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Research Article
Effect of Genetic Polymorphisms in Detoxification Proteins on Treatment Outcome of Atorvastatin

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Abstract

Background: The most effective method of lowering cholesterol is the administration of statins. Cholesterol-lowing effects of statin may be affected by polymorphisms of detoxification genes. **Methodology:** In this study, 130 adult patients suffering from hypercholesterolemia and receiving atorvastatin therapy (40 mg daily) were enrolled. At 12-15 months subsequent to treatment of atorvastatin, Total Cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and genes of cytochrome P_{450} (CYP) 3A4, UDP-glucuronosyltransferase (UGT) 1A1, UGT1A3, multidrug resistance proteins 1 (MDR1) and organic anion transporter polypeptides 2 (OATP2) in the study subjects were determined. **Results:** There were 87 and 43 subjects whose TC concentrations were <5.1 and ≥5.1 mmol L^{-1}, respectively and 93 and 37 patients whose LDL-C concentrations were <3.3 and ≥3.3 mmol L^{-1}, respectively. Odds Ratio (OR) of wild type in the UGT1A1 gene was 0.389 (95% confidence interval = 0.174-0.873, p = 0.02) in the subjects whose TC concentrations were compared between <5.1 and ≥5.1 mmol L^{-1}, while ORs of other haplotypes in the UGT1A1 gene (OR = 0.976-1.464, p = 0.37-0.98) and haplotypes of CYP3A4, UGT1A3, MDR1 and OATP2 genes (OR = 0.561-3.818, p = 0.14-0.99) were not statistically significant. For LDL-C concentrations, ORs of all the haplotypes of CYP3A4, UGT1A1, UGT1A3, MDR1 and OATP2 genes were not statistically significant (OR = 0.371-2.118, p = 0.06-0.93). **Conclusion:** Variant UGT1A1 gene is related to cholesterol-lowing effects in Taiwanese patients treated with atorvastatin. Determination of UGT1A1 gene can be considered for the selection of effective-outcome patients prior to giving of atorvastatin.

Key words: Atorvastatin, cholesterol, genetic polymorphisms in detoxification proteins, UDP-glucuronosyltransferase 1A1

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

There are three phases in detoxification process, named oxidation (phase 1), conjugation (phase 2) and transportation (phase 3). The oxidation reaction is mainly catalyzed by cytochrome P_{450} (CYP)[1]. The CYP3A4, located at chromosome 7q22.1 is known as the most abundant CYP in human liver and a crucial enzyme for human metabolism of therapeutic agents[2]. The UDP-glucuronosyltransferase (UGT) is the major enzyme involved in the conjugation reaction[3]. The members of the UGT1 family are all derived from a single gene on chromosome[4] 2q37. Among the proteins responsible for transportation, multidrug resistance proteins (MDR) and organic anion transporter polypeptides (OATP) are the two transporter families most studied and their genes are located at chromosomes 7q21 and 12p12, respectively[5-7].

Elevated values of low-density lipoprotein-cholesterol (LDL-C) are the most important risk factor for the development of coronary artery disease[8]. The most effective method of lowering LDL-C is the administration of statins[9]. Results of studies show that for an LDL-C reduction of 1.0 mmol L^{-1} (40 mg dL^{-1}) by statins the risk of ischemic heart disease events is reduced by 11% in the first year of treatment, 24% in the second year, 33% in years 3-5 and by 36% thereafter[9]. Four statins, atorvastatin, simvastatin, pravastatin and fluvastatin are currently used at most hospitals in Taiwan. Statins are metabolized in the intestine and in the liver[10]. In phase 1 metabolism, statins are transformed into hydroxylated products mainly[11-14] by CYP3A4. The hydroxylated statins are conjugated with glucuronic acid to form hydrophilic glucuronides mainly by UGT1A1 and UGT1A3 (for atorvastatin, simvastatin and fluvastatin)[14-18]. Sincemost of CYP3A4 metabolites are also substrates for MDR1, the secretion of atorvastatin, simvastatin and fluvastatin is likely to involve MDR1[14,19]. Pravastatin is not extensively metabolized by CYP and a different pathway is assumed for this statin including uptake[20] by OATP2. In recent five years, cholesterol-lowing effects of atorvastatin influenced by CYP3A4[21,22], UGT1A1[23,24], UGT1A3[24,25], MDR1[22,26,27] and OATP2[22,26,28-30] polymorphisms have been studied. However, no any data of such investigations has been reported for Taiwanese population.

The results of recent studies indicate that the variant status of detoxification proteins is different among Taiwanese and other ethnic groups. For example, for Taiwanese, the major single nucleotide polymorphisms (SNPs) of CYP3A4 are CYP3A4*4 (A352G, I118V), CYP3A4*5 (C653G, P218R) and CYP3A4*18A (T878C, L293P) and most of the major CYP3A4 SNPs found in other ethnicities were not observed[31]. The second example is that the frequency of 3435TT MDR1 gene in Taiwanese (14.5%) is in between that in Africans (6.0%) and American Caucasians (25.0%)[32]. The third example is that the frequency of A388G of the OATP2 gene in Taiwanese (0.68)[33] is in between that in European Americans (0.30) and African Americans (0.74)[34]. Therefore, it is hypothesize that, for Taiwanese the SNPs of detoxification proteins modulate cholesterol-lowing effects of statins may be different from those for caucasians. Here we for the first time report effect of genetic polymorphisms in detoxification proteins on treatment outcome of atorvastatin for Taiwanese hypercholesterolemic patients.

MATERIALS AND METHODS

Study subjects: This study consisted of 130 consecutive patients (61 males and 69 females) with hypercholesterolemia. Informed consents were obtained from the participants prior to enrollment in this study and approved by the ethic board of the Zuoying Armed Forces General Hospital, Kaohsiung, Taiwan, ROC (IRB No. 98-1-01). The diagnosis of hypercholesterolemia was based on the criteria of (1) Serum total cholesterol (TC) 5.1 mmol L^{-1} (200 mg dL^{-1}) or (2) Serum LDL-C 3.3 mmol L^{-1} (130 mg dL^{-1}), according to therapy target of Adult Treatment Panel (ATP) III guidelines[35]. Exclusion criteria were active liver disease, pregnancy or breastfeeding, use of contraceptive drugs, other severe disease (e.g., carcinoma or disease of the lung, kidney or hematological system or secondary dyslipidemia caused by hypothyroidism, gout, pancreatitis, alcoholism or medicine).

Study procedures: Venous blood was collected at 12-15 months subsequent to treatment of atorvastatin (40 mg daily). Serum TC and LDL-C were measured by the CHOD-PAP method via Cobas-C501 autoanalyzer, while genomic DNA was isolated from whole blood cells using a blood DNA isolation kit (Maxim Biotech Inc., San Francisco, CA, USA).

Determination of CYP3A4, UGT1A1, UGT1A3, MDR1 and OATP2 genes: The DNA full sequencing or PCR-restriction fragment length polymorphism (RFLP) methods as

Table 1: Methods for the determination of genes

Gene	Methods	References
CYP3A4	RFLP: 653 (Cla I)*, 878 (Msp I)	Cho *et al.*[25]
UGT1A1	RFLP: $A(TA)_nTAA$, 211 (Ava II)	Prado *et al.*[30]
UGT1A3	DNA sequencing for nucleotides 31 and 140	Liu *et al.*[31]
MDR1	RFLP: 1236 (Hae), 2677 (BseY I), 3435 (Mbo I)	Shabana *et al.*[26]
OATP2	RFLP: 388 (Taq I), 521 (Hha I)	Huang *et al.*[32]

*The position of nucleotide and the restriction enzyme used, CYP: Cytochrome P_{450}, MDR: Multidrug resistance proteins, OATP: Organic anion transporter polypeptides, RFLP: Restriction fragment length polymorphism, UGT: UDP-glucuronosyltransferase

Table 2: Number and age of study subjects

Members	N	Range of age (year)	Mean (SD) of age (year)	p*
Male	61	32-83	55.77 (13.59)	0.17
Female	69	21-82	58.72 (10.51)	
Total	130	21-83	57.34 (12.10)	

*Calculated by student's t test, SD: Standard deviation

described previously[31,32,36-38] were utilized to determine CYP3A4, UGT1A1, UGT1A3, MDR1 and OATP2 genes as shown in Table 1. The DNAs of the variants identified by the DNA sequencing method were run as positive controls in each performance of PCR-RFLP genotyping assays.

Statistical analysis: Mean age between the male and the female subjects was compared with student's t test and the significant level was assigned at 0.05. The study subjects were divided into two groups according to their TC and LDL-C concentrations: <5.1 or ≧5.1 mmol L^{-1} for TC and <3.3 or ≧3.3 mmol L^{-1} for LDL-C, respectively. The results of categories according to wild/variant status for the SNPs determined, respectively. Multi-locus genotype patterns with frequency <5% were pooled into a single class called "Other haplotypes". Odds Ratio (OR) was calculated for the comparison of genotype pattern distributions. A 95% Confidence Interval (CI) for the OR for subjects carrying a haplotype either above or below 1.0 or a $p<0.05$ was defined as constituting statistical significance. All data were analysed using SPSS version 13.0 software (SPSS for Windows, Inc., Chicago, IL, USA).

RESULTS

Mean age was not significantly different between the 61 males and the 69 females ($p = 0.17$) as shown in Table 2. Therefore, data of male and female study subjects were pooled for analysis. There were 87 and 43 subjects whose TC concentrations were <5.1 and ≧5.1 mmol L^{-1}, respectively and 93 and 37 patients whose LDL-C concentrations were <3.3 and ≧3.3 mmol L^{-1}, respectively. The UGT1A1 and MDR1 genes were not made for two and three subjects, respectively. Among the 130 study subjects, there were one and nine carrying heterozygous variations at nucleotides (nts) 653 and 878 in the CYP3A4 gene, respectively. Since number of subjects possessing variation was too small, CYP3A4 gene was expressed as wild type and variant for further analysis. Table 3 shows the except for wild type of the UGT1A1 gene [$(TA)_6(TA)_6$ at nt-53 and GG at nt-211], ORs of other haplotypes in the UGT1A1 gene (OR = 0.976-1.464, $p = 0.37-0.98$) and haplotypes of CYP3A4, UGT1A3, MDR1 and OATP2 genes (OR = 0.561-3.818, $p = 0.14-0.99$) were not statistically significant. The OR of wild type in the UGT1A1 gene was 0.389 ($p = 0.02$) in the subjects whose TC concentrations were compared between <5.1 and ≧5.1 mmol L^{-1}. Table 4 indicates that, for LDL-C concentrations, ORs of all the haplotypes of CYP3A4, UGT1A1, UGT1A3, MDR1 and OATP2 genes were not statistically significant (OR = 0.371-2.118, $p = 0.06-0.93$).

DISCUSSION

In previous studies, SNP of CYP3A4*1B was found to be associated with cholesterol-lowing effects in Brazil and Indian patients treated with atorvastatin, respectively[21,22]. However, those variants were not found in Taiwanese, while the major CYP3A4 SNPs in Taiwanese were CYP3A4*4 (allele frequency 2.4%), CYP3A4*5 (0.7%) and CYP3A4*18A (2.7%)[26]. In this study, it is found that allele frequencies of CYP3A4*5 (0.38%) and CYP3A4*18A (3.46%) were similar to those reported for Taiwanese previously[31]. The Km value for CYP3A4*18A was observed to be comparable to those for CYP3A4*1 (wild type) for atorvastatin[39]. Therefore, it is reasonable that variant CYP3A4 gene does not affect treatment outcome of atorvastatin on TC and LDL-C concentrations in Taiwanese as reported in present study. The contrary results between Taiwanese and Brazil (and Indian) populations might be attributable to ethnic factors.

Lactone formation of atorvastatin, the pharmacologically inactive metabolite was significantly lower in carriers of UGT1A1*28 [$A(TA)_7TAA$ instead of $A(TA)_6TAA$ at nt-53][40] but higher in carriers of UGT1A3*2 (SNPs at nts 31 and 140) *in vivo*[23-25]. For 23 Korean healthy-volunteers in a previous study, the maximum percent decreased in TC and LDL-C from baseline in UGT1A3*2 carriers were found being 29 and 18% less than the UGT1A3*2 noncarriers, respectively[25]. However, in the present study, treatment outcome of atorvastatin is not significantly different between UGT1A3*2 carriers and UGT1A3*2 noncarriers.

Table 3: Relationship between genetic polymorphisms and TC concentration

			TC (mmol L^{-1})				
			<5.1	≥5.1			
			N	N	OR	95% CI	p
CYP3A4							
Nt 653	Nt 878						
Wild type			81	40	1.012	0.241-4.260	0.99
Variant			6	3	0.988	0.235-4.155	0.99
UGT1A1							
Nt–53 (TA)*	Nt 211						
66	GG		45	31	0.389	0.174-0.873	0.02
67 or 77	GG		12	0	-----	-----	-----
66	GA or AA		27	10	1.464	0.630-3.404	0.37
67	GA		2	1	0.976	0.086-11.081	0.98
UGT1A3							
Nt 31	Nt 140						
TT	TT		32	16	0.982	0.461-2.092	0.96
TC or CC	TT		29	16	0.844	0.394-1.808	0.66
TT	TC or CC		8	0	-----	-----	-----
TC or CC	TC or CC		18	11	0.759	0.321-1.792	0.53
MDR1							
Nt 1236	Nt 2677	Nt 3435					
CC	GG	CC	6	5	0.585	0.168-2.038	0.40
CT or TT	GG	CC	19	8	1.279	0.508-3.217	0.60
CT or TT	GT or TT	CC	7	1	3.818	0.454-32.089	0.19
CT or TT	GT or TT	CT or TT	45	23	1.003	0.480-2.096	0.99
Other haplotypes**			7	6	0.561	0.176-1.786	0.32
OATP2							
Nt 388	Nt 521						
GG	TT		29	20	0.575	0.272-1.213	0.14
GA or AA	TT		35	15	1.256	0.588-2.685	0.56
GG	TC or CC		18	5	1.983	0.682-5.763	0.20
GA or AA	TC or CC		5	3	0.813	0.185-3.573	0.78

*66: $(TA)_6(TA)_6$, 67: $(TA)_6(TA)_7$, 77: $(TA)_7(TA)_7$, **Pools of multi-locus genotype patterns with frequency <5%, CI: Confidence interval, CYP: Cytochrome P_{450}, MDR: Multidrug resistance proteins, Nt: Nucleotide, OATP: Organic anion transporter polypeptides, OR: Odds ratio, TC: Total cholesterol, UGT: UDP-glucuronosyltransferase

The contrary results between Korean authors and us may be caused by different numbers of study subjects (N = 23 versus N = 130), different healthy situations (healthy volunteers versus hypercholesterolemic patients) and different doses of atorvastatin were given (20 mg daily versus 40 mg daily).

Carriers of the low-expression allele UGT1A1*28$(TA)_7$ were ever found tending to have lower levels of atorvastatin lactone than carriers with the normal-activity allele[23,24] $(TA)_6$. However, UGT1A1 gene has not been ever reported to involve in treatment outcome of atorvastatin previously. In this study, we for the first time, demonstrate that wild type of UGT1A1 gene is inversely associated with TC <5.1 mmol L^{-1} in the patients receiving atorvastatin therapy. In other words, we find that variant UGT1A1 gene significantly affects treatment outcome of atorvastatin for TC <5.1 mmol L^{-1} when compared with wild type of UGT1A1 gene (OR = 2.568, p = 0.02, Table 5). The frequency of the $A(TA)_7TAA$ allele at nt–53 in the UGT1A1 gene is substantially lower, while for the rate of variation within the coding region (such as G211A) is much higher for Taiwanese than for Caucasians (14.3% vs 35.7-41.5% and 29.3% vs 0.1%, respectively)[36]. The UGT1A1 enzyme activities of the subjects featuring $A(TA)_7TAA/A(TA)_7TAA$, $A(TA)_6TAA/A(TA)_7TAA$ (performed in hepatoma cell lines Huh 7), homozygous c.211 G>A variation and heterozygous c.211 G>A variation (performed in COS 7 cells) in the UGT1A1 gene were observed by Dutch and Japanese authors being 30, 55, 32 and 60% of normal, respectively[41,42] and thus are estimated to form less atorvastatin lactonization (pharmacologically inactive) than normal. This may be the reason why in Taiwanese variant UGT1A1 gene is related to TC reduction in atorvastatin therapy. The effect of UGT1A1 gene on LDL-C reduction in our patients receiving atorvastatin therapy is at statistical margin (p = 0.06, Table 4). This may be

Table 4: Relationship between genetic polymorphisms and LDL-C concentration

			LDL-C (mmol L^{-1})				
			<3.3	≧3.3			
			N	N	OR	95% CI	p
CYP3A4							
Nt 653	Nt 878						
Wild type			87	34	1.279	0.303-5.408	0.74
Variant			6	3	0.782	0.185-3.304	0.74
UGT1A1							
Nt-53 (TA)*	Nt 211						
66	GG		50	26	0.458	0.198-1.057	0.06
67 or 77	GG		12	0	-----	-----	-----
66	GA or AA		28	9	1.312	0.547-3.150	0.54
67	GA		2	1	0.778	0.068-8.852	0.84
UGT1A3							
Nt 31	Nt 140						
TT	TT		35	13	1.114	0.503-2.466	0.79
TC or CC	TT		30	15	0.698	0.318-1.535	0.37
TT	TC or CC		8	0	-----	-----	-----
TC or CC	TC or CC		20	9	0.852	0.347-2.095	0.73
MDR1							
Nt 1236	Nt 2677	Nt 3435					
CC	GG	CC	8	3	1.106	0.277-4.421	0.89
CT or TT	GG	CC	21	6	1.572	0.578-4.280	0.37
CT or TT	GT or TT	CC	8	0	-----	-----	-----
CT or TT	GT or TT	CT or TT	46	22	0.713	0.328-1.548	0.39
Other haplotypes**			7	6	0.436	0.136-1.398	0.15
OATP2							
Nt 388	Nt 521						
GG	TT		34	15	0.845	0.387-1.844	0.67
GA or AA	TT		36	14	1.038	0.473-2.274	0.93
GG	TC or CC		19	4	2.118	0.668-6.714	0.20
GA or AA	TC or CC		4	4	0.371	0.088-1.569	0.16

*66: $(TA)_6(TA)_6$, 67: $(TA)_6(TA)_7$, 77: $(TA)_7(TA)_7$, **Pools of multi-locus genotype patterns with frequency <5%, CI: Confidence interval, CYP: Cytochrome P_{450}, LDL-C: Low-density lipoprotein cholesterol, MDR: Multidrug resistance proteins, Nt: Nucleotide, OATP: Organic anion transporter polypeptides, OR: Odds ratio, UGT: UDP-glucuronosyltransferase

Table 5: Relationship between UGT1A1 gene and TC concentration

	TC (mmol L^{-1})				
	<5.1	≧5.1			
	N	N	OR	95% CI	p
UGT1A1 Nts-53/211					
Wild type	45	31	1.0		
Variant	41	11	2.568	1.155~5.702	0.02

CI: Confidence interval, Nts: Nucleotides, OR: Odds ratio, TC: Total cholesterol, UGT: UDP-glucuronosyltransferase

attributable to that the number of our study subjects is not large enough to have significant conclusion. However, these results show the possibility that variant UGT1A1 gene is associated with LDL-C reduction for the patients treated with atorvastatin.

Although, polymorphisms of MDR1 and OATP2 genes were found may be related to pharmacokinetic of atorvastatin[43-45], contrary results of clinical observation were reported among different ethnic groups in recent 5 years. For example, the percentage change in TC and LDL-C did not show any statistically significant difference when compared among the different MDR1 C3435T genotypes in Egyptian hypercholesterolemic patients[26], while the MDR1 gene polymorphisms G2677T and C3435T but not C1236T were associated with the lipid lowering effect of atorvastatin among Jordanians[27]. However, no significant differences were observed in the lipid-lowering effects of atorvastatin between subjects with different OATP2 genotypes in Egyptian[26], Chinese[28], Greek[29] and Chilean[30] individuals. We determined polymorphisms at nts 1236, 2677 and 3435 for the MDR1 gene and polymorphisms at nts 388 and 521 for the OATP2 gene for our study subjects. However, we did not find any relationship between MDR1 gene nor OATP2 gene and cholesterol-lowing effect, in agreement to most of the results performed in other ethnic groups previously[26-30].

CONCLUSION

Variant UGT1A1 gene is related to cholesterol-lowing effects in Taiwanese patients treated with atorvastatin. Therefore, determination of UGT1A1 gene can be considered for the selection of effective-outcome patients prior to giving of atorvastatin.

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