ORIGINAL ARTICLE

Pharmacogenomics of the Efficacy and Safety of Colchicine in COLCOT

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BACKGROUND: The randomized, placebo-controlled COLCOT (Colchicine Cardiovascular Outcomes Trial) has shown the benefits of colchicine 0.5 mg daily to lower the rate of ischemic cardiovascular events in patients with a recent myocardial infarction. Here, we conducted a post hoc pharmacogenomic study of COLCOT with the aim to identify genetic predictors of the efficacy and safety of treatment with colchicine.

METHODS: There were 1522 participants of European ancestry from the COLCOT trial available for the pharmacogenomic study of COLCOT trial. The pharmacogenomic study's primary cardiovascular end point was defined as for the main trial, as time to first occurrence of cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina requiring coronary revascularization. The safety end point was time to the first report of gastrointestinal events. Patients' DNA was genotyped using the Illumina Global Screening array followed by imputation. We performed a genome-wide association study in colchicine-treated patients.

RESULTS: None of the genetic variants passed the genome-wide association study significance threshold for the primary cardiovascular end point conducted in 702 patients in the colchicine arm who were compliant to medication. The genome-wide association study for gastrointestinal events was conducted in all 767 patients in the colchicine arm and found 2 significant association signals, one with lead variant rs6916345 (hazard ratio, 1.89 [95% CI, 1.52–2.35], $P=7.41×10^{-9}$) in a locus which colocalizes with Crohn disease, and one with lead variant rs74795203 (hazard ratio, 2.51 [95% CI, 1.82–3.47]; $P=2.70×10^{-8}$), an intronic variant in gene *SEPHS1*. The interaction terms between the genetic variants and treatment with colchicine versus placebo were significant.

CONCLUSIONS: We found 2 genomic regions associated with gastrointestinal events in patients treated with colchicine. Those findings will benefit from replication to confirm that some patients may have genetic predispositions to lower tolerability of treatment with colchicine.

Key Words: acute coronary syndrome ■ colchicine ■ gastrointestinal diseases ■ myocardial infarction ■ pharmacogenetics

Inflammation plays an important role in atherosclerosis and in processes leading to and following a myocardial infarction. The COLCOT (Colchicine Cardiovascular Outcomes Trial) has recently shown the benefits of the anti-inflammatory medication colchicine in reducing the rate of ischemic cardiovascular events in 4745 patients

Nonstandard Abbreviations and Acronyms

ABCB1	ATP Binding Cassette Subfamily B Member 1 gene
COLCOT	Colchicine Cardiovascular Outcomes Trial
CYP3A4	cytochrome P450 family 3 subfamily A member 4
GWAS	genome-wide association study
HAUS6	HAUS augmin like complex subunit 6 gene
HR	hazard ratio
SAXO1	stabilizer of axonemal microtubules 1 gene
SEPHS1	selenophosphate synthetase 1 gene

included within 30 days after myocardial infarction.[1] The study's primary end point consisting of time to first occurrence of cardiovascular death, resuscitated cardiac arrest, nonfatal myocardial infarction, nonfatal stroke, or urgent hospitalization for angina requiring coronary revascularization was reduced by 23% by low-dose colchicine as compared to placebo after a median follow-up of 23 months.[1]

Considering that patients receive long-term treatment with multiple drugs after a myocardial infarction, genomics can help identify patients more or less unlikely to derive benefits to decrease polypharmacy. Given the effects of colchicine on tubulin and multiple inflammatory pathways,[2,3] the identification of genes associated with clinical outcomes can provide insights into the underlying mechanisms responsible for its benefits in patients with coronary artery disease. Similarly, genes linked to adverse effects may offer clues to their pathophysiology. Here, we present the post hoc pharmacogenomic study of COLCOT in the subgroup of participants who took part in the optional genetic substudy, with the aim to identify genetic predictors of the efficacy and safety of treatment with colchicine.

METHODS

The data underlying this article cannot be shared publicly to preserve the privacy of study participants; however, the data are available from the corresponding authors upon reasonable requests. The analytic methods and study materials may be made available to other researchers for purposes of reproducing the results or replicating the procedure. Summary statistics are available publicly for download and visualization via PheWEB[4] at URL: http://statgen.org/pheweb/colcot. The COLCOT clinical trial was registered at URL: https://www.clinicaltrials.gov under the unique identifier NCT02551094. The study protocol was approved by the Montreal Heart Institute research ethics committee and complies with the Declaration of Helsinki. Written informed consent was obtained from all participating subjects. Full Methods are available in the Data Supplement of the article.

RESULTS

There were 1522 participants included in the pharmacogenomic analysis of COLCOT of which 767 were randomized to colchicine and 755 to placebo (Figure I in the Data Supplement). The baseline characteristics of patients according to the study treatment groups are shown in Table 1. The mean age of participants was 60.9 years and 81.3% were male. The COLCOT study primary cardiovascular end point occurred in 6.2% of patients who consented to the pharmacogenomic substudy, as compared to 6.3% of those in the main trial ($P=0.86$; Table I in the Data Supplement). Gastrointestinal adverse events occurred in 23.4% of the pharmacogenomic study population, as compared to 17.6% of the COLCOT trial participants ($P=1.8\times10^{-7}$).

Genetic Determinants of Cardiovascular Efficacy With Colchicine

The pharmacogenomic analyses of the primary cardiovascular efficacy end point were limited to the 702 participants randomized to colchicine who used the study drug with at least 80% compliance in the first 6 months of treatment. Of those, 39 patients had an event. The prespecified analysis for the ATP binding cassette subfamily B member 1 gene (*ABCB1*) variant rs1045642 and the CYP3A4 (cytochrome P450 family 3 subfamily A member 4) metabolizer phenotype was not associated with the primary cardiovascular efficacy end point ($P=0.77$ and $P=0.91$, respectively), and none of the tested genetic variants passed the genome-wide association study (GWAS) significance threshold ($P<5\times10^{-8}$; Figure IIA in the Data Supplement). However, the GWAS analysis had limited power, and negative results should be interpreted with care. The sex-stratified GWAS with 576 male participants also did not provide any GWAS-significant findings (Figure IIB in the Data Supplement), however, there was some interest for the top signal on chromosome 9 at rs10811106 ($P=5.8\times10^{-8}$) near the stabilizer of axonemal microtubules 1 (*SAXO1*) gene (also known as *FAM154A*), as it encodes the stabilizer of axonemal microtubules 1 (Figure IIIB in the Data Supplement).

Genetic Determinants of Gastrointestinal Adverse Events With Colchicine

There were 767 participants randomized to colchicine who were included in the genetic analyses for gastrointestinal adverse events, of those, 187 had a gastrointestinal event. The *ABCB1* rs1045642 variant and the CYP3A4 metabolizer phenotype were not associated with gastrointestinal adverse events ($P=0.97$ and $P=0.31$, respectively). We found 22 genetic variants significantly associated with gastrointestinal events at

Table 1. Characteristics of the Pharmacogenomics Study Participants

Characteristics	Colchicine (N=767)	Placebo (N=755)
Female sex, N (%)	145 (18.9)	139 (18.4)
Age, mean±SD, y	60.7±10.0	60.8±9.9
BMI,* mean±SD, kg/m²	28.7±4.9	29.1±4.5
Current smoker, N (%)	180 (23.5)	164 (21.7)
Diabetes, N (%)	123 (16.0)	129 (17.1)
Hypertension, N (%)	368 (48.0)	363 (48.1)
Dyslipidemia, N (%)	393 (51.2)	366 (48.5)
Prior MI, N (%)	114 (14.9)	113 (15.0)
Prior PCI, N (%)	141 (18.4)	136 (18.0)
Prior CABG, N (%)	29 (3.8)	33 (4.4)
Prior stroke, N (%)	19 (2.5)	22 (2.9)
Prior heart failure, N (%)	8 (1.0)	10 (1.3)
History of atrial fibrillation, N (%)	39 (5.1)	34 (4.5)
Concomitant medication		
Aspirin, N (%)	762 (99.3)	749 (99.2)
Antiplatelet agent other than aspirin,* N (%)	755 (98.4)	751 (99.5)
Statin, N (%)	762 (99.3)	751 (99.5)
β-blocker, N (%)	683 (89.0)	664 (87.9)

BMI indicates body mass index; CABG, coronary artery bypass graft; MI, myocardial infarction; N, number of patients; and PCI, percutaneous coronary intervention.

*Significantly different between treatment groups, all variables tested by Kruskal-Wallis or χ^2 test.

2 loci located on chromosomes 6 and 10 (Figure). The most significant association on chromosome 6 was the intergenic variant rs6916345 ($P=7.41\times10^{-9}$). When conditioning on rs6916345, no additional genetic variants remained significant at $P<5\times10^{-8}$ in the region, and rs6916345 had the highest probability of being causal by CAVIAR analysis (Data Supplement). The minor allele (A) was associated with gastrointestinal events in the colchicine group (hazard ratio [HR], 1.89 [95% CI, 1.52–2.35], $P=7.41\times10^{-9}$) with an estimated effect in the placebo group of HR=1.30 (95% CI, 1.04−1.62; $P=0.02$). The effect appeared to be mostly driven by the occurrence of diarrhea (Table II in the Data Supplement). The interaction term between rs6916345 and colchicine treatment was significant ($P=2.96\times10^{-8}$; Table 2). Individuals with the AA genotype represented 25% of the trial population. Gastrointestinal adverse events were reported by 36.9% of AA patients in the colchicine group compared with 18.6% in the placebo group (HR, 2.42 [95% CI, 1.57−3.72], $P=5.77\times10^{-5}$; Table 3). We found evidence of colocalization of the locus with Crohn disease (Material and Figure V in the Data Supplement). The risk allele (A) at rs6916345 was previously associated with Crohn disease (odds ratio, 1.07, $P=3.1\times10^{-5}$).[5]

The most significant association at the chromosome 10 locus was at rs10128117 located in intron 2 of the selenophosphate synthetase 1 gene (*SEPHS1*). However, because this variant is triallelic and was imputed as biallelic, we report the findings based on variant, rs74795203, in strong linkage disequilibrium, located in intron 4 of the gene (Figure IVB in the Data Supplement). The G allele of variant rs74795203 was associated with gastrointestinal events with an HR of 2.51 (95% CI, 1.82–3.47; $P=2.70\times10^{-8}$) with an estimated effect in the placebo group of HR of 0.71 (95% CI, 0.46−1.09; $P=0.11$). The interaction term between rs74795203 and colchicine treatment was significant ($P=3.13\times10^{-6}$; Table 2). When conditioning on rs10128117 or rs74795203, no additional genetic variants remained significant at $P<5\times10^{-8}$. Individuals with the AG or GG genotype at rs74795203 represented 13% of the trial population. Gastrointestinal adverse events were reported by 47.1% of patients with the AG or GG genotype in the colchicine arm compared with 18.9% in the placebo arm (HR, 3.98 [95% CI, 2.24−7.07], $P=2.33\times10^{-6}$; Table 3). The GWAS limited to 622 male participants did not identify additional association signals.

DISCUSSION

In this pharmacogenomic study of the randomized, placebo-controlled COLCOT trial, genetic variants were found to be associated with gastrointestinal events in patients treated with colchicine, offering insights into the biological mechanisms underlying the tolerability of treatment with colchicine. Although the signal did not reach the significance threshold, we have found an interesting genetic region on chromosome 9 in the prespecified analysis in males that is possibly associated with the cardiovascular benefits of colchicine. The locus is particularly interesting as it spans the *SAXO1* gene, and it colocalizes with the expression of the HAUS augmin like complex subunit 6 (*HAUS6*) gene which is involved in microtubule generation from existing microtubules and in kinetochore-microtubule attachment and central spindle formation during anaphase.[6] The cardiovascular event risk allele at the leading variant reduces *HAUS6* expression, and it may possibly interact with the effects of colchicine on tubulin binding and microtubule polymerization. However, replication of this locus in future cardiovascular studies with colchicine is necessary.

The genome-wide analysis of gastrointestinal adverse events found 2 associated regions. The first region on chromosome 6 is particularly appealing as it colocalizes with a previously identified locus for Crohn disease.[5] The risk allele of the lead variant at this locus was previously associated with Crohn disease risk and with reticulocyte counts and hemoglobin concentrations, which are common extraintestinal complication of Crohn disease. The second genetic locus on chromosome 10 overlaps the *SEPHS1*, which encodes an enzyme that synthesizes selenophosphate from selenide and ATP. We found evidence of colocalization of the region with expression of
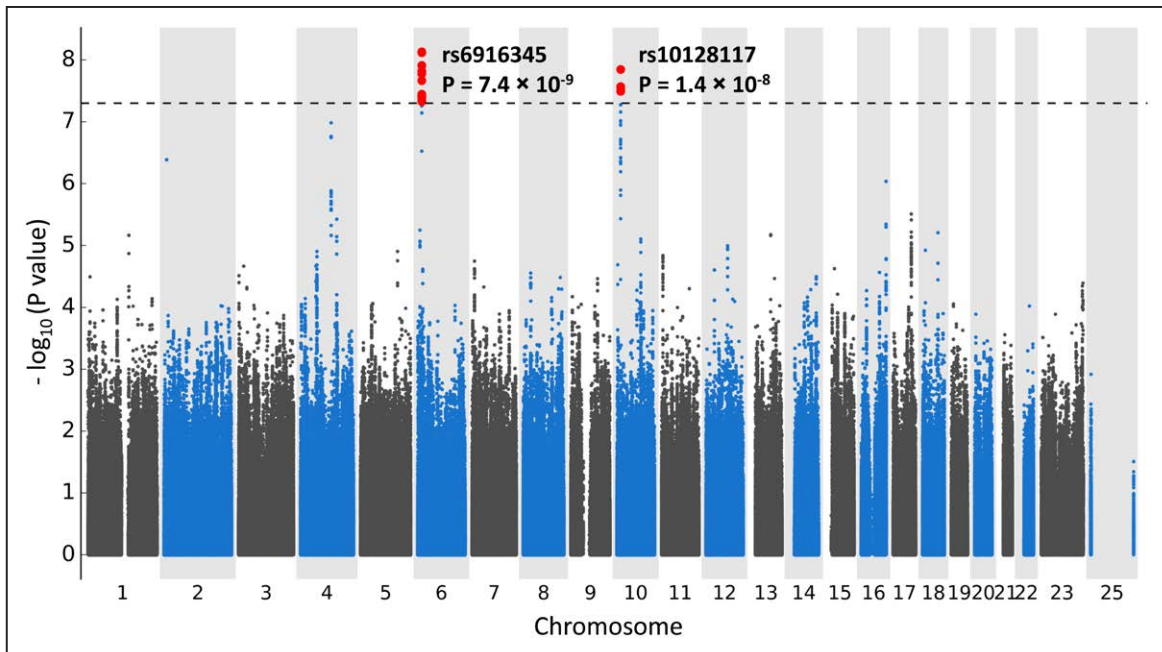
Figure. Manhattan plot for the genome-wide association study (GWAS) of gastrointestinal adverse events in COLCOT (Colchicine Cardiovascular Outcomes Trial) using Cox proportional hazards regression with 4 468 817 genetic variants of minor allele frequency ≥5% with 767 patients from the colchicine arm of COLCOT, controlling for age, sex, and principal components for genetic ancestry.

SEPHS1, with correlation between the gastrointestinal disorder risk allele and lower *SEPHS1* gene expression.

Despite the relatively small proportion of participants who consented to take part in the pharmacogenomic substudy of COLCOT (32%), we have found significant and credible association signals predictive of gastrointestinal events with colchicine use. There may be volunteer bias in the pharmacogenomic subgroup compared with the main trial population, and we observed a lower occurrence of deaths, possibly attributable to the fact that not all patients were recruited into the pharmacogenomic substudy at the baseline visit. This may have contributed to reducing the statistical power for detecting genetic association signals with the primary cardiovascular end point which included cardiovascular death. We also noted an overrepresentation of patients who reported suffering from gastrointestinal disorders during the course of the trial from both the colchicine and the placebo arm. This could be due to correlation between patient willingness

to participate and to share information on milder gastrointestinal adverse events. We do not expect that this observation had an impact on the pharmacogenomic findings with gastrointestinal events, as the 2 genetic association signals identified were strong and had strong interaction effects with colchicine treatment.

Because this study was a post hoc investigation, these results are considered as hypothesis-generating, and they will have to be replicated before using the information for clinical decision-making. Colchicine is used throughout the world for indications of gout, familial Mediterranean fever, pericarditis, and, since the COLCOT trial, for secondary cardiovascular prevention. There are other ongoing and planned clinical trials designed to assess the cardiovascular benefits of colchicine where it may be possible to replicate the findings if genetic material is collected. Reliance on observational studies and registries to conduct replication studies will become an option as the long-term use of colchicine for the

Table 2. Genetic Association Results of the Leading Genetic Variants Found to be Significantly Associated in the COLCOT Pharmacogenomic Study

End point	Leading variant	EA	EAF	COLCOT arm	No. of total	No. of events (%)	HR (95% CI)	P value	Interaction P value*
Gastrointestinal adverse events	rs6916345 chr6:14649353	A	0.50	Colchicine	751	183 (24.4)	1.89 (1.52–2.35)	7.41×10^{-9}	2.96×10^{-8}
				Placebo	741	168 (22.7)	1.30 (1.04–1.62)	0.02	2.96×10^{-8}
	rs74795203 chr10:13377992	G	0.06	Colchicine	764	187 (24.5)	2.51 (1.82–3.47)	2.70×10^{-8}	3.13×10^{-6}
				Placebo	751	173 (23.0)	0.71 (0.46–1.09)	0.11	3.13×10^{-6}

Reported results are for Cox proportional hazards regression adjusted for age, sex, and 10 principal components for genetic ancestry. Chr indicates chromosome; COLCOT, Colchicine Cardiovascular Outcomes Trial; EA, effect allele; EAF, effect allele frequency in COLCOT population; HR, hazard ratio; and N, number of patients.

*Interaction *P* value represents the association result for the variant by colchicine interaction term. Chromosomal position reporting according to GRCh37.

Table 3. Effect of Colchicine on Gastrointestinal Adverse Events Compared With Placebo Stratified by Genotype Groups

End point	Leading variant	Genotype	Group %	No. of total	No. with events	% events colchicine	% events placebo	HR (95% CI)	P value*
Gastrointestinal adverse events	rs6916345 chr6:14649353	GG	25%	383	80	13.7%	28.0%	0.43 (0.26–0.69)	5.45×10^{-4}
		AG	50%	742	167	23.2%	21.8%	1.08 (0.80–1.47)	0.61
		AA	25%	367	104	36.9%	18.6%	2.42 (1.57–3.72)	5.77×10^{-5}
	rs74795203 chr10:13377992	AA	87%	1319	299	21.6%	23.8%	0.88 (0.70–1.11)	0.28
		AG	12%	186	59	47.6%	19.2%	3.79 (2.13–6.73)	5.57×10^{-6}
		GG	1%	10	2	…	…	…	…
		AG+GG	13%	196	61	47.1%	18.9%	3.98 (2.24–7.07)	2.33×10^{-6}

Chr indicates chromosome; HR, hazard ratio; and N, number of patients.

*P value is comparing colchicine vs placebo by Cox proportional hazards regression adjusted for age, sex, and 10 principal components for genetic ancestry. Chromosomal position reporting according to GRCh37.

prevention of secondary cardiovascular disease gains in popularity in the coming years. Shorter-term use of colchicine for the treatment of gout could provide useful data for replication of the genetic variants associated with gastrointestinal events.

In conclusion, in the present pharmacogenomic study of the COLCOT trial, we have found genetic variants associated with gastrointestinal events in patients treated with colchicine. Those findings will benefit from replication to confirm our observations that some patients may have genetic predispositions to lower tolerability of treatment with colchicine.

ARTICLE INFORMATION

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Disclosures

Supplemental Materials

Online Methods and Results
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Online Figures I–V
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