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Review

Association of MTHF 677TT with adverse drug reactions and RFC G80A with non-response and adverse drug reactions in methotrexate therapy

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ABSTRACT

Being an anti-metabolite and anti-inflammatory agent, Methotrexate, a folate analogue, is indicated for a wide spectrum of diseases including moderate to severe chronic inflammatory disorders like psoriasis and rheumatoid arthritis and malignant diseases such as childhood acute lymphoblastic leukaemia and choriocarcinoma. The outcome of Methotrexate treatment varies. Though up to 50% of patients with inflammatory disorders show a favourable response; one third discontinues Methotrexate due to adverse drug reactions or non-response. Such diversity suggests an inter-individual variation due to multiple factors including genetic polymorphisms. This review was conducted to identify genotypes predictive of Methotrexate treatment outcome. More than 15 alleles located in eight genes were explored by over 25 studies. Among those, we identified MTHFrs1801133TT genotype to be likely associated with adverse drug reactions and RFCrs1051266A allele to be associated with both, non-response and adverse drug reactions. We recommend the conduction of meta-analysis to verify these findings.

1. Introduction

Methotrexate, a folate analogue, is widely used in systemic inflammatory disorders like psoriasis, moderate to severe active rheumatoid arthritis and Crohn's disease. Being an anti-metabolite, Methotrexate is also indicated as a maintenance therapy for childhood acute lymphoblastic leukaemia (ALL),[1] choriocarcinoma, non-Hodgkin's lymphoma and other solid tumours; a central nervous system prophylactic drug from childhood ALL and lymphomas; and a therapy for established meningeal cancer or lymphoma [1].

Among those receiving Methotrexate as an anti-inflammatory agent, more than 50% continue the treatment course for over three years [2,3], 35–50% exhibits a good response, yet up to one third of patients discontinue Methotrexate [4–6] due to adverse drug reactions (ADRs)[2] rather than lack of efficacy [7,8]. Reported ADRs are complicated pregnancy in 40% of women on a weekly low-dose of Methotrexate [9]; haematological toxicities like thrombocytopaenia in 22% [10] and pancytopenia in 1.4% [11]; pulmonary toxicity in up to 11.6% [12]; and serious hepatotoxicity in 0.01% of patients [13]. In contrast, one third of low risk patients with persistent gestational trophoblastic disease on Methotrexate change their chemotherapeutic agent due to poor response rather than ADRs [14]. Such variations observed in Methotrexate treatment outcome suggest considerable underlying inter-individual differences including variations of renal function where dose adjustment is essential and genetic polymorphisms.

Hence, multiple articles reviewed the association between gene polymorphism and Methotrexate response and toxicity. For instance, Ranganathan [15–19] has looked into the impact of gene polymorphism on Methotrexate-rheumatoid arthritis interaction; and likewise did Restrepo and colleagues [20] and Qiu and colleagues [21]. On the other hands, Kremer [22] had a broader scope and looked into the impact of pharmacogenetics on Methotrexate response and toxicity in variable diseases including leukaemia, rheumatoid arthritis and other unspecified diseases; likewise did Hider and colleagues [23]. The focus of previously published work was either too narrow (a single disease) or too broad (combination of irrelevant multiple diseases).

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[1] Acute lymphoblastic leukaemia (ALL).
[2] Adverse drug reactions (ADRs).

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This review is based on the current knowledge of the pharmacodynamics and pharmacokinetics of Methotrexate. The impact of genetic polymorphisms on Methotrexate treatment outcome is examined, aiming towards identifying a genotype(s) that can be utilized for the prediction of response or toxicity. As some diseases may share a common unique underlying pathophysiology, and hence their outcome is comparable, we looked into the two different effects of Methotrexate: anti-inflammatory and anti-metabolite; and accordingly combined and subsequently classified the reviewed articles based on this criteria, which makes this article different that previously published scientific work.

2. Methodology

EBSCOhost (Academic Search Complete, CINAHIL Plus with Full Text, eBook Clinical Collection, eBook Collection, Medline, Medline with Full Text, Psychology and Behavioural Sciences Collection and PsycInfo) and ScienceDirect were used to retrieve original articles based on clinical trials and contain Methotrexate and Polymorphism in their titles, regardless of the study design, disease of interest and ethnicity of subjects.

3. Methtrexate: pharmacodynamics and pharmacogenetics

3.1. Pharmacodynamics of methotrexate

Methotrexate polyglutamate acts, directly or indirectly, on different enzymes including the Dihydrofolate Reductase (DHFR),[3] the Thymidylate Synthase (TS),[4] and the 5-Aminoimidazole-4-Carboxamide Ribonucleotide Transformylase (ATIC)[5] as follows:

- It binds to the DHFR and inhibits the transformation of dihydrofolate to tetrahydrofolate, interfering with Methylenetetrahydrofolate Reductase (MTHFR)[6] and Methionine Synthase (MTR)[7] leading to Homocysteine accumulation, Methionine depletion and subsequently, DNA hypomethylation;
- It binds to the TS and inhibits the synthesis of deoxythymidine monophosphate needed for pyrimidine synthesis; and
- It inhibits ATIC, resulting in 5-Aminoimidazole-4-Carboxamide Ribonucleotide build-up, and elevation of extracellular adenosine which if bound to its receptors, it increases cyclic Adenosine Monophosphate, an inhibitor of pro-inflammatory cytokines.

Being a folate analogue that targets multiple enzymes, Methotrexate is capable of competitively and reversibly exerting anti-proliferative, anti-inflammatory and immunosuppressive effects [as reviewed by [24], as reviewed by [25]]. A summary of the pharmacodynamics of Methotrexate is illustrated in Fig. 1.

3.2. Pharmacogenetics of methotrexate targets

Considering the pharmacodynamics of Methotrexate, and as shown above, Methotrexate displays its anti-metabolite and anti-inflammatory effects through different pathways. For a better interpretation of genetic polymorphisms of Methotrexate targets, administration of Methotrexate in inflammatory disorders should be differentiated from malignancies, especially when drug response is studied.

3.2.1. Methotrexate as an anti-inflammatory agent

A total of 14 polymorphisms located on seven genes were investigated in 11 studies recruited patients with chronic inflammatory disorders. Table 1 summarizes the findings of these studies along with the function of each allele, where available.

Jekic et al. (2013) [36] assessed the efficacy and safety profile of Methotrexate in 184 patients with rheumatoid arthritis who were on Methotrexate as a monotherapy or in combination with other systemic therapies. Efficacy was assessed based to the European League against Rheumatism (EULAR)[8]-Disease Activity Score 28 (DAS28)[9] and accordingly, patients were classified into good, moderate or poor responders. Assessment of ADRs was clinical (pulmonary, dermatological or gastrointestinal symptoms), or based on laboratory investigations (hepatotoxicity or bone marrow suppression). Genotyping by polymerase chain reaction (PCR)[10]-restriction fragment length polymorphism (RFLP)[11] was done for TS, involved in folate metabolism and cell proliferation [37]; and Cyclin D1, a cell cycle regulator involved in the regulation of enzymes targeted by Methotrexate [38,39]. Investigated polymorphisms were TS tandem repeat number in the enhancer region of the gene which was linked to gene expression [40]; TS guanine-to-cytosine substitution in the repeats which were found to normalize TS expression level if it took place in the three repeats [40]; and Cyclin D1 rs603965, associated with alternative splicing, upregulation of Cyclin D1 and hence cancer and was proposed to increase sensitivity to Methotrexate [41–45]. Results showed that 9.2%, 70.1% and 20.7% were good, moderate and non-responders, respectively. Of those recruited, 26.1% experienced mild to moderate, and 2.7% had severe ADRs. Analysis revealed that neither efficacy nor safety profile were associated with these polymorphisms. Though enrolled patients were also on combined systemic therapies making it difficult to draw solid conclusions, these findings are consistent with (Borman et al., 2015) [35] and (Ghodke et al., 2008) [34], and in partial concordance with (Campalani et al., 2007) [27].

Borman et al. (2015) [35] investigated the effect of TS polymorphism on the safety profile in 64 patients with rheumatoid arthritis. Current or previous history of Methotrexate-related ADRs was retrieved. Genotyping for the number of repeats at the 5′untranslated region was done through PCR followed by polyacrylamide gel electrophoresis. Results revealed that among the recruited patients, 30 were on Methotrexate as a monotherapy. Yet, number of tandem repeats was not associated with risk of ADRs.

Campalani et al. (2007) [27] examined the impact of six polymorphisms: MTHFRrs1801133, MTHFRrs1801131, TS tandem repeats in the enhancer region, TS G > C substitution in the triple repeats, TS six base pair insertion/deletion and ATICrs2372536, on Methotrexate response and safety profile. Two-hundred and three patients with psoriasis on Methotrexate monotherapy were recruited and classified, at three months, as responders if subjective or objective (>75% of Psoriasis Activity and Severity Index) improvement was documented, non-responders if Methotrexate was discontinued due to lack of efficacy or if improvement in Psoriasis Activity and Severity Index was <50%, or otherwise intermediate responders if patients did not fulfil the aforementioned criteria. ADRs were classified into hepatotoxicity resulting in dose reduction or discontinuation; bone marrow toxicity resulting in dose reduction or discontinuation; or symptomatic neurological, gastrointestinal or dermatological side effects. Genotyping was done through PCR followed by electrophoresis. Results showed that

[3] Dihydrofolate Reductase (DHFR).
[4] Thymidylate Synthase (TS).
[5] 5-Aminoimidazole-4-Carboxamide Ribonucleotide Transformylase (ATIC).
[6] Methylenetetrahydrofolate Reductase (MTHFR).
[7] Methionine Synthase (MTR).
[8] European League against Rheumatism (EULAR).
[9] Disease Activity Score 28 (DAS28).
[10] Polymerase chain reaction (PCR).
[11] Restriction fragment length polymorphism (RFLP).

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