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TRIALS AND TRIBULATIONS: AN IN-DEPTH ANALYSIS OF TREATMENT FAILURES IN RA

Mubeena Thousiya AP*, Vivek D, Shahin Muhammed TK, Mohammed Mubashir

College of Pharmaceutical Science, Government Medical College,Pariyaram, Kannur, Kerala University of Health Sciences, Kerala-670503.

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent inflammation and progressive joint damage, presenting significant treatment challenges. This review article provides a critical examination of the multifactorial nature of treatment resistance and failure in RA management.We explore the genetic basis of RA, including the impact of genetic variants on therapy results, including the CD84 gene, PDE3A–SLCO1C1 locus, IL6R genetic variants, MTHFR gene, and NLRP3 and CARD8 variants. The review further explores the role of epigenetic regulation in RA, highlighting how epigenetic modifications can alter gene expression and contribute to the treatment response. The formation of antidrug antibodies (ADAs) is scrutinized as a key factor in the attenuation of biologic therapy efficacy, underscoring the need for personalized treatment approaches. We also address the exacerbation of RA symptoms through cytokine storms, a phenomenon that can lead to severe systemic manifestations and complicate disease management. Lastly, the review assesses the genetic susceptibility to hepatotoxicity induced by methotrexate, a cornerstone in RA treatment, emphasizing the importance of genetic screening for personalized medication strategies. Through this comprehensive analysis, we aim to shed light on the complexities of RA treatment failures and pave the way for more effective, individualized therapeutic interventions that can improve patient outcomes in this debilitating disease.

Corresponding author
Mubeena Thousiya AP
College of Pharmaceutical Science,
Government Medical College,
Pariyaram, Kannur,
Kerala University of Health Sciences,
Kerala-670503.
mubeenathousiyaap@gmail.com
7025009795

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INTRODUCTION

Rheumatoid arthritis (RA) a chronic inflammatory illness with a diverse origin affects 0.5–1% of the general population.[1]Though more recently identified as a more comprehensive syndrome encompassing osteoporosis, increased cardiovascular morbidity, psychological impairment, and an increased risk of cancer, it is primarily linked to articular inflammation, progressive synovial joint damage, and increasing disability over time.[2]The last three decades have seen a significant shift in the management of RA due to the development of new techniques based on early diagnosis and treatment using a treat-to-target approach based on assessment of disease activity. Common autoimmune diseases like rheumatoid arthritis (RA) result in chronic inflammation and permanent joint degradation, which eventually cause disability and death.[1,2] The majority of data from immunological and biomolecular research suggests that stromal tissue dysregulation and immune-mediated pathogenesis are linked and that these factors together cause persistent inflammation and joint destruction in RA. Thus, dysregulated cytokine and signal transduction networks, disordered innate and adaptive immunological responses, and disease-progressing semi-autonomous properties of joint stromal synovial fibroblasts are the characteristics that define RA.

Disease-modifying anti-rheumatic medications (DMARDs) are typically used as first-line therapy; oral methotrexate (MTX) is the most often prescribed DMARD.[3]A first-line DMARD's insufficient response at an ideal or maximally tolerated dose may need switching to a different DMARD, such as leflunomide, sulfasalazine, or a DMARD combination.[4]While the exact cause of RA remains unknown, pro-inflammatory cytokines like TNF-α, IL-1, and IL-6 have been shown to be important in the development of chronic inflammatory diseases, including RA.[5] This has prompted the creation of a new class of medications targeted at counteracting their biological activity. TNF antagonists were the first biological treatments to be licensed for the treatment of RA, and three of these are now widely used: etanercept, a soluble receptor antibody; adalimumab, a completely human monoclonal antibody; and infliximab, a chimeric monoclonal antibody.[6]Certolizumab pegol, a PEGylated humanized monoclonal antibody, and golimumab, a human anti-TNF monoclonal antibody, have been added to the arsenal of biological therapy for patients with RA.A thorough understanding of the pathophysiology of RA has been gained over the past thirty years through basic and translational research, and the resulting clinical availability of targeted medicines has revolutionized the treatment of RA.[7]As of right now, there are two kinds of targeted medications for RA that have shown clinical success: 1) injectable biologic disease-modifying anti-rheumatic drugs, or bDMARDs; these include small molecules that inhibit the JAK pathway, IL-6 blockers, TNF-α inhibitors, and agents that deplete B cells. 2) oral targeted synthetic DMARDs, or tsDMARDs. Even thoughpatients with RA are making significant progress in preventing joint deformities and reaching disease remission there are certain failures also.[8]The genetic variance among people including CD84 gene,PDE3A–SLCO1C1 locus, IL6R genetic variants and MTHFR gene linked to responsiveness to treatment.[9]The epigenetic variation will regulate the accessibility of DNA to transcription factors. The use of mAbs may result in the generation of antidrug antibodies (ADAs) leading to the RA treatment failure and results in several adverse effects.

Genetic variations

Treatment failure affects a significant portion of patients receiving any DMARDfor RA. One-fourth of patientsdo not respond effectively to these drugs. The interesting hereditary component is linked to the response to therapy. Therefore, efforts are being made to find biomarkers that can accurately predict how each patient will react to these medications. Consequently, research is being done to identify biomarkers that can precisely predict each patient's response to these drugs.There have been discovered two noteworthy genetic associations pertaining to the TNF-α inhibitor response in RA. Research has demonstrated that the response to the soluble TNF receptor 2 fusion protein etanercept is predicted by variation in the CD84 gene, which encodes SLAM family member 5 (also referred to as leukocyte differentiation antigen CD84).[10]The TNF inhibitor reactivity towards etanercept, infliximab, and adalimumab has been linked to the PDE3A–SLCO1C1 locus. This locus carries the genes for cGMP-inhibited 3',5'-cyclic phosphodiesterase A, and solute carrier organic anion transporter family member 1C1.[11]Nevertheless, neither of these correlations is predictive enough to guide clinical judgments about which treatment is best for a given patient. Thus, the focus has shifted to examining other putative genomic indicators of therapy responses, including as epigenetic modifications and expression profiling.[12]

CD84 Gene

CD84 is a co-stimulatory molecule that aids in the generation of IFN-γ and T-cell maturation. A single nucleotide polymorphism (SNP) in the CD84 gene (rs6427528) and response to etanercept are associated; however, adalimumab and infliximab are not. The 3' untranslated region of CD84 may have altered transcription factor binding motifs due to this SNP or others in linkage disequilibrium with it.[12]

PDE3A–SLCO1C1 locus

PDE3A–SLCO1C1 locus is an additional genomic area associated with treatment response. In RA, the PDE3A–SLCO1C1 locus has been strongly linked to the response to etanercept and infliximab (but not adalimumab).[13]A phosphodiesterase that is encoded by PDE3A is involved in the hydrolysis of secondary messengers like cAMP and cGMP. These messengers have the ability to control immunity. Possible indicators of RA's susceptibility to TNF inhibitors include the PDE3A–SLCO1C1 locus.

IL6R Genetic Variants

The first-line biologic medication for RA that modifies the disease and reduces inflammation is sarilumab, an IL-6 receptor antagonist. Researchers have looked into the possible predictive ability of specific SNPs in the IL6R gene for the effectiveness and adverse reactions of sarilumab.[14]Six SNPs were genotyped using DNA samples from patients on sarilumab treatment: rs12083537, rs11265618, rs4329505, rs2228145, rs4537545, and rs4845625. Three SNPs, rs4845625, rs4329505, and rs11265618, were found to be strongly correlated with treatment response outcomes. These results imply that genetic markers, in particular rs4845625, may be valuable biomarkers for predicting RA patients' responses to sarilumab.There has been progress in both biologic and non-biologic medicines, but finding trustworthy biomarkers is still difficult. Research is still being done to determine the best disease-modifying anti-rheumatic medications (DMARDs) for each patient based on hereditary factors.

MTHFR gene

Research on the relationship between RA patients' reaction to methotrexate, an antifolate medication, and polymorphisms in thegene, MTHFR which codes for a crucial enzyme in the folate system, it ismethylenetetrahydrofolate reductase which yields inconsistent results. Moreover, a meta-analysis found that while there was a great deal of variation among these studies, there was insufficient proof to establish that MTHFR was linked to toxicity or efficacy in patient cohorts from Europe.[15]

NLRP3 and CARD8 Variants

In relation to RA, research has been done on the NLRP3-inflammasome complex, which is implicated in inflammatory processes. SNPs in NLRP3 and CARD8, in particular, are NLRP3 inflammasome proteins that are highly correlated with both disease activity and RA risk. Patients receiving infliximab, an anti-TNF medication, had their peripheral blood mononuclear cells tested for the expression of different NLRP3-inflammasome components. As previously reported, it is proven that the NLRP3 gene is associated with the EULAR anti-TNF response in a sample of RA patients.The NLRP3 variant (T) allele is associated with a worse response to treatment, particularly in smokers who are presently quitting.[16] We also find that a functional variation in the interferon-γ gene is associated with anti-TNF therapy.Each outcome should be confirmed by replication in distinct validation cohorts and complemented by the assessment of the activity and cytokine levels of the relevant gene products. ASC, MEFV, NLRP3-FL, NLRP3-SL, and CASP1 gene expression were all significantly higher in RA patients at baseline than in controls, but CARD8 expression was lower. In the BRAGGSS cohort, SNPs in the NLRP3 gene were linked to the responsiveness to anti-TNF therapy as well as the susceptibility to RA.[17] Expression quantitative trait loci (e QTL) study revealed these relationships in monocytes but not in B cells.CARD8 SNPs were also linked to RA susceptibility and improvement in disease activity in response to anti-TNF treatment.

Epigenetic regulation in RA

Chromosomal structural alterations that do not involve changes in nucleotide sequence are described by the term epigenetics, regardless of whether the changes are absolutely heritable. Two types of epigenetic modifications include covalent histone modifications and DNA methylation. Histone modifications encompass sumoylation, ubiquitination, (de)methylation, and (de)acetylation.[18]These modifications regulate the accessibility of DNA to transcription factors.As more and more epigenetic enzymes are found to operate as "writers" or "erasers" in the modifications of DNA and histones, controlling gene expression by adding or deleting specific functional groups. Furthermore, certain proteins, known as "readers," have the ability to identify areas that have undergone epigenetic modification and play a crucial role in controlling the expression of genes.

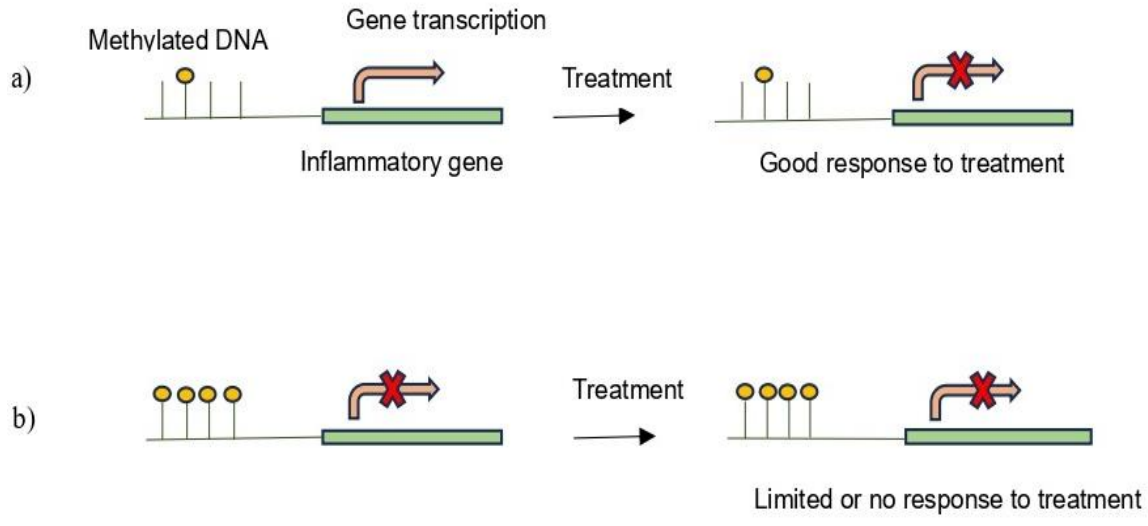

Figure 1: DNA methylation status before the treatment as a prognostic indicator of response.

The graphic provides a simple illustration of how a patient's baseline DNA methylation profile can serve as a predictive biomarker of their likelihood to respond to therapy. a) The encoded protein must be produced at a high level in patients whose DNA methylation in the gene's promoter region is low, which is linked to active transcription. The locus displayed in each panel corresponds to the same gene in each patient; for example, a gene that codes for an inflammatory cytokine-like IL 6.In this instance, increased DNA methylation may come indirectly from a treatment that specifically targets the pathway by which this protein is implicated in anti-IL 6 therapy, hence limiting gene transcription and the production of proinflammatory mediators. Consequently, this response would reduce or cease the inflammation, indicating that the patient would react favorably to the medication. b) A patient with high levels of DNA methylation within the same promoter region is unlikely to benefit from the same medication; this suggests that the patient's inflammation may be mediated by a different pathway, such as B cell activation rather than IL 6 production.The gene has already been "switched off" in this case, hence the patient is unlikely to benefit from medicines that targetthe pathway in which the particular gene is involved.[19]

DNA methylation has the benefit of maintaining inheritance when compared to other epigenetic alterations. The binding of a methyl group at the cytosine 5 carbon location of the CpG dinucleotide in the genome by DNA methyltransferase, without altering the DNA sequence, is known as DNA methylation. DNA methylation most frequently takes place in CpG islands. DNA methyltransferases, or DNMTs, promote DNA methylation; DNMT1 is the most significant DNMT. The pattern of DNA methylationof osteoarthrosis synovial fibroblasts (OASFs) and rheumatoid arthritis synovial fibroblasts (RASFs) differ.DNMT1 expression is low and RASF is hypomethylated.Patients with RA have hypomethylated CD4+ T cells, and larger quantities of IFN-γ can be produced by CD4+ and CD8+ T cells with considerably hypomethylated IFN-γ promoters. Gene promoter regions that are hypermethylated typically block transcription factors from binding, which results in transcriptional suppression.[19]

In the early phase of rheumatoid arthritis, low-dose methotrexate (MTX) is the recommended course of treatment. MTX treatment may not be beneficial for up to 40% of RA patients. One-carbon metabolism, which is involved in the donation of methyl groups, has been demonstratedto be inhibited by MTX. In one study, the relationshipbetween clinical non-response following three months of MTX treatment and baseline global DNA methylation as well as changes in DNA methylation throughout treatment is examined.[20] It is clear that the MTX response is related to the patterns of cell-specific differential global methylation. DNA methylation alterations specific to individual cells have been found to be connected with MTX therapy response in individuals with RA. Measurements of DNA methylation from sorted cells should be included in future research on DNA methylation and the response to MTX treatment.[21]

Formation of antidrug antibodies

In the treatment of RA, the use of biologics like monoclonal antibodies has been crucial. Anti-drug antibodiesthat appear early during therapy with TNF inhibitors, IL1 antagonists, IL6 antagonists, etc. are frequently the cause of treatment failure and side effects.[22] The ability of a therapeutic protein product to elicit immunological responses against itself and other related proteins, or to result in unfavorable clinical outcomes related to the immune system, is known as immunogenicity, according to the FDA. Immunogenicity in the context of therapeutic proteins thus refers to undesirable immunological reactions, in contrast to other biotechnological products, like vaccines, where the immune response is desired. Treatment strategy heavily depends on how the immune system reacts to biological stimuli, especially the production of ADAs. Either T-cell dependent/independent or T-cell independent/dependent B cell activation technique can result in the production of ADAs. When MHC class II molecules and T-cell receptors engage properly, antigens are internalized by antigen-presenting cells, processed, and presented to T cells.

This is how mAbs work in the T-cell-dependent pathway. The development of a Th1 or Th2 phenotype in T helper cells (Th) that, following suitable interactions with B cells, promotes the growth of PCs that release anti-drug antibodies.It is possible to distinguish between two types of ADAs: neutralizing ADAs, often referred to as binding antibodies, or BAbs, which physically obstruct the drug's ability to engage its target by attaching to an epitope within or close to the molecule's active site or sites, or by causing conformational changes.[23]On the other hand, non-neutralizing ADAs selectively bind the medication but do not alter the interaction of the drug with the target.

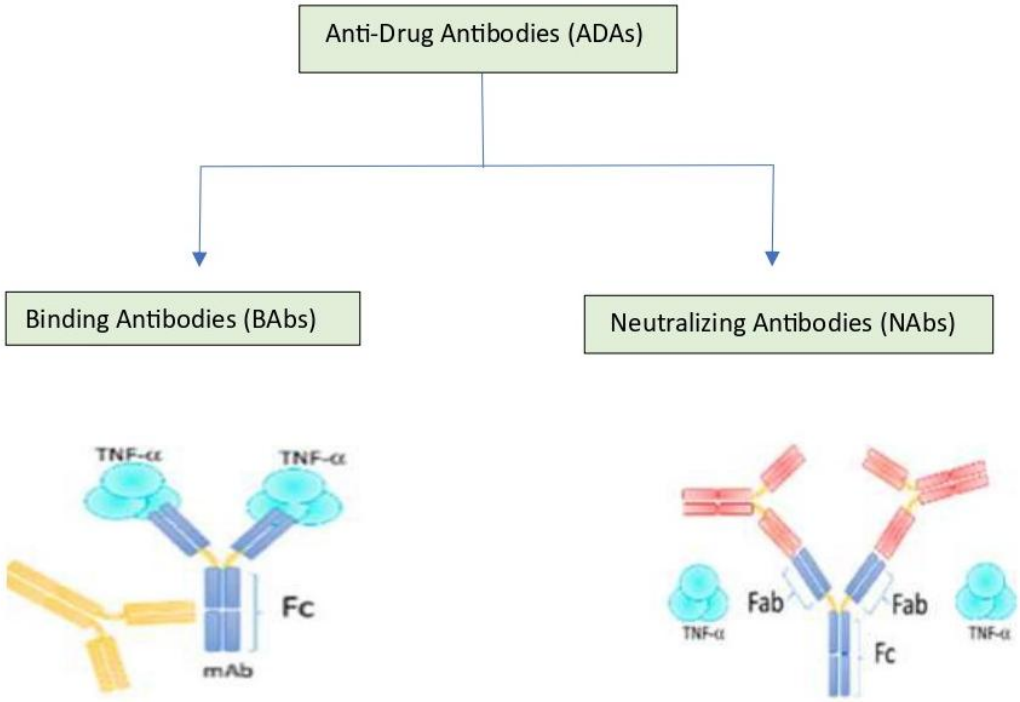

Figure 2: Inhibition of TNF-α inhibitors by ADAs.[23]

A chimeric monoclonal antibody called infliximab is used as a treatment in a number of inflammatory diseases. Tumour necrosis factor-alpha (TNF-α) soluble and transmembrane versions are highly bound by infliximab. In doing so, it interferes with the TNF-α-mediated pro-inflammatory cascade signalling. In essence, the antibody stops TNF-α from engaging with the cell's receptors. Three conserved methionine residues (Met252, Met358, and Met428) may be found in the human IgG1 Fc region. These residues are found close to the point where the nascent Fc receptor, or FcRn, interacts, at the C H2-C H3 contact. Infliximab's efficacy hinges on its ability to neutralize TNF-α and modulate the immune response.[24]Here, in case of BAbs formation,they tend to bind with the Fc region of TNF-α inhibitors like infliximab and in case of NAbs, they are able to bind with the Fab region of TNF-α inhibitors. Thereby lowering the efficacy of TNF-α inhibitors.

Worsening of RA symptoms by cytokine storms

The cytokine storm is caused by the release of a wide range of cytokines triggered by mAbbecause they recognize and respond to pathogen-associated molecular patterns (PAMPs), which are elements of invasive infections, toll-like receptors are crucial members of the innate immune system. PAMPs consist of nucleic acids, lipids, proteins, and lipopeptides.[25]The TLR signalling cascade is triggered when PAMPs bind to TLRs. The innate and adaptive immune systems are impacted by the subsequent release of various chemokines, interferons, and cytokines.[26–28] The toll/interleukin 1 (TIR) domain, a cytoplasmic signalling domain, and the outer ligand-binding domain, which consists of 19–25 leucine rich repeat (LRR) motifs, make up type 1 membrane glycoproteins, or TLRs.[25]

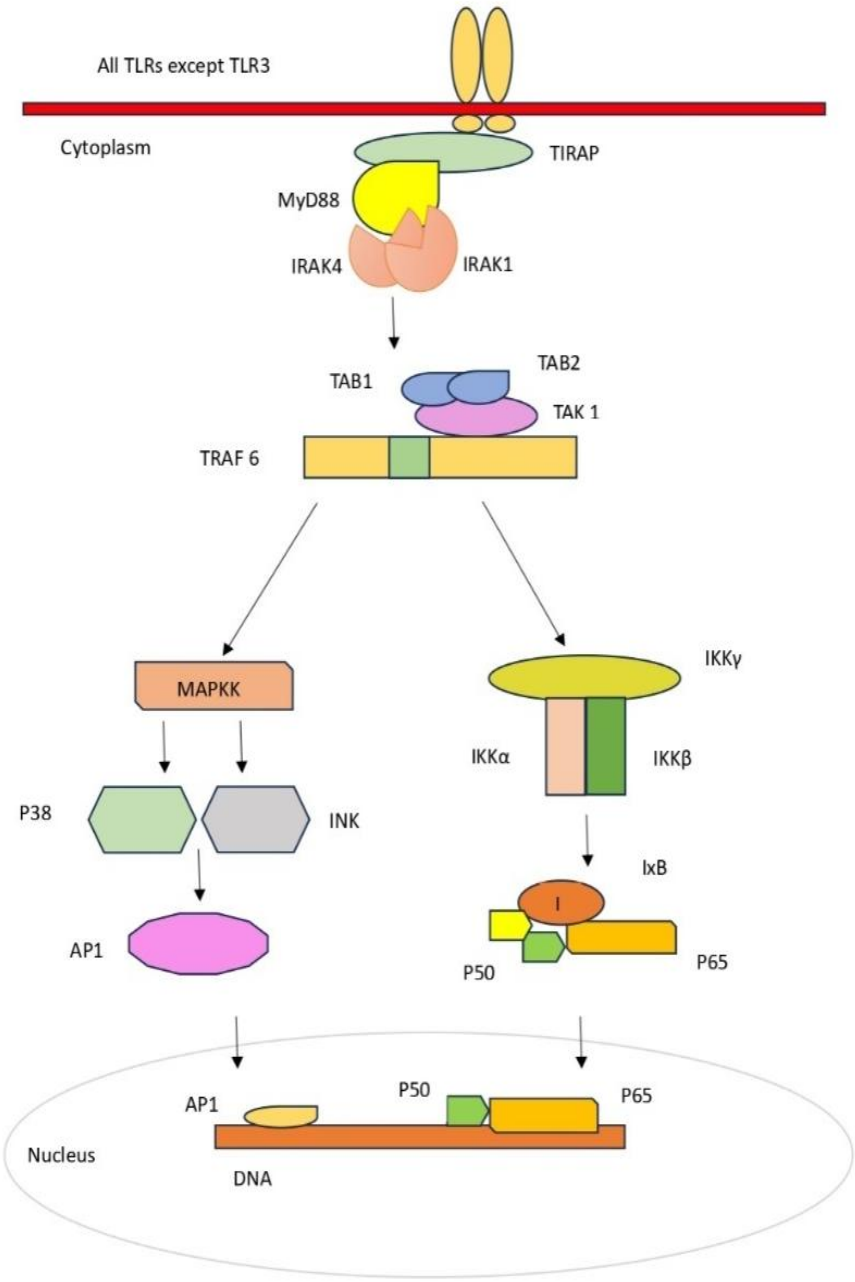

Figure 3: TLR MyD88 signaling pathway.[26].

The TLR signalling pathway includesTRIF-dependent pathway as well as a MYD88-dependent one.Proinflammatory cytokines and chemokines are activated and produced through a mechanism that is reliant on MYD88. On the other hand, the TRIF-dependent pathway produces Type 1 interferons.Cell membrane contains TLR-4 monomers associated with MD2 molecules. CD 14 proteins are also associated withthe cell membrane. In the extracellular fluid contains the LBP(Ligand Binding Protein),LPS molecules from the pathogen(Structural component fromgram-negative bacteria) go and bind with the LBP and later give LPS to the CD 14 molecule. These CD 14 molecules interact with the MD2-TL 4 complex and LPS, and is given to the MD2 protein later it gets transferred into the TL4 protein. Dimerization of TLR 4 monomers occurs and lead to the activation of intracellular domains of TLR4.Recruitment of TIRAP protein followed by MYD88 leads to the activation of IRAK 1 and IRAK 4 proteins later to the activation of TRAF 6 molecule, TAB-1, TAB-2proteins and TAK 1 protein. Activation of IKK protein complex having kinase activity.NFKβ is found in association with NFKβ and NFKBα mask the nuclear localization of signals of NFKβ protein. As a result, NFKβ is unable to get into the nucleus for freeing NFKβ.The IKK protein phosphorylates NFKBα and mark for degradation and further degraded by proteosomes. Now the NFKβ is free to go to the nucleus as its NLS signals has been unmasked. NFKβ move in to the nucleus, drive the transcription of genes that produce proinflammatory cytokines and chemokines. The TAK 1 acts via MAPKs and lead to the formation of AP-1. This AP-1 as a transcription factor get into the nucleus and trigger thepro inflammatory cytokines genes transcription.[26,27]The TRIF dependent pathway leads to the type 1 interferon formation. This cytokine storm formation and worsening of symptoms in RA lead to the treatment failure for various monoclonal antibodies.

Hepatotoxicity

Genetic susceptibility

Genetic factors that impact the absorption, metabolism, and clearance of methotrexate can alter a person's vulnerability to hepatotoxicity. An increased risk of methotrexate-related toxicity was linked to the MTHFR C677T polymorphism, according to a meta-analysis of eight studies. The function ofSNPs in MTHFR (encoding methylenetetrahydrofolate reductase) as a predictor of methotrexate-related toxicity has been investigated in a number of genetic association studies.[28] Numerous populations have also been examined for A1298C and other MTHFR gene SNPs, although the findings of these studies have been inconsistent.SNPs in genes encoding proteins involved in methotrexate absorption (cellular transporter 1; SLC19A1) and export (ATP-binding cassette (ABC) transporters) may also influence a person's vulnerability to severe reactions.[29] Several studies have shown links between methotrexate hepatotoxicity and RFC1 A80G (an SNP in the gene encoding replication factor C subunit 1 that may change the carrier's affinity for folate), ABCB1 C3435T (which may reduce the activity of the efflux transporter), and ABCC2 G1058A. It is challenging to determine the clinical significance of the relationships reported because research on genetic susceptibility has employed varying case definitions and, in certain cases, combined hepatotoxicity with other adverse reactions (like gastrointestinal or biochemical abnormalities).Antioxidant enzymes that are affected by MTX include glutathione peroxidase, superoxide dismutase, and catalase. Additionally, MTX causes a reduction in SAM (S-adenosyl methionine) in the cerebral fluid of patients. Increased reactive oxygen species (ROS) might be caused by a SAM deficiency brought on by MTX. Increased ROS generation is one reason for the drug's direct toxicity.[30] Oxidative stress, the result of an imbalance between the generation of ROS and antioxidant defences, can lead to a number of clinical disorders. RFC1 A80G, ABCB1 C3435T, and ABCC2 G1058A are among the genetic variables associated with MTX hepatotoxicity. The transporter and metabolism of folate are impacted by these genetic variants. Liver fibrosis may be exacerbated by activation of hepatic stellate cells due to genetic causes. Malondialdehyde, a sign of lipid peroxidation, has been demonstrated to decrease with antioxidant treatment.

CONCLUSION

The genetic makeup of the patient population is a major factor to consider while investigating the causes of therapy failures in RA. Specifically, two genetic polymorphisms—the PDE3A–SLCO1C1 locus and CD84have been strongly linked to treatment response. Additionally, correlations between SNPs in NLRP3 and CARD8 with RA susceptibility and anti-TNF treatment responsiveness have been demonstrated. Notably, there was a strong correlation found between three SNPs (rs4845625, rs4329505, and rs11265618) with treatment outcomes. With the exception of rs12083537, most SNPs also displayed correlations with hepatotoxicity or dyslipidemia. Although the effects of epigenetic modifications on RA are still poorly understood, they may be able to link genetics and treatment outcomes. These findings demonstrate how crucial it is to comprehend genetic aspects while developing customized RA treatments. In conclusion, while genetics has a role in both treatment response and RA susceptibility, more investigation is required to identify more predictive biomarkers and improve individualized treatment plans.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Abbreviations

CD84 Cluster of Differentiation 84
PDE3A–SLCO1C1 Phosphodiesterase 3A-Solute Carrier Organic Anion Transporter Family Member 1C1
IL6R Interleukin-6 Receptor
MTHFR Methylenetetrahydrofolate reductase
NLRP3 Nucleotide-binding domain, Leucine-rich–containing family, Pyrin domain–containing-3
CARD8 Caspase recruitment domain-containing protein 8
TNF-α Tumour necrosis factor alpha
IL-1 Interleukin 1
SLAM Signaling lymphocyte activation molecule
IFN-γ Interferon- gamma
cAMP Cyclic adenosine monophosphate
cGMP Guanosine 3',5'-cyclic monophosphate
ASC The apoptosis-associated speck-like protein containing a caspase recruitment domain
MEFV Familial Mediterranean fever gene
CASP1 Caspase-1
TRIF TIR (Toll/interleukin-1 receptor)
MYD88 Myeloid differentiation primary response 88
MD2 Myeloid differentiation factor 2
TIRAP Toll/interleukin-1 receptor domain-containing adaptor protein
IRAK 1 Interleukin-1 receptor-associated kinase 1

IRAK 4 Interleukin-1 receptor-associated kinase 4
TRAF 6 Tumor necrosis factor receptor associated factor 6
TAB-1 Transforming growth factor β1-activated kinase 1 binding protein 1
TAB-2 Transforming growth factor β1-activated kinase 1 binding protein 2
TAK 1 Transforming growth factor beta-activated kinase 1
IKK Inhibitor of nuclear factor-κB (IκB) kinase
NFKβ Nuclear factor kappa B
MAPKs Mitogen-activated protein kinases
AP-1 Activator protein 1
SLC19A1 Solute carrier family 19 member 1
RFC1 A80G Reduced folate carrier-1 A80G

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