UGT1A9 Gene Polymorphism in Egyptian Systemic Lupus Patients Receiving Mycophenolate Mofetil

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ABSTRACT

Background: Mycophenolic acid (MPA), an efficient immunosuppressive medication used in SLE, is glucuronidated by UGTs into an inert 7-O-glucuronide. Studies have shown that the -275T>A and-2152C>T SNPs in the UGT1A9 promoter region are associated with greater hepatic production of UGT1A9 and higher MPA in vitro glucuronidation activity.

Subjects and Methods: patients were selected from outpatient Clinics of Rheumatology and immunology department, UGT1A9 -275T>A and-2152C>T (SNPs) were genotyped in 50 SLE Egyptian patients and 100 healthy controls using PCR-RFLP. In addition, MPA serum concentrations were measured in patients by homogeneous particle enhanced turbidimetric inhibition immunoassay (PETINIA) technique.

Results: UGT1A9-2152C>T and -275T>A distribution of genotypic analysis in SLE patients and controls revealed that the -2152C>T mutation is present in 14% patients and 21% of the control group (P = 0.3), whereas the -275T>A mutation is present in 50% of patients and only in 11% of the control group (P = 0.001). In comparison to the (TT) genotype, the combined (TA+AA) genotype exhibited significant correlation with greater GIT symptoms (68% versus 5%, respectively, P = 0.001). In SLE patients taking MPA with CT+TT genotype against CC genotype, -2152C>T mutations revealed a higher incidence of anemia (85.7% versus%, 30.2 respectively P =0.009). Both SNP genotype carriers had statistically lower C0 MPA values compared to non-carriers (1.25 umol/L (0.62-7.8) versus 4.68 umol/L (0.62-25.9), P = 0.028.

Conclusion: Carrier of both UGT1A9-2152C>T and -275T>A SNPS is associated with lower C0 MPA in comparison to non-carrier in Egyptian SLE patients.

Keywords: UGT1A9, polymorphism, SLE, MPA.

Abbreviations: MPA (Mycophenolic acid), SNPs (Single nucleotide polymorphisms), UGT (uridine diphosphate-glucuronosyltransferases).

INTRODUCTION

SLE is a multiorgan autoimmune illness that typically affects girls between the ages of 20 and 30. Its etiology is unclear. SLE has remission and exacerbations and affects several organs, including the skin, CNS, kidneys, lungs, heart, and blood cells. Positive antinuclear antibodies with a titer of 1/80 or above utilizing indirect immunofluorescence on HEP-2 cells or any similar approach serve as the diagnostic characteristic[(1)].

An immunosuppressive medication known as mycophenolic acid (MPA) is frequently used to avoid acute rejection in kidney transplants. It is also utilized in several SLE patients, most notably Lupus nephritis, to induce and maintain remission. Inosine-5'-monophosphate dehydrogenase (IMPDH), a crucial enzyme involved in the de novo synthesis of guanosine nucleotides, is reversibly inhibited by MPA. This prevents DNA replication and stops the proliferation of T and B cells, which suppresses humoral and cell-mediated immunity and induces tolerance[(2)].

Uridine5'-diphospho-glucuronosyltransferase (UDP-glucuronosyl transferase) is an enzyme that transfers glucuronic acid to small hydrophobic molecules[(3)], Numerous cells, including those in the liver, kidney, and gastrointestinal system, express this enzyme. A single nucleotide polymorphism (SNP) in the UGT1A9 promoter (-2152C>T and -275T>A) affects the expression and activity of this enzyme, and it is believed that these SNPs have pharmacologic importance in terms of MPA activity and concentration[(4)].

This study sought to examine the distribution of the T-275A and C-2152T single nucleotide polymorphisms (SNPs) in the UGT1A9 promoter region in Egyptian patients with SLE as well as how these SNPs affected the pharmacokinetics of mycophenolic acid (MPA).

PATIENTS AND METHODS

The patients were selected from outpatient Clinics of Rheumatology and immunology department, Mansoura university hospitals between January and august 2021. The present study included 150 patients divided into two groups; the control group included 100 seemingly healthy subjects: 10 males & 90 females, whose ages ranged from 18-50 years with a median age of 34 years. The patient group included 50 systemic lupus

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patients: 5 males and 45 females, with their ages ranging from 18 to 51 years with a median age of 35 years.

They were diagnosed with SLE according to new ACR and EULAR criteria for the classification of SLE[5]. Classification of lupus nephritis was done according to the World Health Organization (WHO) and International Society of Nephrology/Renal Pathology Society's recommendations[6].

Patients with primary hematological disorders, metabolic or nutritional problems, an association with another autoimmune disorder, or a history of malignancy were excluded from this study.

Patients had a clinical examination that included a history-taking process, pulse, blood pressure, temperature, neurological testing, and examinations of the eyes, mouth, chest, abdomen, skin, and musculoskeletal system.

Routine laboratory tests, such as CBC, serum creatinine, protein in 24-hour urine, ANA, Anti-ds-DNA, C3, and C4, were collected from the patient's medical record. 98.0% of patients also got steroids, and 96.0% received Plaquenil. MMF was given to all patients at a median dosage of 2 gm per day.

Genotyping of UGT1A9 c.-2152C >T and c.-275T >A polymorphism:

With the help of Thermo Scientific Gene JET Genomic DNA Purification Kit #K0721, #K0722, genomic DNA was isolated from venous EDTA blood. Polymerase chain reaction-Restriction fragment length polymorphism (PCR-RFLP) was used to genotype UGT1A9 c.-2152C > T and c.-275T > A, according to Mazidi et al [7].

The following primers were used in the PCR study of the UGT1A9 gene on patients and control samples. In the case of UGT1A9 c.-2152C>T, the forward primer is 5-TTGAGACAGAGTCGTGCTGTTT-3, and the reverse primer is 5-AGGTCAAGGTGGGCGTAT C-3. In the case of UGT1A9 c.-275T >A, the forward primer is 5-TCAGTGCTAAGGGCCTTGTT-3, and the Reverse primer: 5-CCTGTGCTGCAATGTTAAGTC TA-3, the reaction Eppendorf tube contains: 12 µL EmeraldAmp® GT PCR Master Mix, 0.5µL from each forward and reverse primer, 2µL of DNA and 10 µL of Distilled Water (DW) to final volume 25 micron.

PCR:

The reaction conditions were carried out by the Arctic Thermal Cycler (Finland), and the cycling parameters for the reactions were as follows: for the reaction -2152C >T35 cycles of 93°C for 30 seconds, 63°C for 35 seconds, and 72°C for 30 seconds, with a final extension at 72°C for 5 min, were performed after an initial 95°C for 12 min.; and for the reaction c.-275T >A, an initial period of 94°C for 4 minutes, followed by 30 cycles of 94°C for 30 seconds, 55°C for 30 seconds, and 72°C for 45 seconds, and a final period of 72°C for 10 minutes.

RFLP:

The PCR products for *c.-2152C >T* were digested MseI (Fermentas) as follows: Nuclease-free water 16µ, 10x buffer 2µ, PCR product 1µ, enzyme 1µ, then mixed gently and spun down, then incubated for 1 hour at 65 °c. The PCR products for *c.-275T >A* were digested XbaI (Fermentas) as follows: Nuclease-free water 17µ, 10x buffer 2µ, PCR product 10µ, enzyme 1µ to 30 µL total volume, then mixed gently and spun down, then incubated for 5 minutes at 37 °c. The restriction products were separated by electrophoresis in 2% agarose gel and get stained with ethidium bromide (EB) then visualized by a UV trans-illuminator and photographed.

The genotype was interpreted as follows:
-2152C >T: CC (one band at 242 bp), CT (3 bands at 242, 161, 81 bp) and TT (2 bands at 81 and 161 bp) figure (1)
-275T >A: TT (two bands at 200 and 24 bp), TA (3 bands at 224, 200and 24 bp), AA (one band at 224 bp) figure (2).

MPA concentration measurements:

MPA serum concentrations were measured by a homogeneous particle enhanced turbidimetric inhibition immunoassay (PETINIA) technique (Dimension® X pand plus clinical chemistry system Serial number 2004082036.

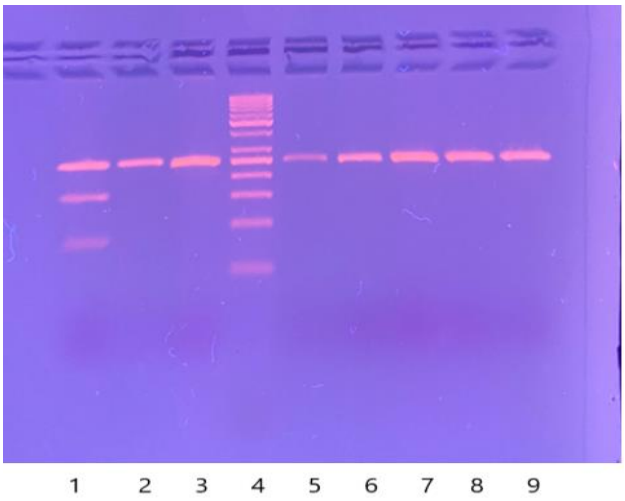

Figure (1): shows PCR –RFLP of *c.-2152C >T digestion by* MseI (Fermentas):

- Lane 1: shows CT genotype at 242,161,81 bp.
- Lane 2,3,5,6,7,8: shows CC genotype at 242 bp.
- Lane 9: PCR product at 242 bp.
- Lane 4: DNA ladder 50 bp.

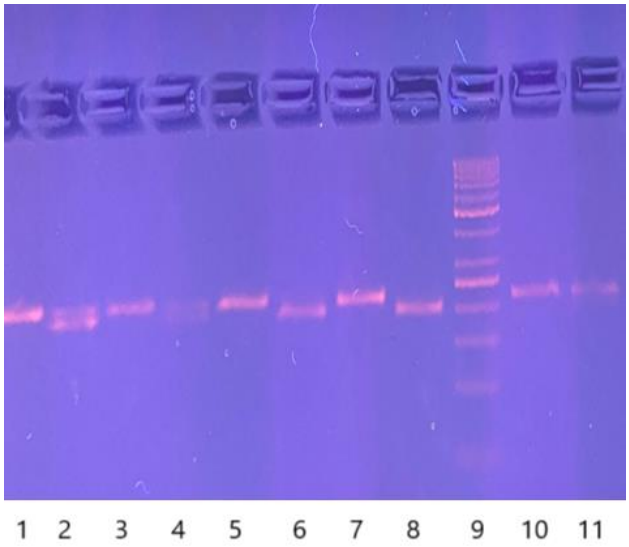

Figure (2): shows PCR –RFLP of *c.-275T >A* digested by XbaI (Fermentas) *:*

- lane1, 3, 5, 7, and 10: show PCR product at 224bp of different samples.
- Lane 2 and 4: show the digested product of samples 1 &3 at 224, 200, and 24 bp for TA genotype
- Lane 6 and 8: show the digested product of samples 5 &7 at 200 and 24 bp for TT genotype
- Lane 9: DNA ladder 50 bp.
- Lane 11: shows the digested product of sample 10 at 224 bp for AA genotype.

Ethical Approval

The ethics approval and written agreement to participate in the study have been signed by all patients and controls. The Institutional Review Board (IRB), Mansoura University MD.18.12.117, Faculty of Medicine, authorized the study. All participants have given their written approval and consent for DNA tests and the gathering of pertinent clinical data. All authors have read the author rules and given their agreement for this work to be published. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The data were analyzed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Number and percentage were used to express qualitative data, while quantitative data was tested for normalcy Kolmogorov-Smirnov test then expressed as range and median, regarding data comparison Chi-Square test or Fisher's exact test was used for qualitative data, while Mann-Whitney U test used for quantitative data between 2 groups and Kruskal-Wallis test used for quantitative data for more than 2 groups. By using direct counting, genotypic and allelic frequencies were evaluated. Genetic models using allelic and dominant traits have been used.

The Hardy-Weinberg equilibrium was used to examine the SNP allele frequencies (HWE). The estimated odds ratios (ORs) are provided with 95% confidence intervals (CI). At CI 95%, a P value of less than 0.05 was deemed statistically significant. A valuable tool for assessing the sensitivity and specificity of quantitative diagnostic measures that divide patients into two categories is the receiver operating characteristic, or ROC Curve.

RESULTS

The study involved 50 SLE patients most of them were lupus nephritis (74.0%), 2.8% was grade I,21.6% grade II, 21.6% grade III, 40.5% grade IV and 13.5% grade V. GIT complications, anemia, leucopenia and thrombocytopenia were detected in 44.0%, 38.0%, 16.0% and 6.0% of patients respectively.

Distribution of *UGT1A9-2*152C>T and -*2*75T>A genotype in SLE patients versus controls showed that the mutation of *UGT1A9-2*152C>T was found in 14% among patients and 21% among the control group while -*2*75T>A mutation was found in 50% of patient versus 11 % in the control group.

SLE patients had significantly higher UGT1A9-275T>A (TA) and (AA) genotypes frequency compared to controls with a higher risk to develop SLE. A allele also showed significant higher frequency in SLE patients versus control {(*P*<0.001, 0.002, <0.001,<0.001), (OR=5.501,28.48,8.090 and 7.716)} respectively. On the other hand, the UGT1A9-2152C>T genotype showed no significant association when comparing frequency in SLE patients versus controls **(Table 1).**

In all patients tested, no significant connection was discovered between these genotypes and any demographic, laboratory, or clinical data. (data not shown)

Table (1): Distribution of UGT1A9-2152C>T and UGT1A9-275T>A) genotype in SLE patients versus controls.

		Control group (n=100)	SLE patient group (n=50)	Relative risk of SLE			
				OR	95%CI		P
UGT1A9--152C>T	CC	79 (79.0%)	43 (86.0%)	**1**	-	-	**R**
	CT	21 (21.0%)	7 (14.0%)	0.612	0.241	1.556	0.302
	TT	0 (0.0%)	0 (0.0%)	-	-	-	-
	C	179 (89.5%)	93 (93.0%)	0.641	0.263	1.564	0.329
	T	21 (10.5%)	7 (7.0%)				
UGT1A9-275T>A)	TT	89 (89.0%)	25 (50.0%)	**1**	-	-	**R**
	TA	10 (10.0%)	17 (34.0%)	**5.501**	**2.285**	**13.24**	**<0.001**
	AA	1 (1.0%)	8 (16.0%)	**28.48**	**3.399**	**238.62**	**0.002**
	TA + AA	11 (11.0%)	25 (50.0%)	**8.090**	**3.505**	**18.676**	**<0.001**
	T	188 (94.0%)	67 (67.0%)	**7.716**	**3.766**	**15.807**	**<0.001**
	A	12 (6.0%)	33 (33.0%)				

Odds ratio. Significant (P-value < 0.05)

Regarding complications; patient having mutation in *UGT1A9* promoter (c.-2152C>T) CT genotype showed increased rate of anemia compared to the wild (CC) genotype (85.7% versus %, 30.2 respectively) (P-value= 0.009), while patients with mutation in *UGT1A9* promoter (c.-275T>A) (TA+AA) showed increased GIT complications as compared to wild (TT) genotype (68% versus 5%, respectively) (P value= 0.001) **(Table 2).**

ROC analysis was conducted to identify the optimal MPA for the prediction of a carrier of both mutations. MPA's best cut-off values for diagnosis of the carrier were 2.03 umol/l. The area under the curve (AUC) was 2.5 (p=0.028) (data not shown).

Table (2): Complication and response as regard UGT1A9-2152C>T & UGT1A9-275T>A genotypes in SLE patients group:

Parameters		TT (n=25)	TA + AA (n=25)	P-value	CC (n=43)	CT + TT (n=7)	P-value
Leucopenia	**Count (%)**	3 (12.0%)	5 (20.0%)	0.702	8 (18.6%)	0 (0.0%)	0.580
Anemia	**Count (%)**	9 (36.0%)	10 (40.0%)	0.771	13 (30.2%)	6 (85.7%)	**0.009**
Thrombocytopenia	**Count (%)**	2 (8.0%)	1 (4.0%)	1.00	3 (7.0%)	0 (0.0%)	1.00
GIT symptoms	**Count (%)**	5 (20.0%)	17 (68.0%)	**0.001**	18 (41.9%)	4 (57.1%)	0.684

Studying the association between serum MPA trough level (C0) and patients characteristics regarding gender, diagnosis and the adverse event showed statistically insignificant association except for the presence of statistically significant leucopenia in patients with high exposure to MPA(P= 0.044) **(Table 3)**.

Table (3): Association between serum MPA level and patients characteristics.

Parameter		MPA level Median (Min-Max)	P
Gender	**Male**	2.35 (0.5-8.3)	0.222
	Female	1.5 (0.2-6.8)	
Diagnosis	**LN**	1.5 (0.2-8.3)	0.438
	Non-LN	1.7 (0.6-6.8)	
LN grade**	**Grade I &II**	1.7 (0.2-3.8)	**P[1]**=0.673 **P[2]**=0.861 **P[3]**=1.00 **P[4]**=0.925 **P[5]**=1.00 **P[6]**=0.933 **P[7]**=0.996
	Grade III	1.9 (0.3-4.5)	
	Grade IV	1.4 (0.3-8.3)	
	Grade IV	1.5 (0.2-3.4)	
Leucopenia	**No**	1.5 (0.2-6.2)	**0.044**
	Yes	2.6 (0.8-8.3)	
Anemia	**No**	1.5 (0.3-8.3)	0.406
	Yes	1.5 (0.2-3.4)	
Thrombocytopenia	**No**	1.5 (0.2-8.3)	0.817
	Yes	1.7 (1.3-2.4)	
GIT symptoms	**No**	1.4 (0.2-4.5)	0.148
	Yes	2.05 (0.2-8.3)	

Impact of both UGT1A9 mutations on MPA pharmacokinetics, it was observed that cases with heterozygous -2152C>T (CT) had lower C0 MPA in comparison to the wild type (CC) (1.87 umol /L versus 4.68 umol/L) respectively, however, this is not statistically significant**.**

Regarding UGT1A9-275T>A SNP, mutant AA genotype also showed non statistically significant lower C0 MPA in comparison to the wild type (TT) and heterozygous genotype (TA) (1.87 versus 4.68 and 5.3 umol/L) respectively.

On the other hand, carrier of both SNPs (CT+TA) or (CT+AA) showed statistically significant lower C0 MPA in comparison to non-carrier genotypes 1.25 umol/L (0.62-7.8) versus 4.68 umol/L (0.62-25.9), P value=0.028 **(Table 4)**

Table (4): Association between serum MPA level and UGT1A9-2152C>T & UGT1A9-275T>A genotypes

Parameter		MPA level (umol/L) Median (Min-Max)	P
UGT1A9-2152C>T	**CC**	4.68 (0.62 - 25.9)	0.141
	CT	1.87 (0.62 - 14.04)	
UGT1A9-275T>A	**TT**	4.68 (0.62 - 14.04)	**P[1]**=0.959 **P[2]**=0.138 **P[3]**=0.440 **P[4]**=0.416
	TA	5.3 (0.62 - 25.9)	
	AA	1.87 (0.94 - 11.86)	
Carrier of both mutation	**No**	4.68 (0.62 - 25.9)	**0.028**
	Yes	1.25 (0.62 - 7.8)	

DISCUSSION

Mycophenolic acid is an immunosuppressive drug used primarily in renal transplant patients to prevent acute allograft rejection and it has been introduced in the treatment of SLE, especially in patients intolerant to the standard immunosuppressive regimens [8]. The pharmacogenomics studies demonstrated many genes related to MPA-metabolizing enzymes and transporters, the variants of these genes may be associated with variations in MPA plasma concentration[9]. One of these metabolizing enzymes is the UGT enzyme which is responsible for glucuronidation of MMF thus affecting its plasma concentration [7]. Although it is also found in the kidney and gastrointestinal tract, UGT1A9 is mostly expressed in the liver. There is evidence that the two SNPs UGT1A9-275T>A and UGT1A9-2152C>T, located in the promoter region of the UGT1A9 gene, increase the conversion of MPA to MPAG and hence reduce MPA exposure [10]

Most of the previous studies concerning these SNPs were done on renal transplant patients, In this work, T-275A and C-2152T single nucleotide polymorphisms (SNPs) in the UGT1A9 promoter region were distributed among SLE Egyptian patients, and their effects on the pharmacokinetics of mycophenolic acid (MPA) were also examined.

Regarding UGT1A9 T-275A SNP, 50% of SLE patients in the present study had TT genotype, 34% had TA genotype and 16 % had TA genotype. As regards UGT1A9 -2152C>T promoter region SNP, 86% of our patients showed CC genotype and 14% had heterozygous CT genotype.

In the Iranian population only 16%(6 individuals) of renal transplant patients found to be heterozygous carriers of UGT1A9 T-275A mutation and no homozygous carriers to be found[7], while the mutation is found in 12.03 % of the Caucasian population and 9.77 % for C-2152T mutation in renal transplant patients [11]

In Belgium renal transplant recipients, the *T-275A* mutation was seen in 16 out of 95 patients (16.8%) whereas the *C-2152T* mutation was detected in 12 out of 95 patients (12.6%), the carriers of both heterozygous mutations were 11 out of 95 (11.6%) and only 1 was carried homozygous mutation for both genes[10]

Regarding the impact of both UGT1A9 SNPs on demographic data, laboratory data, and clinical features in all studied patients, insignificant associations were detected.

Similar to this study, no association between T-275A SNP and age, gender, and laboratory data was found in Iranian patients[7]

Regarding UGT1A9-275T>A, in SLE patients receiving MPA, combined genotype (TA+AA) showed a statistically significant association with increasing GIT symptoms like heartburn, gastritis compared to (TT) genotype (68% versus 5%, respectively), P-value =0.001. Another study agreed with this study and reported that patients with one of the polymorphisms or both suffered from various GIT symptoms leading to hospital admission (P <0 .05)[11]. However, some writers found the opposite results, reporting that the non-carriers experienced higher occurrences of diarrhea. [10]**.**

As regards serum MPA level and *UGT1A9* promoter (-275T>A) & (-2152C>T) polymorphism, the carrier of each mutation showed a lower MPA level however this isn't statistically significant. While carriers of both mutations had statistically significant lower serum levels of MPA compared to non-carriers.

In agreement with this study, ***Sanchaz et al.*** postulated that all individuals with the C-2152T mutation also had the T-275A mutation., as regard pharmacokinetics showed that post-transplant patients carrying one or two mutations exhibited a lower concentration of MPA when measured by area under concentration (AUC 0-12)[11]. While Kuypers et al assumed that lower MPA concentration occurred in patients taking a 2 mg daily dose of mycophenolate mofetil and bearing one or both mutations in the T-275A or the C-2152T polymorphism and this result was shown in decreased AUC (0- 12), AUC (6-12) and C0 MPA level[10].

As regards, ***Mazidi et al.*** MPA AUC 0-12 was substantially lower in T-275A polymorphism carriers compared to wild type. But C0 did not significantly differ between the two groups[7]

Lévesque et al revealed that lower MPA exposure AUC 6- 12 was found in UGT1A9 T-275A / C-2152T carriers while MPAG showed no significant change, regarding (AUC 6-12/ AUC 0- 12) an estimate for enterohepatic recycling there was a significant decrease in concentration for MPA, MPAG, and AcMPAG[12]

A multicenter study carried out on 338 kidney transplant patients receiving mycophenolate mofetil (fixed dose vs concentration controlled) were genotyped for *UGT1A8*, *UGT1A9*, *UGT2B7*polymorphisms and followed up for one year to assess biopsy-proven acute rejections (BPARs) showed that patients who are treated with tacrolimus and carriers with *UGT1A9* -275T>A and/or -2152C>T mutations had lower MPA level as observed by the area under the concentration curve (AUC 0–12) by 20 % compared with non-tacrolimus treated patients, also showed signs of acute rejection in MMF-

treated patients with fixed dose and also consuming tacrolimus[13]

CONCLUSION

We can conclude that in a group of Egyptian SLE patients, UGT1A9 T-275A and C-2152T carriers are associated with low trough level of MPA and this proves the fact that these SNPs is associated with higher expression of UGT enzymes in the liver and increased in vitro glucuronidation activity for MPA compared with those of wild-type patients.

Conflict of interest

There are no conflicts of interest, according to the authors.

Availability of data

The paper itself contains the data sets that are used to support the findings**.**

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