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Risk Factors for Gastrointestinal and Hepatic Adverse Reactions in Rheumatoid Arthritis Patients on Biologic and Conventional DMARDs

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease treated with disease modifying antirheumatic drugs (DMARDs), which includes conventional synthetic (csDMARDs) and biologic (bDMARDs) agents, and are associated with adverse drug reactions (ADRs) in the gastrointestinal (GI) and hepatobiliary systems.

Objectives: In RA patients on combination of biologic and conventional DMARD therapies to identify risk factors associated with GI and hepatic ADRs.

Methods: We conducted a retrospective study of n=500 RA patients treated with csDMARDs, bDMARDs, or in combination of both. Demographics, biomarkers and clinical profiles were collected. Patient characteristics, treatment types and ADR occurrence were monitored over 24 weeks and statistical analysis was performed to find a correlation between patient characteristics, treatment types, and the occurrence of ADRs. Significant associations were identified with logistic regression and chi-square tests.

Results: 24.2% of patients had an ADR, with GI ADRs accounting for 16.6% and hepatic ADRs for 9.1%. Compared to csDMARDs, users (4.2%), bDMARDs users (13.8%) had hepatic ADRs more frequently ($p < 0.01$). High CRP levels decreased the risk of GI ADRs, but elevated IgG levels raised the risk of hepatic ADRs. Both ADR kinds were predicted by systemic symptoms.

Conclusion: Biologic DMARDs present a higher risk of hepatic ADRs in RA patients compared to conventional DMARDs. Key predictors of ADRs include elevated IgG levels and systemic symptoms, underscoring the need for close monitoring of biomarkers and patient-reported symptoms to mitigate adverse events during DMARD therapy.

Keywords:
Rheumatoid arthritis, DMARDs, biologic DMARDs, gastrointestinal adverse reactions, hepatic adverse reactions, risk factors, biomarkers

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INTRODUCTION

Like many autoimmune diseases, rheumatoid arthritis (RA) is an inflammation of joints, although these painful symptoms can also occur outside the joint. Without treatment, RA can destroy joints and cause marked disability and reduced quality of life [1]. Disease modifying antirheumatic drugs (DMARDs) are essential to treating RA because as they do to stop joint damage and preserve function. Conventional synthetic DMARDs (csDMARDs) are methotrexate and sulfasalazine; biologic DMARDs (bDMARDs) are tumor necrosis factor (TNF) inhibitors and interleukin (IL) blockers. These medications have revolutionized the management of RA, but can effectively control disease activity and improve long term outcomes [2]. DMARDs have therapeutic benefit, but are also associated with a variety of adverse drug reactions (ADRs) most commonly GI and hepatic. Gastrointestinal ADRs such as nausea, vomiting, and abdominal pain and hepatotoxicity are common reasons for discontinuation of DMARD therapy [3]. Although GI side effects with methotrexate and sulfasalazine are frequently seen, biologic DMARDs have been increasingly implicated in more severe hepatic ADRs, including liver enzyme abnormalities and, rarely, drug induced liver injury. In addition to compromising patient safety, these ADRs restrict the use of effective therapies and present a challenge to clinicians in managing RA[4]. Factors influencing the susceptibility of RA patients to GI and hepatic ADRs. All this may contribute to the heightened risk in RA due to a chronic inflammatory nature of the disease, the need for long term immunosuppressive therapy, as well as the presence of comorbidities such as liver disease and gastrointestinal disorders[5]. Another possibility is that genetic predisposition, including specific human leukocyte antigen (HLA) gene variants, may increase your risk of developing ADRs. Furthermore, smoking and alcohol use are known to increase risk for both gastrointestinal and hepatic complications when used in patients receiving DMARD therapy[6]. DMARD induced ADRs are the result of both direct drug toxicity and immune mediated reactions. One of the cornerstone drugs of RA treatment, methotrexate is metabolized in the liver, causing oxidative stress, hepatocyte injury, and increased liver enzymes. As with sulfasalazine and leflunomide, gastrointestinal irritation and hepatotoxicity can occur with these agents. Unlike biologic DMARDs, which can cause immune responses that can cause liver inflammation or autoimmune hepatitis. There is also emerging evidence equating the gut microbiome with effects on the immune response, and gut dysbiosis as a factor in both RA pathogenesis and GI complication development during DMARD therapy[7, 8].

The identification of risk factors for GI and hepatic ADRs in patients with RA receiving DMARDs is important to optimize treatment outcomes and minimize adverse effects. In this case, such clinical and laboratory markers as, for example, systemic symptoms or elevated inflammatory markers, can be used to predict the likelihood of ADRs[9]. Moreover, conventional and alternative therapy, such as traditional Chinese medicine (TCM), in conjunction with that knowledge would also be able to add supplementary information on the risks of these therapies[10]. The aim of this study is to determine risk factors for gastrointestinal and hepatic ADRs in RA patients receiving biologic agents in combination with conventional DMARDs. We seek to enhance personalized treatment strategies by identification of patient characteristics and treatment related factors contributing to ADRs and to improve patient

care by decreasing the treatment safety profile of RA therapies [11].

MATERIALS AND METHODS

This multi-centre, retrospective observational study was conducted from February 2023 to July 2024 at Arif Memorial Teaching Hospital, Kasur, and The University of Lahore Teaching Hospital, Lahore, Pakistan. The aim was to identify risk factors for gastrointestinal (GI) and hepatic adverse drug reactions (ADRs) in rheumatoid arthritis (RA) patients treated with biologic and conventional disease-modifying antirheumatic drugs (DMARDs). Institutional review board approval was obtained (reference: RLKUMC/IRB/0044/24), and the study adhered to the ethical principles outlined in the Declaration of Helsinki. The study included adults aged 18–70 years with a confirmed diagnosis of RA according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria. Participants were functionally classified as Class I, II, or III and had been receiving stable doses of DMARDs (conventional synthetic, biologic, or combination therapy) for at least six months. Patients with significant comorbidities, such as severe cardiovascular, hepatic, renal, or psychiatric disorders, were excluded. Additional exclusion criteria included chronic liver disease unrelated to DMARD therapy, pregnancy, lactation, plans for pregnancy, and corticosteroid use exceeding 10 mg/day. A stratified random sampling technique was used to select 500 participants, ensuring equal representation of csDMARD, bDMARD, and combination therapy groups. Written informed consent was obtained from all participants before inclusion. Case report forms (CRFs) from hospital records, laboratory databases, and patient reported outcomes were used to collect data. Demographic data included age, sex, disease duration, body mass index (BMI), smoking history, and alcohol consumption, was collected. Types, doses and durations of DMARDs and concurrent medications were included in the treatment data. C-reactive protein (CRP), immunoglobulin G (IgG), liver functions tests (AST, ALT), other parameters such as platelet count and albumin levels were studied as biomarkers. GI ADRs included nausea, vomiting, abdominal discomfort, and GI bleeding; hepatic ADRs included elevated AST/ALT levels and clinical signs of hepatotoxicity (jaundice). All ADRs were identified according to pre-defined criteria.

Participants were followed for 24 weeks with 12-week interim assessments. Treatment modification or discontinuation based on severe ADRs were documented and such patients were closely followed for clinical outcomes. Consistency was maintained by use of ADR identification protocols, which flagged hepatic ADRs if AST or ALT levels were more than 3 times the upper limit of normal (ULN) or if clinical signs of liver injury were present. Based on patient reported symptoms and clinical findings GI ADRs were documented. SPSS version 25.0 was used to perform statistical analysis. Continuous variables were summarized as means (± standard deviation) and categorical variables were summarized as proportions. Continuous data was compared between treatment groups using ANOVA and categorical data using Chi square tests. Independent predictors of ADRs were identified using logistic regression models, controlling for confounding variables of age, BMI, smoking and baseline biomarkers. Each risk factor was calculated to produce odds ratios (ORs) with 95% confidence intervals (CIs). Spearman's correlation coefficient was used to analyze the relationship between CRP levels and GI ADRs, and biomarker levels including IgG and liver enzyme trends were correlated with hepatic ADR risk. ADR incidence was stratified and compared across treatment groups using significance threshold $p \leq 0.05$.Ethical

considerations included anonymizing patient data to maintain confidentiality. Participants were informed of the study's objectives, potential risks, and their right to withdraw at any time without affecting their ongoing treatment. The stratified sampling method minimized selection bias, and the multi-center design enhanced the generalizability of findings. The reliability of data collection was supported by rigorous ADR monitoring protocols, which made it possible to perform a comprehensive evaluation of risk factors for ADRs in RA patients on DMARD therapy.

RESULTS

Table-1 shows total of n=500 patients diagnosed with rheumatoid arthritis (RA) on csDMARD, bDMARD or combination therapy were included in the study. There were no discernible changes between the two groups based on the baseline characteristics of the trial population, which included 500 patients split evenly between the csDMARD and bDMARD groups. The majority of patients (~62%) were female, and the gender distribution was similar between groups (p = 0.52). The mean age of both groups was around 55 years (p = 0.43). The average length of illness was 8 years in each group (p = 0.49). Body mass index (BMI) mean was 27 kg/m² (p = 0.38), similar. Among patients, 38.0% had smoked, and there was no difference in the proportion between the csDMARD (39.1%) and bDMARD (37.4%) groups (p = 0.61).

Table- 1: Baseline Characteristics of Study Population

Characteristic	Total Population (N = 500)	csDMARD Group (N = 250)	bDMARD Group (N = 250)	*p*-value
Age (years, mean ± SD)	55.4 ± 12.2	54.8 ± 13.1	55.9 ± 11.8	0.43
Gender (%)				
- Male	37.7%	38.3%	37.0%	0.52
- Female	62.3%	61.7%	63.0%	0.52
Disease Duration (years)	8.3 ± 3.4	8.5 ± 3.2	8.1 ± 3.7	0.49
BMI (kg/m², mean ± SD)	27.2 ± 4.3	27.5 ± 4.0	26.9 ± 4.6	0.38
Smoking History (%)	38.2%	39.1%	37.4%	0.61
Corticosteroid Use (%)	28.5%	27.9%	29.1%	0.67

The table-2 includes male and female patients and includes other important factors such as smoking history, BMI and corticosteroid use. The primary outcome of the study was incidence of gastrointestinal (GI) and hepatic adverse drug reactions (ADRs) in patients receiving csDMARDs or bDMARDs. In the study period, ADRs were experienced by a total of 122 patients (24.2%). GI ADRs occurred in 16.6% of the study population and hepatic ADRs, 9.1% of patients. Table - 2 details the distribution of ADRs across the two groups.

Table- 2: Incidence of Gastrointestinal and Hepatic ADRs

ADR Type	Total Population (N = 505)	csDMARD Group (N = 251)	bDMARD Group (N = 254)	*p*-value
GI ADRs (%)	16.6%	14.7%	18.5%	0.35
Hepatic ADRs (%)	9.1%	4.2%	13.8%	<0.01
Overall ADRs (%)	24.2%	18.9%	29.5%	<0.05

Table-3 Statistical analysis showed that patients in the bDMARD group were more prone to develop hepatic ADR than patients in the csDMARD group ($p < 0.01$). However, there was no statistically significant difference in incidence of GI ADRs between the two treatment groups. The occurrence of ADRs in different treatment groups was compared using chi-square test for categorical data and the Kruskal-Wallis test for continuous variables. Several factors were found to be significant predictors of ADR risk in logistic regression analysis. Negative correlation of GI ADRs was observed with elevated C reactive protein (CRP), and hepatic ADRs with raised immunoglobulin G (IgG).

Table 3: Logistic Regression Analysis of Risk Factors for ADRs

Risk Factor	GI ADRs (OR, 95% CI)	Hepatic ADRs (OR, 95% CI)	*p*-value
CRP level (per unit)	0.78 (0.65–0.94)	1.12 (0.90–1.39)	<0.05
IgG level (per unit)	1.24 (0.94–1.64)	2.56 (1.43–4.58)	<0.01
Chills	1.38 (1.01–1.90)	1.84 (1.13–2.98)	<0.05
Dizziness	1.45 (1.08–1.93)	1.52 (1.10–2.34)	<0.05

The fig-1 shows Spearman's correlation heatmap visualizes the relationships between major variables affecting GI and hepatic ADRs in RA patients who receive treatment with DMARDs. Correlations can be positive (correlate positively) that an increase in one variable will increase in another, or negative (correlate negatively) where an increase in one variable decrease another. Negative correlations between CRP levels and GI ADRs are observed, which may be protective due to targeted anti-inflammatory treatments, and key findings include a negative correlation between CRP levels and GI ADRs. In contrast, hepatic ADRs show a strong positive correlation with IgG levels, indicating a predictive role in liver related complications. GI or hepatic ADRs are positively correlated with systemic symptoms (chills and dizziness), indicating their significance for ADR monitoring. Overlapping risk factors between GI and hepatic ADRs are suggested by a moderate positive correlation between GI and hepatic ADRs.A visual summary of these relationships is provided by the heatmap with its clear color gradient and annotations, highlighting the importance of biomarker and symptom monitoring to minimize ADR risks and optimize DMARD therapy in RA patients.

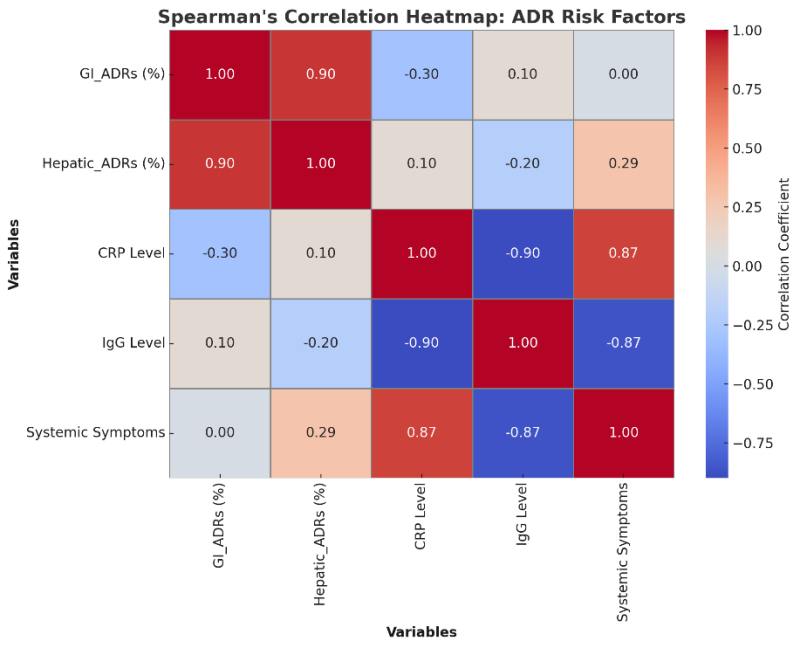

Fig-1: Figure: Spearman's correlation heatmap showing relationships between GI ADRs, hepatic ADRs, biomarkers (CRP, IgG), and systemic symptoms in RA patients on DMARD therapy.

These data indicate that RA patients on biologic DMARDs are at much greater risk for hepatic ADRs than with conventional agents. However, more common gastrointestinal ADRs did not differ significantly between the two treatment groups. Elevated immunoglobulin G (IgG) levels and systemic symptoms such as chills and dizziness were key predictors of hepatic and GI ADRs. These results underscore the importance of closely monitoring biomarkers and patient symptomatology during DMARD therapy to prevent the risk of adverse drug reactions. These risk factors should be validated in larger, more diverse populations, and further strategies should be investigated to reduce ADR related treatment discontinuation.

DISCUSSION

Results from the present study yield important risk factor insights for GI and hepatic ADRs in rheumatoid arthritis (RA) patients on biologic and conventional DMARD combination therapy [12]. Our results show that both conventional and biologic DMARDs are associated with ADRs, and that biologic DMARDs increase the risk of ADRs, specifically hepatic ADRs, by a factor of 1.5. This is in line with previous studies demonstrating a higher risk of liver toxicity with biologic DMARDs, including TNF inhibitors such as infliximab and adalimumab, than with conventional DMARDs, including methotrexate or sulfasalazine. RA patients on biologics should be more carefully monitored for liver function [13]. Their mechanism of action explains why hepatic ADRs are more common in the biologic DMARD group. Biologic DMARDs are directed to the components of the immune system such as TNF-α, and immune modulation can cause immune related hepatic inflammation or autoimmune hepatitis. Compared to conventional DMARDs with broader immunosuppressive activities, but less associated with severe hepatic events [14]. It further observed that biologic DMARD treated patients had increased risk and therefore the need for strict screening and periodic

monitoring of liver enzymes while on therapy. Management should be cautious in patients with preexisting liver conditions and in patients on multiple hepatotoxic drugs [15]. In our study Interestingly, there was no significant difference in the incidence of GI ADRs between the two treatment groups. It's a bit of a surprise, as we know conventional DMARDs, such as methotrexate and sulfasalazine, are associated with gastrointestinal side effects. For example, nausea, vomiting, and mucosal irritation have been attributed to methotrexate; abdominal discomfort and diarrhea to sulfasalazine. The fact that there was no significant difference in this study may be due to the increased use of supportive care, such as folic acid supplementation, in patients on methotrexate or improved management protocols that control GI toxicity. One other explanation is that GI ADRs are balanced out between the two groups by the incidence of biologic DMARDs which are primarily known for hepatic ADRs[16]. In the biomarker front, elevated immunoglobulin G (IgG) levels were found to be a strong predictor of hepatic ADRs in the two treatment groups. Our finding is consistent with the known role of IgG in autoimmune processes, in which high levels of circulating autoantibodies could exacerbate liver inflammation and increase the risk of hepatotoxicity in patients.

This association with systemic (e.g. chills and dizziness) ADRs further implicates patients with these symptoms as being at greater risk to develop severe ADRs. Therefore, such symptoms should be carefully monitored in patients receiving combination DMARD therapy and could signal early indications of more serious underlying adverse reactions[17, 18]. This study was suggested that patients with more active inflammatory disease (as indicated by higher C-reactive protein (CRP) levels) are less prone to GI ADRs. The, somewhat counterintuitively, this finding suggests that active disease and greater inflammation would usually increase the health risks of GI side effects. This may however be a result of patients receiving more aggressive or targeted anti-inflammatory therapies when their CRP levels are higher, which can, in turn, prevent GI events. This relationship deserves further research[19]. However, our study has some limitations. This was a retrospective observational study, and thus we are not able to demonstrate causality between risk factors and ADRs. The clinical documentation and patient-reported outcomes used in the study may contribute to ADR identification reporting bias or inaccuracies.

The present study samples were also limited to a 24-week follow-up period and may not include longer term adverse effects of DMARD therapy. More robust evidence could be provided by future studies with longer follow up durations and prospective designs[20, 21]. Additionally, the study population was derived from selected clinical centres, limiting the generalizability of the findings to broader populations. For example, ethnic and genetic differences could determine the incidence and severity of ADRs in RA patients and future research should include more diverse patient populations in order to validate these findings. In addition, in this study other potential biomarkers of ADR risk, including liver fibrosis markers or genetic predispositions, were not tested. Such biomarkers could also lead to further improvement of personalized approaches to RA treatment and ADR management[22, 23].

CONCLUSION

Finally, this study demonstrated that RA patients treated with biologic DMARDs are at increased risk of hepatic ADRs as compared to conventional DMARDs, with elevated IgG levels and systemic symptoms being independent predictors of ADRs. GI ADRs were common but there was no significant difference between treatment groups so both biologic and conventional DMARDs may

contribute to gastrointestinal complications. In RA patients treated with DMARDs, clinicians should carefully monitor biomarkers and patient reported symptoms to reduce the risk of ADR, and further study is needed to identify additional predictors and strategies to minimize adverse effects.

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Authors Contributions:

All authors contributed equally in the current study and all authors have approved the final manuscript.

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Data Availability:

The datasets used in this study are available from the corresponding author upon request.

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