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Personalization of Treatment with Methotrexate in Rheumatoid Arthritis Patients

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Abstract

Personalized therapy is the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Methotrexate is antimetabolite approved for management of rheumatoid arthritis (RA). Personalization of treatment with methotrexate in RA patients has been studied. The most common non-synonymous variants studied were the C677T (Ala222Val) and A1298C (Glu429Ala). They were described for the Methylenetetrahydrofolate reductase gene and associated with a decreased enzymatic activity and an alteration of intracellular folate distribution. Identification and validation of polygenic determinants is essential to translate these discovered pharmacogenetic markers into widespread clinical practice with development of pre-treatment standardised genetic tests and molecular diagnostic commercial kits. Such diagnostic tools would lead to a better management of RA, might minimizing patient exposure to unnecessary medications and toxicities. Further studies addressing these key points are essential.

Introduction

Methotrexate (MTX) is a cell cycle specific (S phase) cytotoxic drug classified as antimetabolite. It has been in clinical use since 1984. It is a folate antimetabolite that inhibits DNA synthesis and irreversibly binds to dihydrofolate reductase (DHFR), inhibiting the formation of reduced folates, and thymidylate synthase, resulting in inhibition of purine and thymidylic acid synthesis. 1,2

The cytotoxicity of methotrexate results from three actions: inhibition of DHFR, inhibition of

thymidylate, and alteration of the transport of reduced folates. Inhibition of DHFR results in a deficiency of thymidylate and purines and therefore a decrease in DNA synthesis, repair and cellular replication. The affinity of DHFR to methotrexate is far greater than its affinity for folic acid or dihydrofolic acid, therefore large doses of folic acid given simultaneously will not reverse the effects of methotrexate. However, leucovorin calcium, a derivative of tetrahydrofolic acid, may block the effects of methotrexate if given shortly after the methotrexate since it does not require DHFR for activation. 1

Methotrexate approved for two major fields of indication: 1) the treatment of certain neoplastic diseases such as choriocarcinoma, acute lymphoblastic leukaemia (ALL), Burkitt's lymphoma and advanced stages of childhood lymphoma 2) severe psoriasis and rheumatoid arthritis. 3 It is available as oral and injection form that might be given as subcutaneous (SC), intramuscular (IM) and intravenous (IV) form. Moderate ($> 100 \text{ mg/m}^2$) to high-dose methotrexate ($>1000 \text{ mg/m}^2$) plus leucovorin rescue is routinely used therapeutically in cancer treatment. 1 While in case of rheumatoid arthritis it is known as a disease modifying anti-rheumatic drug (DMARD) because it not only decreases the pain and swelling of arthritis, but it also can decrease damage to joints and long term disability and slow the progression of arthritis over time. 4 The dose of MTX as DMARD ranges between 15-25mg/week and 10-15 mg/m^2 in Juvenile Idiopathic Arthritis (JIA).

Methotrexate is the most commonly used and the first line anti-rheumatic agent in the treatment of rheumatoid arthritis (RA). Since 1980s several investigators have demonstrated that the potential antirheumatic and anti-inflammatory properties of low dose MTX make it one of the most useful therapeutic agents. Even though the efficacy of MTX compared to other anti-inflammatory agents in management of RA, patients treated with MTX can experience various side effects. Around 30% of patients treated with MTX will experience treatment discontinuation due to various side effects. 3,4

Methotrexate Toxicity:

Methotrexate has the potential for serious toxicities. Toxic effects may be related in frequency and severity to dose or frequency of administration and duration of exposure but seen at all doses. Methotrexate side effects might be immediate onset (hours to days), early onset (days to weeks) or delayed onset (weeks to years). The most common adverse effects are stomatitis, myelosuppression and gastrointestinal effects such as nausea and vomiting. Other toxicities include nephrotoxicity, hepatotoxicity, pulmonary toxicity, hyperuricemia, and neurologic complications. Because toxicities can occur at any time during therapy, it is necessary to follow patients closely. Most adverse reactions are reversible if detected early. 1
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Personalized Medicine in RA Patients

Personalized medicine refers to the tailoring of medical treatment to the individual

characteristics of each patient. It is the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not. 8, 9

Recent rapid advances in genomics and molecular biology are beginning to reveal a large number of possible new, genome-related, molecular markers for the presence of disease, susceptibility to disease, or differential response to treatment. Such markers can serve as the basis of new genomics-based diagnostic tests for identifying and/or confirming disease, assessing an individual's risk of disease, identifying patients who will benefit from particular interventions, or tailoring dosing regimens to individual variations in metabolic response. These new diagnostics can also pave the way for development of new therapeutics specifically targeted at the physiological consequences of the genetic defect(s) associated with a patient's disease. 8,9

The current high level of interest in personalized medicine from a policy perspective is attributable not only to the promise of improved patient care and disease prevention, but also to the potential for personalized medicine to positively impact two other important trends – the increasing cost of health care and the decreasing rate of new medical product development. The ability to distinguish in advance those patients who will benefit from a given treatment and those who are likely to suffer important adverse effects could result in meaningful cost savings for the overall health care system. Moreover, the ability to stratify patients by disease susceptibility or likely response to treatment could also reduce the size, duration, and cost of clinical trials, thus facilitating the development of new treatments, diagnostics, and prevention strategies. 8,9

Rheumatoid arthritis is a disease showing considerable heterogeneity in all its aspects, including response to therapy and toxicities. The variability in treatment response between individuals has given rise to an extensive search for prognostic markers in order to personalize and optimize therapy. Accordingly, pharmacogenetics, the study of genetic variation underlying differential responses to drugs, is a rapidly progressing field in rheumatology that might enable personalized therapy in rheumatic disease. 10

Pharmacogenetics represents an exciting, new promising tool for the individualisation of therapy. Several genetic polymorphisms and haplotypes have been considered in an attempt to optimise therapy with specific drugs but, up to now, their clinical applications remain limited. 5,10-Methylenetetrahydrofolate reductase (MTHFR), a key enzyme of one-carbon metabolism, catalyses the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. Two common non-synonymous variants, the C677T (Ala222Val) and A1298C (Glu429Ala), were described for the MTHFR gene and associated with a decreased enzymatic activity and an alteration of intracellular folate distribution. Other MTHFR polymorphisms with marginal impact on enzymatic activity were also reported. Several published clinical studies have investigated the potential predictive role of C677T and A1298C genetic variants on toxicity and efficacy of antifolate and fluoropyrimidine agents, such as methotrexate (MTX), 5-fluorouracil (5-FU) and raltitrexed. Many of these studies show significant associations with MTHFR variants, but others report neither association nor

opposite results. A significant interaction between MTHFR polymorphisms and nutrient/environmental factors (i.e. folate status) as well as the ethnicity was reported. A haplotype approach and the combined analysis of multiple folate pathway gene variants seem to provide a more comprehensive strategy compared to single-locus investigations. The aim of this review is to critically analyse the available data on the importance of MTHFR polymorphisms in modulating the clinical outcome of antifolate and fluoropyrimidine therapies. 11, 12, 13

Hepatotoxicity induced by long time use of low dose MTX for treatment of RA is one of the most feared side effects. It is associated with an increase of hepatic transaminase enzymes such as ALT and AST in some patients. At present histological evaluation of liver biopsies is the gold standard to diagnose MTX induced liver damage. These procedures are invasive and uncomfortable for patients and have serious complications as hemorrhage and pneumothorax. Therefore availability of non-invasive methods for detecting and monitoring liver fibrosis are highly desirable. Davila-Fajardo et al conducted literature review on candidate genetic markers for the risk of MTX induced hepatotoxicity. The MTHFR gene is the best studied gene with respect to MTX metabolism. At least 82 polymorphisms have been described. Functional data are available for only a few. The single nucleotide polymorphism (SNPs) found to be related to MTX hepatotoxicity are C677T and A1298C. 14

R Caliz conducted a study to assess the involvement of the C677T and A1298C polymorphism in the MTHFR gene in the toxicity of MTX in a Spanish RA population. The results demonstrated that the C677T polymorphism is significantly associated with increased MTX toxicity, while the A1298C polymorphism was not associated with increased MTX toxicity. The most prevalent adverse effects were gastric toxicity and hepatic toxicity. 15

Fisher et al conducted a meta-analysis of published studies including 1400 patients for association of the C677T polymorphism and over 660 for the A1298C variant. He demonstrates that C677T variant was significantly related to toxicity of MTX, including hepatotoxicity. 16

Conclusion

After identification and validation of polygenic determinants it is essential to translate these discovered pharmacogenetic markers into widespread clinical practice with development of pre-treatment standardised genetic tests and molecular diagnostic commercial kits. Such diagnostic tools would lead to a better management of RA. This will enhance tailoring therapy individually, minimizing patient exposure to unnecessary medications and toxicities minimize unjustified cost and probably improve patient adherence to MTX due to absence of un-tolerated toxicities. This might lead to better clinical treatment outcome. Further studies addressing these key points are essential.

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