the tested population were shown in (Table 3) demonstrated the distribution and percentage of individuals having rs 717620 differ from those expected under Hardy–Weinberg equilibrium {number of observed vs expected were: CC (56, 51.12); TT (13, 8.12); CT (31, 40.75) (goodness-of-fit $\chi 2$ for rs 717620 = 6.551, $P < 0.0167$ (S)} and therefore it was statistically significant.

Effect of Deferasirox Treatment on Laboratory Biomarkers in Thalassemia Patients Having ABCC2 (G>A, rs 8187710) genotype

Table 4 show the mean levels of biomarkers AST, ALT, ALP, and TBIL based on the genotypes of rs 8187710 SNP groups. Data were analyzed by combining the control, wild, heterozygous and homozygous variant groups. Results were indicted that there was highly significant difference found between the measured biomarkers and ABCC2 (G>A, rs 8187710) genotype, ($P = <0.001$).

Table 1. **Specific primers of ABCC2 gene (rs 717620) and (rs 8187710)**

Rs 717620	**C>T polymorphism**		
Reverse 1	5-ATTCCTGGACTGCGTCTGGAACG-3	C allele T allele	385 bp
reverse 2	5-ATTCCTGGACTGCGTCTGGAACA-3		
Forward	5-CCCTCTACTGATGCTGCCCTTTGTG -3		
rs 8187710	**G>A polymorphism**		
Forward 1	5-CCTAGACAACGGGAAGATTATAGAGTG-3	G allele An allele	550 bp
Forward 2	5-CCTAGACAACGGGAAGATTATAGAGTA-3		
reverse	5-GCATCACCATGGATGAATCTCAGATA-3		

Table 2. **Hardy–Weinberg equilibrium for G>A, rs 8187710) in patients**

Variable			**Frequency**	**Percent**	**Alleles**		**Hardy–Weinberg equilibrium X^2 test**
rs 8187710	GG wild	Observed expected	58 54.76	58 (%) 54.76 (%)	G	A	$P < 0.0922$ (NS)
	GA hetero	Observed expected	32 38.48	32 (%) 38.48 (%)	148 (74%)	52 (26%)	
	AA homo	Observed expected	10 6.67	10 (%) 6.67 (%)			

Table 3. **Hardy–Weinberg equilibrium for (C>T, rs 717620) in patients**

Variable			Frequency	Percent	Alleles		Hardy–Weinberg equilibrium X^2 test
rs 717620	CC wild	Observed expected	56 51.12	56 (%) 51.12 (%)	C	T	$P < 0.0167$ (S)
	CT hetero	Observed expected	31 40.75	31 (%) 40.75 (%)	143 (71.5 %)	57 (28.56%)	
	TT homo	Observed expected	13 8.12	13(%) 8.12 (%)			

Table 4. **Diference between alleles of (G> A, rs 8187710) genotype genotype with mean levels of biomarkers in thalassemia patients**

Parameters	rs 8187710				Pairwise comparison	*P* value
	Control Mean ± SD	GG Mean ± SD	GA Mean ± SD	AA Mean ± SD		
BMI	25.39 ± 3.71	19.89 ± 2.59	19.65 ± 2.88	20.71 ± 1.83	Control > GG, GA, AA	0.001
ALT	25.85 ± 8.54	40.97 ± 37.35	30.46 ± 22.38	20.47 ± 12.02	GG > control GG > AA	0.021 0.011
AST	23.05 ± 35.41	43.11 ± 35.41	31.91 ± 19.32	22.88 ± 14.11	GG > control GG > AA	0.001 0.021
ALP	80.95 ± 21.57	181.04 ± 99.42	197.21 ± 122.45	143.64 ± 64.14	GG, GA > control	0.001
TBIL	0.33 ± 0.20	2.42 ± 1.65	2.41 ± 1.05	2.00 ± 0.71	GG, GA, AA > control	0.001

One way ANOVA test was used with a significant *P* value of less than 0.05. Results are presented as mean ± SD.

Effect of Deferasirox Treatment on Laboratory Biomarkers in Thalassemia Patients Having ABCC2 (C>T, rs717620) Genotype

Table 5 show the mean levels of biomarkers AST, ALT, ALP, and TBIL based on the genotypes of rs717620SNP groups. Data were analyzed by combining the control, wild, heterozygous and homozygous variant groups. Results were indicted that there was highly significant difference found between the measured biomarkers and ABCC2 (C>T, rs717620) genotype, ($P = <0.001$).

In order to find out the relationship between parameters under the study and genetic variations of rs8187710 and rs717620, a multiple linear regression model was used in which rs8187710 and rs717620 were considered as explanatory variables and the parameters under the study as dependent variables. Pearson correlation brief the relationship between the genetic variation and the parameters. for ALT, Pearson correlation of rs8187710 is –0.218 means the correlation is inversely between ALT and rs8187710 (as the genetic variation decrease (GG), the ALT level will increase). *P* value is 0.015 significant while Pearson correlation rs717620 is –0.045 weak correlation. *P* value is 0.328 nonsignificant. R squared means the effect of both rs8187710 and rs717620 on the parameters. R squared for ALT is 0.049 is weak for AST, Pearson correlation of rs8187710 is –0.235 means the correlation is inversely between AST and rs8187710 (as the genetic variation decrease (GG), the AST level will increase). *P* value is 0.009 significant while Pearson correlation rs717620 is 0.120 means the correlation is directly proportional between AST and rs717620 (as the genetic variation increase, the AST level will increase). *P* value is 0.117 nonsignificant. R squared for AST is 0.72. F significance is 0.026 significant. for ALP, Pearson correlation of rs8187710 is –.044 means the correlation is inversely between ALP and rs8187710 (as the genetic variation decrease (GG), the ALP level will increase). *P* value is 0.333 nonsignificant while Pearson correlation rs717620 is –0.039 weak correlation. *P* value is 0.351 nonsignificant. R squared for ALP is 0.003 is very weak. For TBIL, Pearson correlation of rs8187710 is –0.067 means the correlation is inversely between TBIL and rs8187710 (as the genetic variation decrease (GG), the TBIL level will increase). *P* value is 0.255 nonsignificant while Pearson correlation rs717620 is 0.150 means the correlation is directly proportional between TBIL and rs717620 (as the genetic variation increase, the ALP level will increase). R squared for TBIL is 0.028 is weak.

Discussion

The present study, is the first study which focused on the genetic polymorphism of ABCC2 gene in Iraqi patients with thalassemia which treated with Deferasirox. The genetic polymorphisms related to the Abcc2 gene, which encodes the MRP2 protein, may influence individual susceptibility to hepatotoxicity related to Deferasirox. The previous studies shows the effect of genetic polymorphism in ABCC2 gene, which encodes MRP2protein on patients treated with Deferasirox including: According to a Korean study involving 98 patients with hematologic disorders, those who carried two MRP2 haplotypes with the mutations 21774 del and/or 224T were susceptible to hepatotoxicity more than those who carried (the wild-type allele).[9] Deferasirox (DFX) was administered to 15 sickle cell disease and hemochromatosis patients in a Brazilian study, and it was shown that four of

Table 5. **Diference between alleles of (C>T, rs717620) genotype with mean levels of biomarkers in thalassemia patients**

Parameters	C>T, rs717620				Pairwise comparison	*P* value
	control Mean ± SD	CC Mean ± SD	CT Mean ± SD	TT Mean ± SD		
BMI	25.39 ± 3.71	19.95 ± 2.81	20.23 ± 2.03	18.84 ± 2.92	Control > CC, CT, TT	0.001
ALT	25.85 ± 8.54	38.12 ± 34.56	29.59 ± 24.56	38.74 ± 36.22	-----	0.065
AST	23.05 ± 7.44	33.81 ± 23.97	42.61 ± 38.27	41.24 ± 32.28	CC> control CT> control	0.010 0.047
ALP	80.95 ± 21.57	187.0 ± 96.50	175.1 ± 125.70	180.1 ± 90.53	CC, CT > control TT> control	0.001 0.011
TBIL	0.33 ± 0.20	2.19 ± 1.28	2.55 ± 1.58	2.74 ± 1.51	CC, CT, TT > control	0.001

One way ANOVA test was used with a significant *P* value of less than 0.05. Results are presented as mean ± SD.

Table 6. **Multiple linear regression for the effect of genetic polymorphism of rs8187710 and rs717620 on the parameters under study**

Dependent variable	Pearson correlation rs8187710	*P* value	Pearson correlation rs717620	*P* value	R squared	F value	F significance	Beta value
ALT	–0.218	0.015	–0.045	0.328	0.049	2.482	0.089	rs8187710 (–0.216) rs717620 (–0.034)
AST	–0.235	0.009	0.120	0.117	0.72	3.786	0.026	rs8187710 (–0.241) rs717620 (0.132)
ALP	–.044	0.333	–0.039	0.351	0.003	0.158	0.854	rs8187710 (–0.042) rs717620 (–0.037)
TBIL	–0.067	0.255	0.150	0.068	0.028	1.395	0.253	rs8187710 (–0.074) rs717620 (0.154)

these individuals experienced hepatotoxicity: Three people suffered hepatotoxicity but had no polymorphism in any of their alleles, while one had the rs717620 (–24C>T) polymorphism in heterozygosity. The homozygous-17774 delG polymorphism was present in just one of the four patients with hepatotoxicity, and three of these patients still experienced hepatotoxicity despite not possessing the polymorphism.[10] In a different study, 38 healthy Chinese volunteers received a single dose of 20 mg/kg. For the ABCC2 c.–24 C>T rs717620; (25) wild, (12) hetero, and (1) variant in this investigation. ABCC2 c.–24 C>T (rs717620) was strongly connected with the pharmacokinetics of Deferasirox in the human body and was linked to the Deferasirox pharmacokinetic variations in Chinese subjects. People with the c.–24 T allele had a 65% greater clearance than people without it.[11] Another study examined a 3-year-old girl who had major thalassemia in Italy. Deferasirox (DFR), an oral iron chelator, was used to treat her. The girl was admitted to the hospital with abnormal liver and kidney function tests. Genetic testing reveals the functional role of the MRP2 ABCC2 c.–24C>T rs717620 mutation, decreased activity with rs8187710 c.4544G>A ATPase activity is compromised. Deferasirox is eliminated from the body through the action of the proteins multidrug resistance protein 2 (MRP2) and breast cancer resistance protein (BCRP).[6] Since MRP2 carries the drug, decreased transporter activity causes drug buildup and toxicity inside the cells.[12] In contrast, to the present study. The genotype testing determined the frequencies and percentages of ABCC2 gene polymorphisms within thalassemia patients of this study as existing in Tables 2 and 3. In the present study, for ABCC2 (G>A, rs 8187710), the percentage of wild genotype (GG) in 100 thalassemia patients was 58%, the heterozygous type (GA) presented with percentage of 32%, and finally the homozygous type (AA) appeared with percentage of 10%. And forABCC2 (C>T, rs 717620), the percentage of wild genotype (CC) in 100 thalassemia patients was 56%, the heterozygous type (CT) presented with percentage of 31%, and finally the homozygous type (TT) appeared with percentage of 13%. Table 4 show the mean levels of biomarkers AST, ALT, ALP, BTIL, s. based on the genotypes of rs 8187710 SNP groups. Results were indicted that there was highly significant difference found between the measured biomarkers and ABCC2 (G> A, rs 8187710) genotype, (*P* = <0.001). The observed results for rs 8187710 and liver biomarker levels showed that the patients who were carrying the (GG) genotype have more effect on ALTand AST. ALP levels are high in the patients who were carrying the (GG) and (GA) genotypes. TBIL levels were affected in patients with (GG), (GA) and (AA) genotypes. Table 5 show the mean levels of biomarkers AST, ALT, ALP, BTIL, s. based on the genotypes of rs 717620 SNP groups. Results were indicted that there was highly significant difference found between the measured biomarkers and ABCC2 (C>T, rs717620) genotype, (*P* = <0.001) the patients who were carrying the (CC) and (CT) genotypes have more effect on AST than those with (TT) genotype, ALP and TBIL levels were affected in patients with (CC), (CT) and (TT) genotypes. ALT not be affected by genetic variation in this snp. Table 6 brief the effect of both ABCC2 (G>A, rs 8187710) and (C>T, rs717620) genotypes on the parameters. ALT, from Pearson correlation and R squared we observed (as the genetic variation decrease, the ALT level

will increase). For AST, ABCC2 (G>A, rs 8187710) affect inversely and (C>T, rs717620) genotype affect proportionally (as the genetic variation increase, the AST level will increase). Both ABCC2 (G>A, rs 8187710) and (C>T, rs717620) genotypes have little effect on ALP and TBIL levels. The parameters are high in the patients who were carrying wild (GG) and (CC) this means those patients at risk of hepatotoxicity. The explanation of this results that shows all biomarkers are highly statically significant difference among different groups, which means that the genetic polymorphism can affect on the hepatotoxicity. The genetic polymorphism in ABCC2 gene that encodes MRP transporters that by which Deferasirox is eliminated, the polymorphism in this gene decreases MRP activity as a result Deferasirox will be accumulated in organ. One of the main causes of organ dysfunction in people is medication toxicity.[13] The heart, kidney, and liver are examples of aerobic organs where mitochondria are commonly targets of damage.[14] Medicines may influence mitochondria in a variety of ways, although it is frequently assumed that toxicity occurs from oxidative stress and/or the reduction of respiratory chain (RC) activity. While the liver, which has a very high number of mitochondria and depends on aerobic metabolism to make ATP, can be impacted by toxicity.[15,16] Iron is necessary for several aspects of mitochondrial function, including the citric acid cycle, RC, and antioxidant defenses. Iron-sulfur clusters are one such co-factor.[17] Thus, the observed toxicity may be explained by the possibility that DFX's results in depletion of mitochondrial iron which causes unfavorable alterations in RC activity or redox status.[15] Additionally, iron chelators can have positive effects in mitochondria, such as preventing cell death brought on by ferroptosis.[18] As a result, it is currently unknown why DFX by itself could be toxic for organs like the liver. that DFX partially decouples the respiratory chain and marginally modifies the inner mitochondrial membrane's (IMM) permeability, without depolarizing the cell. Due to its high lipophilicity, DFX likely inserts partially into the inner mitochondrial membrane's hydrophobic region, although this does not significantly alter the membrane's permeability to small molecules. Deferasirox includes polar groups (OH, COOH), and because it is negatively charged at physiological pH, it may enhance enrichment of nearby water, protons, and H_3O^+, specifically enhancing the passage of protons and water across the inner mitochondrial membrane. Water flow across the IMM is essential for the control of mitochondrial shape in living cells and the development of pathological swelling. Because of oxidative stress, chronic iron overload is known to induce the liver to proliferate,[19] and since patients receiving chelation therapy may be at risk for hepatotoxicity as a result of iron overload.[20] In a prior study, There was no correlation between the ferritin level and the onset of hepatotoxicity, despite it being used as an independent variable to predict the risk of hepatotoxicity. Additionally, all individuals who experienced hepatotoxicity demonstrated lower AST/ALT and bilirubin levels after stopping Deferasirox. These results suggested that the administration of Deferasirox was primarily responsible for the hepatotoxicity seen in our study.

Conclusions

Depending on the results that obtained, the followings may be concluded:

- ABCC2 gene was highly polymorphic and detected with different genotypes and variable frequencies in Iraqi thalassemia patients.
- The genetic polymorphism can affect on the hepatotoxicity.
- The genetic polymorphism in ABCC2 gene that encodes MRP transporters that by which Deferasirox is eliminated, the polymorphism in this gene decreases MRP activity as a result Deferasirox will be accumulated in organ and causes toxicity.

Recommendations

- Study a large number of SNPs for ABCC2 gene along with a large number of thalassemia patients.
- Study the genetic variations in enzymes that involved in metabolism of Deferasirox might contribute to individual variations in drug response.
- Research the genetic effects of other genes that may impact on the renal toxicity.
- Prevention of thalassemia by prenuptial screening through a medical examination and by avoiding the marriage of people in same family who carrying genetic diseases.

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Conflicts of Interest

The authors declare no conflict of interest.

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