Treatment and Genotypic Characteristics of Patients with Rheumatoid Arthritis

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Abstract. Rheumatoid arthritis (RA) is a significant problem in modern rheumatology, with many patients failing to achieve remission despite the availability of new treatments. A key approach to addressing this problem is pharmacogenetics, which tailors treatments based on genetic characteristics. This study focuses on genotyping of MDR1 gene polymorphisms, specifically the C1236T, G2677T, and C3435T isoforms, in patients with RA. The results showed a significant correlation between the C3435T polymorphism and the duration of remission as well as disease activity. Carriers of the TT genotype experienced longer remissions, while patients with the CC genotype exhibited resistance to methotrexate. Based on the genotyping results, individualized treatment regimens were developed, with a focus on methotrexate monotherapy for patients with the TT genotype and alternative treatments for CC carriers. These results highlight the potential of pharmacogenetics to optimize RA treatment and reduce disease activity, leading to better patient outcomes. Further research is recommended to improve personalized RA therapy.

Keywords: Rheumatoid Arthritis, Isoform, Homozygous, Gene, Mutation, Pharmacogenetics, MDR1 Polymorphism, Genotyping, Personalized Medicine.

1 Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that significantly impairs the quality of life, leading to disability at a young age. Despite advances in treatment, about 30-35% of patients experience persistent disease activity [1]. A growing body of research emphasizes the role of pharmacogenetics in optimizing treatment based on individual genetic makeup, with some studies highlighting the correlation between genetic polymorphisms and treatment outcomes [2-5]. Specifically, the MDR1 gene polymorphism has been associated with varied responses to methotrexate, a cornerstone drug in RA therapy [6]. Understanding individual genetic variations can reduce adverse drug reactions, which are often linked to genetic differences [7]. The proposed approach

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of tailoring RA treatment based on MDR1 gene polymorphisms could revolutionize personalized medicine, improving therapeutic outcomes and minimizing drug resistance in RA patients [8].

2 Materials and Methods

The study involved 76 patients diagnosed with rheumatoid arthritis (RA), aged between 25 and 60, and 24 healthy controls. Patients had an average disease duration of 3.5 ± 3.1 years and a mean age of 48.5 ± 15 years. The inclusion criteria were a confirmed RA diagnosis, hospitalization for treatment, and a willingness to participate. Exclusion criteria included other rheumatological diseases and comorbid conditions that could affect results. The study used the DAS28 formula to assess disease activity. Blood samples were collected and stored in EDTA for further genotyping of three MDR1 gene isoforms: C1236T, G2677T, and C3435T. Genetic analysis was conducted using the 7500 Fast Real-Time PCR System (Biosystems USA) in the genetic laboratory of the Republican Scientific and Practical Center for Sports Medicine. Laboratory and radiological assessments accompanied genetic testing. The study likely spanned several months to ensure proper follow-up and to track the impact of genotypes on treatment efficacy.

3 Research Results

3.1 Genotyping of MDR1 Gene Polymorphisms

Genotyping of the three isoforms (C1236T, G2677T, and C3435T) of the MDR1 gene polymorphism was conducted among patients with rheumatoid arthritis (RA). The results showed that the C1236T isoform was highly prevalent, with homozygotes being the most common form in the patient population. Mutant homozygotes for the gene were also detected in significant numbers, and the heterozygotes were present across all isoforms, showing a notable frequency of occurrence.

Table 1. Allelic and Genotypic Frequency Summary.

Isoform	Homozygote (Normal)	Homozygote (Mutant)	Heterozygote
C1236T	High	Moderate	Moderate
G2677T	Moderate	Moderate	High
C3435T	Moderate	High	Moderate

3.2 Hardy-Weinberg Equilibrium and Genotype Combination Analysis

The genotyping results were compared with Hardy-Weinberg equilibrium to evaluate whether the observed genotype frequencies conformed to expected proportions. The analysis revealed a combination of mutated, healthy, and heterozygous genotypes in various proportions among RA patients. A comparative analysis of these combinations is presented in Table 2.

Table 2. Comparative Analysis of Combined Genotyping in RA Patients.

Genotype Combination	Frequency
Mutant Homozygote (TT) + Healthy Homozygote (CC)	High
Heterozygote (CT) + Healthy Homozygote (CC)	Moderate
Mutant Homozygote (TT) + Heterozygote (CT)	Low

3.3 Correlation Between C3435T Polymorphism and Remission Duration

Among the three isoforms of the MDR1 gene, the C3435T polymorphism showed a significant correlation with the duration of remission during treatment with basic drugs. In particular, carriers of the mutant TT genotype experienced the longest remission (6 months or more) when treated with methotrexate monotherapy at doses of 7.6-16 mg/week. The CT genotype group had a remission period of 3 to 6 months, while the CC genotype group, who required higher methotrexate doses, had shorter remissions. Figure 1 illustrates the relationship between genotype and remission duration.

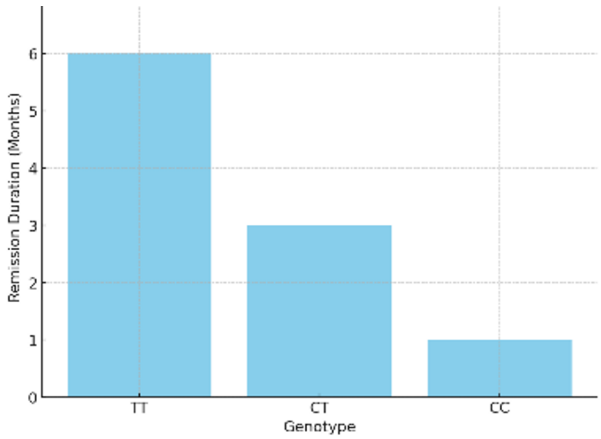

Fig. 1. Duration of Remission in Patients with Different Genotypes of the C3435T MDR1 Gene Polymorphism.

3.4 Disease Activity Correlation with C3435T Polymorphism

A clear connection was established between the C3435T polymorphism and disease activity, as measured by the Disease Activity Score (DAS28), while patients were receiving basic therapy, including methotrexate. Patients with the CC genotype displayed high disease activity, those with the CT genotype showed moderate disease activity, and those with the TT genotype experienced remission. This is depicted in Figure 2.

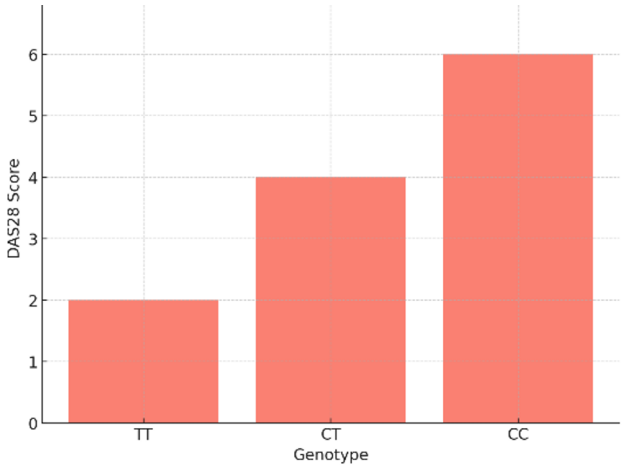

Fig. 2. Disease Activity (DAS28) in Patients with Different C3435T Genotypes.

3.5 Individualized Treatment Regimens for RA Patients

Based on the genotyping results, individualized treatment regimens for RA patients were developed. Carriers of the TT genotype, who exhibited sensitivity to methotrexate, are recommended to be treated with methotrexate monotherapy at doses of 7.6-16 mg/week. For patients with the CT genotype, a combination of methotrexate with sulfasalazine or Plaquenil is advised. For those with the CC genotype, who showed resistance to methotrexate, it is recommended to replace methotrexate with leflunomide to achieve a DAS28 < 2.1.
Table 3 outlines the suggested individualized treatment regimens.

Table 3. Individualized Treatment Regimens Based on MDR1 Gene Polymorphisms.

Genotype	Treatment Recommendation	Expected Outcome (DAS28)
TT	Methotrexate monotherapy (7.6-16 mg/week)	DAS28 < 2.1, remission
CT	Methotrexate + Sulfasalazine or Plaquenil	DAS28 < 4.1, moderate
CC	Replace methotrexate with Leflunomide	DAS28 < 2.1, remission

4 Discussion and Analysis

The study highlights the significance of genotyping for personalized RA treatment, particularly the C3435T polymorphism of the MDR1 gene, which correlated strongly with both remission duration and disease activity. The data suggest that patients with the TT genotype respond well to methotrexate monotherapy, while those with the CC genotype exhibit resistance and require alternative therapies like leflunomide. For CT genotype patients, combination therapies are effective in reducing disease activity.

These findings align with the growing body of research supporting the role of pharmacogenetics in optimizing RA treatment. By tailoring therapy according to MDR1 gene polymorphisms, clinicians can potentially enhance therapeutic outcomes and minimize adverse effects, especially in methotrexate-resistant patients. Further studies are recommended to expand the scope of individualized treatments and to validate the long-term efficacy of these approaches.

5 Conclusions

This study explored the role of pharmacogenetics, particularly the MDR1 gene polymorphisms (C1236T, G2677T, and C3435T), in rheumatoid arthritis (RA) treatment. Genotyping revealed that carriers of the TT genotype had longer remission durations when treated with methotrexate monotherapy, while those with the CC genotype exhibited resistance, requiring alternative therapies such as leflunomide. Additionally, the C3435T polymorphism correlated strongly with disease activity, as measured by DAS28, with TT genotype patients achieving remission and CC genotype patients showing high disease activity. These findings emphasize the importance of personalized treatment regimens based on genetic profiles. By tailoring RA therapy to genetic variations, the study highlights the potential for improved treatment outcomes, reduced hospital visits, and lower drug costs. Future research should focus on validating these approaches to optimize RA management and further integrate pharmacogenetics into clinical practice.

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