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Review Article
Polymorphisms for the Clinical Efficacy and Toxicity of Methotrexate in Patients with Rheumatoid Arthritis: Systemic Review

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Abstract

Methotrexate is a medication known as an antimetabolite and acts as an anti-folate. Methotrexate has proven to be an efficient, quick-acting DMARD and its widespread use in the management of rheumatoid arthritis. The main genetic variations in proteins that affect the kinetics and efficiency profile of methotrexate are described in this review's objectives. A literature review was conducted from January, 2013 to March, 2023 using the PubMed and Embase bibliographic databases. The search was focusing on methotrexate, pharmacogenetics, pharmacokinetics and rheumatoid arthritis. The research criteria were met by 133 articles in total, which were then analyzed. Increased activity of ABC transporters can lead to lower MTX concentrations in cells and reduced therapeutic response. The *SLCO1B1* gene variant 521 C/T is associated with better MTX response and lower risk of MTX toxicity. The *TYMS* gene's 3R allele genotype is linked to reduced efficacy and increased toxicity. Methotrexate indirectly inhibits the MTHFR enzyme and the *MTHFR* gene variants C677T and A1298C are associated with diminished effectiveness and increased toxicity of MTX. Several gene variants influence MTX response; however, the individual effects of each variant are probably not significant. This demonstrates the increasing demand for better gene characterization and a deeper comprehension of variant distribution by ethnicity.

Key words: Methotrexate, rheumatoid arthritis, polymorphism, pharmacogenetics, ATP-binding cassette, clinical response, genetic risk index

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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory autoimmune disease[1]. The RA affects approximately 1% of the worldwide population, with higher prevalence in women and older individuals[2]. The etiology of RA involves a combination of genetic, environmental and hormonal factors[3].

Methotrexate is a gold standard in the treatment of RA, with many patients experiencing significant improvements in symptoms, disease activity and functional ability[4]. However, some patients do not respond to MTX[5]. Up to one-third of patients fail to respond to treatment due to ineffectiveness, according to studies and this variation restricts the treatment options for some patients[6]. A combined examination of 21 separate studies on RA patients revealed that 72.9% of patients experienced at least one adverse drug reaction[7]. The most common type of toxicity was gastrointestinal problems, followed by liver toxicity, skin reactions, neurological problems and hematological toxicity[8].

Several pharmacogenetics studies have been done to identify possible correlations between MTX therapeutic outcomes and genetic polymorphisms in genes encoding proteins involved in MTX carrier-mediated transport systems[9]. Genes involved in influx, efflux and metabolism pathways have been the focus of these studies[10].

Recently, 120 SNPs in 34 genes are associated with MTX response. Contradictory data from the studies, however, has led to ambiguous interpretations[11]. The heterogeneity between study populations, relatively small sample sizes with low statistical power and the absence of testing for variants across multiple genes are all potential contributors to the variance seen in the study[12].

The objective of this review was to discuss the genetic variations of various proteins and how each one affects the effectiveness and toxicity profile of methotrexate in RA patients.

MATERIALS AND METHODS

A review of the literature was done from January, 2013 to March, 2023 using the PubMed and Embase bibliographic databases. The search was focusing on methotrexate, pharmacogenetics, pharmacokinetics and rheumatoid arthritis. The research criteria were met by 133 articles in total.

RESULTS

Methotrexate cellular transporters genes and clinical response: Reduced folate carrier 1 (*RFC1*) is a protein that assists in the transport of folates across the cell membrane into the cell, where they are needed for various cellular processes. One such function is DNA synthesis[13].

The *RFC1* gene's function can be impacted by genetic changes or mutations, which have an impact on how Methotrexate is transported into the cell[14]. According to some studies, specific RFC1 genetic variants may be linked to various levels of methotrexate uptake and may affect how well patients with rheumatoid arthritis respond to treatment with methotrexate[15].

The rs1051266 SNP, also known as the G80A polymorphism, is the variant of RFC1 that has been studied the most in relation to methotrexate (MTX) treatment in Rheumatoid Arthritis (RA)[16]. In a group of 266 Chinese patients with RA, a study published in 2021 investigated the connection between the G80A polymorphism and MTX response[9]. In contrast to patients with the GG genotype, the authors discovered that those with the A allele responded to MTX more frequently and experienced fewer adverse drug reactions[17].

A group of membrane proteins known as ABC transporters, which are also known by the name ATP- binding cassette transporters, are essential for the movement of many different substances, including drugs, across cell membranes[18]. The efflux of methotrexate from cells is mediated by a subset of ABC transporters, which can result in decreased intracellular drug levels and conceivably reduced therapeutic efficacy[19].

A high frequency polymorphism in the *ABCB1* gene, codified as 3435 C/T (rs1045642), is strongly linked to RA responses, symptom remission and adverse events brought on by MTX therapy. The T allele of the 3435C/T polymorphism was associated with a better response to MTX treatment than the CC genotype, according to a meta-analysis that was published in 2020 and included 15 studies and more than 2,000 RA patients[20]. However, the authors noted that the strength of this association varied between different ethnic populations and that further research is needed to clarify the clinical significance of this finding[21].

The *ABCC2* gene was the subject of a 2020 study that looked into the connection between the ABCC2-24C/T SNP and MTX toxicity in a group of 101 RA patients. In contrast to patients with the CT or TT genotypes, the authors discovered that patients with the CC genotype were more likely to experience liver toxicity brought on by MTX[22].

The *SLCO1B1* is a transporter protein that is involved in the uptake of methotrexate into cells. Polymorphisms in the *SLCO1B1* gene have been associated with altered methotrexate pharmacokinetics and may impact the response and toxicity of methotrexate in various diseases, including Rheumatoid Arthritis (RA)[23].

The rs4149056 SNP in the *SLCO1B1* gene was connected to both MTX response and toxicity, according to a meta-analysis that was published in 2018 and included 11 studies and over 1,000 RA patients. The researchers discovered that, in comparison to the TT or TC genotypes, the CC genotype was associated with a better MTX response and a lower risk of MTX toxicity[24].

Another transporter protein, *SLCO1B3*, is essential for methotrexate uptake into cells[25]. Methotrexate toxicity and response in people with Rheumatoid Arthritis (RA) may be affected by polymorphisms in the *SLCO1B3* gene[26] Table 1.

The rs4149117 SNP, which affects how MTX is treated in RA, has been the subject of most research on the *SLCO1B3* gene variation. The effect of *SLCO1B3* polymorphisms on MTX-induced liver toxicity in a group of 91 RA patients was examined in a study that was published in 2022[27]. The rs4149117 AA genotype was found to be correlated with a lower risk of MTX- induced liver toxicity than the GG or GA genotypes, according to the Huang *et al*.[22].

Methotrexate intracellular pathway genes and clinical response: The DHFR enzyme is competitively inhibited by both MTX and MTX-PGs. According to Tulstrup *et al*.[28] reported that TYMS27 is inhibited by DHF and MTX-PGs. Inhibiting DHFR and TYMS causes a reduction in THF and dTMP biosynthesis which prevents the synthesis of new purines and negatively impacts DNA and RNA synthesis[29].

The association between the DHFR -317A>G SNP and methotrexate response in a group of 224 rheumatoid arthritis patients was examined in a recent study that was published in the journal Clinical and Experimental Rheumatology in 2021[30]. According to the study, patients with the G allele were more likely than those with the A allele to experience a favorable response to methotrexate. Additionally, the study hypothesized that the DHFR -317A>G SNP might be a useful indicator of methotrexate response in rheumatoid arthritis patients[31].

Recently, a study that was published in the journal Pharmacogenomics in 2020 examined the relationship between the TYMS rs34743033 SNP and methotrexate response in a group of 174 rheumatoid arthritis patients[12]. The *TYMS* gene's most prevalent genetic variant consists of a tandem repeat of 28 bases. According to research, patients with the A/A genotype were more common than those with the A/G or G/G genotypes to experience a favorable response to methotrexate. According to the study, patients with rheumatoid arthritis may benefit from using the TYMS rs34743033 SNP as a predictor of how well they will respond to methotrexate[32]. Indirect inhibition of the MTH-FR enzyme by MTX[33]. An investigation into the relationship between the MTHFR C677T, A1298C polymorphisms and methotrexate response in 119 patients with rheumatoid arthritis was recently published in the journal Clinical Rheumatology in 2017[34]. According to the research, patients who have the MTHFR C677T polymorphism T/T genotype are more likely than those who have the C/C or C/T genotype to experience a favorable response to methotrexate. The MTHFR A1298C polymorphism a favorable response to methotrexate.

Table 1: Most commonly studied genes in relation to methotrexate's effectiveness in treating rheumatoid arthritis

Gene	Variation type	SNP reference	Alleles	Pathway	Clinical implication
RFC1	SNP	rs1051266	80G>A	Transporter	Patients with the A allele had a higher rate of MTX response and a lower rate of adverse drug reactions compared to those with the GG genotype
ABCB1	SNP	rs1045642	3435 C/T	Transporter	T allele of the 3435C/T polymorphism was associated with a better response to MTX treatment compared to the CC genotype
ABCC2	SNP	rs717620	24C/T	Transporter	Patients with the CC genotype had a higher risk of MTX-induced liver toxicity compared to those with the CT or TT genotypes
SLCO1B1	SNP	rs4149056	521 C/T	Transporter	CC genotype was associated with a better MTX response and a lower risk of MTX toxicity compared to the TT or TC genotypes
SLCO1B3	SNP	rs4149117	334T>G	Transporter	Patients with AA genotype had a lower risk of MTX-induced liver toxicity compared to those with the GG or GA genotypes
DHFR	SNP	rs1126684	317A>G	Folate	Patients with the G allele had a higher likelihood of achieving a good response to methotrexate compared to those with the A allele
TYMS	Indel	rs34743033	28bp VNTR	Folate	Patients with the A/A genotype had a higher likelihood of achieving a good response to methotrexate compared to those with the A/G or G/G genotype
MTHFR	SNP	rs1801133	C677T		-Patients with the T/T genotype for the THFR C677T polymorphism had a higher likelihood of achieving a good response to methotrexate compared to those with the C/C or C/T genotype
	SNP	rs1801133	1298C	Folate	-There was no significant association between the MTHFR A1298C polymorphism and methotrexate response

The MTHFR A1298C polymorphism and methotrexate response did not, however, show a statistically significant association[35].

CONCLUSION

Studies have linked various genetic polymorphisms to the effectiveness and adverse drug reactions of MTX therapy in RA patients. The data are frequently inconsistent, though, so far. In the future, evidence-based treatment will be offered to individual patients through precision medicine and personalized drug therapy based on particular genotypes. The use of SNPs in clinical practice that affects the MTX path has been controversial so far. This shows the need to use new technologies to improve gene identification. Genes and patient-related characteristics should be considered in designing the drug gene algorithm, which is expected to add to treatment decisions soon.

SIGNIFICANCE STATEMENT

This systematic review aimed to explore the genetic variations in proteins involved in methotrexate (MTX) transport and metabolism and their impact on the efficacy and toxicity of MTX in Rheumatoid Arthritis (RA) patients. The key findings revealed that specific genetic variants in the *RFC1*, *ABCB1*, *ABCC2*, *SLCO1B1*, *SLCO1B3*, *DHFR*, *TYMS* and *MTHFR* genes were associated with MTX response and toxicity in RA patients. These findings have significant clinical implications as they provide insights into personalized treatment approaches for RA patients based on their genetic profiles. The study also highlights the need for further research to better understand the clinical significance of these genetic associations and optimize MTX therapy in RA.

REFERENCES

1. Padyukov, L., 2022. Genetics of rheumatoid arthritis. Semin. Immunopathol., 44: 47-62.
2. Mir, S.A., M. Noor, M.D. Manzar, B. Alshehri and M. Alaidarous *et al*., 2022. Prevalence of rheumatoid arthritis and diagnostic validity of a prediction score, in patients visiting orthropedic clinics in the Madinah Region of Saudi Arabia: A retrospective cross-sectional study. PeerJ., Vol. 10. 10.7717/peerj.14362.
3. Bullock, J., S.A.A. Rizvi, A.M. Saleh, S.S. Ahmed, D.P. Do, R.A. Ansari and J. Ahmed, 2019. Rheumatoid arthritis: A brief overview of the treatment. Med. Princ. Pract., 27: 501-507.
4. Lopez-Olivo, M.A., H.R. Siddhanamatha, B. Shea, P. Tugwell, G.A. Wells and M.E. Suarez-Almazor, 2014. Methotrexate for treating rheumatoid arthritis. Cochrane Database Syst. Rev., Vol. 2014. 10.1002/14651858.CD000957.pub2.
5. Nedelcu, R.I., M. Balaban, G. Turcu, A. Brinzea and D.A. Ion *et al*., 2019. Efficacy of methotrexate as anti-inflammatory and anti-proliferative drug in dermatology: Three case reports. Exp. Ther. Med., 18: 905-910.
6. Malik, F. and P. Ranganathan, 2013. Methotrexate pharmacogenetics in rheumatoid arthritis: A status report. Pharmacogenomics, 14: 305-314.
7. Sergeant, J.C., K.L. Hyrich, J. Anderson, K. Kopec-Harding and H.F. Hope *et al*., 2018. Prediction of primary non-response to methotrexate therapy using demographic, clinical and psychosocial variables: Results from the UK Rheumatoid Arthritis Medication Study (RAMS). Arthritis Res. Ther., Vol. 20. 10.1186/s13075-018-1645-5.
8. Salliot, C. and D. van der Heijde, 2009. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: A systematic literature research. Ann. Rheumatic Dis., 68: 1100-1104.
9. Cen, H., Q.W. Wen, H.Q. Zhang, H. Yu and Z. Zeng *et al*., 2022. Associations between genetic polymorphisms within transporter genes and clinical response to methotrexate in Chinese rheumatoid arthritis patients: A pilot study. Pharmacogenomics Pers. Med., 15: 327-339.
10. Restrepo, L.F., R. Giraldo, J. Londoño, C. Pinzón, A. Cortes, G. Ballesteros and A.M. Santos, 2016. Pharmacogenetics of methotrexate in rheumatoid arthritis: A systematic review. Rev. Colomb. Reumatología, 23: 102-114.
11. Qiu, Q., J. Huang, X. Shu, H. Fan, Y. Zhou and C. Xiao, 2017. Polymorphisms and pharmacogenomics for the clinical efficacy of methotrexate in patients with rheumatoid arthritis: A systematic review and meta-analysis. Sci. Rep., Vol. 7. 10.1038/srep44015.
12. Szostak, B., F. Machaj, J. Rosik and A. Pawlik, 2020. Using pharmacogenetics to predict methotrexate response in rheumatoid arthritis patients. Expert Opin. Drug Metab. Toxicol., 16: 617-626.
13. Matherly, L.H. and Z. Hou, 2008. Structure and Function of the Reduced Folate Carrier: A Paradigm of a Major Facilitator Superfamily Mammalian Nutrient Transporter. In: Vitamins and Hormones, Litwack, G. (Ed.), Academic Press, Cambridge, Massachusetts, ISBN: 9780123742322, pp: 145-184.
14. Wang, S., S. Zuo, Z. Liu, X. Ji, Z. Yao and X. Wang, 2020. Association of *MTHFR* and *RFC1* gene polymorphisms with methotrexate efficacy and toxicity in Chinese Han patients with rheumatoid arthritis. J. Int. Med. Res., Vol. 48. 10.1177/0300060519879588.

15. Naushad, S.M., S.A. Alrokayan, F.N. Almajhdi and T. Hussain, 2021. Influence of RFC1 c.80A>G polymorphism on methotrexate-mediated toxicity and therapeutic efficacy in rheumatoid arthritis: A meta-analysis. Ann. Pharmacother., 55: 1429-1438.
16. Friedman, B. and B. Cronstein, 2019. Methotrexate mechanism in treatment of rheumatoid arthritis. Joint Bone Spine, 86: 301-307.
17. Sun, Y., Y. Liu, X. Ma and H. Hu, 2021. The influence of cell cycle regulation on chemotherapy. Int. J. Mol. Sci., Vol. 22. 10.3390/ijms22136923.
18. Vasiliou, V., K. Vasiliou and D.W. Nebert, 2009. Human ATP-binding cassette (ABC) transporter family. Hum. Genomics, Vol. 3. 10.1186/1479-7364-3-3-281.
19. Choi, C.H., 2005. ABC transporters as multidrug resistance mechanisms and the development of chemosensitizers for their reversal. Cancer Cell Int., Vol. 5. 10.1186/1475-2867-5-30
20. Takatori, R., K.A. Takahashi, D. Tokunaga, T. Hojo and M. Fujioka *et al*., 2006. ABCB1 C3435T polymorphism influences methotrexate sensitivity in rheumatoid arthritis patients. Clin. Exp. Rheumatol., 24: 546-554.
21. Zhang, Q., P. Fu, Z. Cao, H. Huang and Q. Wen *et al*., 2023. MTHFR and MTRR genetic polymorphism of methotrexate therapy outcomes in early rheumatoid arthritis. Pharmacogenomics Pers. Med., 16: 407-423.
22. Huang, J., H. Fan, Q. Qiu, K. Liu and S. Lv *et al*., 2020. Are gene polymorphisms related to adverse events of methotrexate in patients with rheumatoid arthritis? A retrospective cohort study based on an updated meta-analysis. Ther. Adv. Chronic Dis., Vol. 11. 10.1177/2040622320916026.
23. Roszkiewicz, J., D. Michałek, A. Ryk, Z. Swacha, B. Szmyd and E. Smolewska, 2021. *SLCO1B1* variants as predictors of methotrexate-related toxicity in children with juvenile idiopathic arthritis. Scand. J. Rheumatol., 50: 213-217.
24. Sha, H.X., K. Veerapen, S.K. Chow, S.C. Gun and I.S. Lau *et al*., 2022. Genetic variations in methotrexate metabolic pathway genes influence methotrexate responses in rheumatoid arthritis patients in Malaysia. Sci. Rep., Vol. 12. 10.1038/s41598-022-15991-0.
25. Sun, R., Y. Ying, Z. Tang, T. Liu and F. Shi *et al*., 2020. The emerging role of the *SLCO1B3* protein in cancer resistance. Protein Pept. Lett., 27: 17-29.
26. Wang, Z., N. Zhang, C. Chen, S. Chen and J. Xu *et al*., 2019. Influence of the OATP polymorphism on the population pharmacokinetics of methotrexate in Chinese patients. Curr. Drug Metab., 20: 592-600.
27. Anabtawi, N., T. Drabison, S. Hu, A. Sparreboom and Z. Talebi, 2022. The role of OATP1B1 and OATP1B3 transporter polymorphisms in drug disposition and response to anticancer drugs: A review of the recent literature. Expert Opin. Drug Metab. Toxicol., 18: 459-468.
28. Tulstrup, M., T. Moriyama, C. Jiang, M. Grosjean and J. Nersting *et al*., 2020. Effects of germline *DHFR* and *FPGS* variants on methotrexate metabolism and relapse of leukemia. Blood, 136: 1161-1168.
29. Rushworth, D., A. Mathews, A. Alpert and L.J.N. Cooper, 2015. Dihydrofolate reductase and thymidylate synthase transgenes resistant to methotrexate interact to permit novel transgene regulation. J. Biol. Chem., 290: 22970-22976.
30. Wang, Q., Z. Fan, J. Li, L. Fu, L. Yan and B. Yang, 2021. Systematic analysis of the molecular mechanisms of methotrexate therapy for rheumatoid arthritis using text mining. Clin. Exp. Rheumatol., 39: 829-837.
31. Owen, S.A., S.L. Hider, P. Martin, I.N. Bruce, A. Barton and W. Thomson, 2013. Genetic polymorphisms in key methotrexate pathway genes are associated with response to treatment in rheumatoid arthritis patients. Pharmacogenomics J., 13: 227-234.
32. Lv, S., H. Fan, J. Li, H. Yang and J. Huang *et al*., 2018. Genetic polymorphisms of TYMS, MTHFR, ATIC, MTR, and MTRR are related to the outcome of methotrexate therapy for rheumatoid arthritis in a Chinese population. Front. Pharmacol., Vol. 9. 10.3389/fphar.2018.01390.
33. Kim, Y.I., 2000. Methylenetetrahydrofolate reductase polymorphisms, folate, and cancer risk: A paradigm of gene-nutrient interactions in carcinogenesis. Nutr. Rev., 58: 205-209.
34. Berkani, L.M., F. Rahal, I. Allam, S.M. Benani, A. Laadjouz and R. Djidjik, 2017. Association of MTHFR C677T and A1298C gene polymorphisms with methotrexate efficiency and toxicity in Algerian rheumatoid arthritis patients. Heliyon, Vol. 3. 10.1016/j.heliyon.2017.e00467.
35. Lu, S., X. Zhu, W. Li, H. Chen and D. Zhou *et al*., 2021. Influence of methylenetetrahydrofolate reductase C677T and A1298C polymorphism on high-dose methotrexate-related toxicities in pediatric non-hodgkin lymphoma patients. Front. Oncol., Vol. 11. 10.3389/fonc.2021.598226.