

Research Article

Prospective Evaluation of Liver Function Abnormalities and Psychological Symptoms in Rheumatoid Arthritis Patients Receiving Conventional and Targeted Synthetic DMARD

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Abstract

Background: Disease-modifying antirheumatic drugs (DMARDs) play a key role in the treatment of rheumatoid arthritis (RA), and abnormalities of liver-function parameters are an important safety concern. Depression and anxiety can also occur as part of RA and can increase the load of illness.

Objective: To determine the frequency of liver-function abnormalities among patients with RA receiving conventional synthetic DMARDs (csDMARDs) and targeted synthetic DMARDs (tsDMARDs) and to describe associated treatment patterns and psychological symptoms.

Methods: Prospective observational study carried out in an outpatient setting in a tertiary-care hospital in adult RA patients on therapy with csDMARDs or tsDMARDs. Demographic and lifestyle data, DMARD therapy and results of liver-function tests were recorded. Symptoms of depression and anxiety were measured using the Patient Health Questionnaire-9 (PHQ-9) and the Generalised Anxiety Disorder-7 (GAD-7) questionnaires, respectively. Descriptive statistics, Pearson's chi-square test and Mann-Whitney U test were used to analyse the data.

Results: They evaluated a total of 114 patients with a mean age of 48.46 ± 10.32 years, 76.3% of whom were female. Overall, 18 patients (15.8%) had abnormal liver-function test results. 18.2 % of persons taking methotrexate and leflunomide, 12.5 % of persons taking tofacitinib, 16.7 % of persons taking methotrexate alone and 14.3 % of persons taking leflunomide alone and other DMARD combinations had abnormal lab results. Overall class of the broad DMARD was not significantly associated with liver-function status. Significantly higher SGPT/ALT ratios were found in patients with abnormal liver-function findings. Moderate or greater depressive symptoms were detected by the PHQ-9 in 23 (20.2%) patients and moderate or greater anxiety symptoms by the GAD-7 in 20 (17.5%) patients.

Conclusion: Liver-function abnormalities were observed in approximately one in six patients with RA receiving DMARD therapy. While these differed in number across treatment regimens, broad DMARD class was not significantly related to liver-function status. A sufficient Number of patients were also identified who had moderate or greater depressive and anxiety symptoms, indicating that biochemical monitoring and psychological screening as a comprehensive follow-up for RA.

Keywords: Rheumatoid Arthritis, CsDMARDs, TsDMARDs, Methotrexate, Leflunomide, Tofacitinib, Liver Function Tests, Depressive Symptoms, Anxiety Symptoms.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune, inflammatory condition that affects the joints primarily, but also other areas of the body, and results in pain, stiffness and decreased function. It affects more than musculoskeletal symptoms and can have a

marked effect on the quality of life and long-term health. In 2020, the global number of people with RA was estimated to be 17.6 million, with an age-standardised prevalence of 208.8 per 100,000 people. The prevalence ratio and sex of the disease is approximately 2.45:1 (F:M). Disease-modifying antirheumatic drugs

(DMARDs) are the mainstays of RA therapy, which help prevent structural damage and lower disease activity. Today, there are a variety of traditional synthetic DMARDs (csDMARDs) (such as methotrexate, leflunomide and sulfasalazine) and targeted synthetic DMARDs (tsDMARDs) (mainly Janus kinase inhibitors including tofacitinib) available for the treatment of RA. Methotrexate is an important component of first-line treatment strategies, and in certain patients leflunomide is a second-line or add-on csDMARD. Although therapeutic, liver laboratory abnormalities should still be taken into consideration when using DMARDs. Levels of serum aminotransferases can be elevated during methotrexate therapy, as well as leflunomide and other antirheumatic agents, especially in patients with other liver or metabolic risk factors. Biochemical monitoring of treatment was important, as biochemical abnormality at baseline and concurrent use of leflunomide were predictive of hepatotoxicity in a study of 730 RA patients on methotrexate. Importantly, abnormal liver-function tests should not be assumed to be an indication of definite drug-induced liver injury (DILI). [3] Today, hepatologists rely on specific thresholds for values of ALT/AST, alkaline phosphatase, bilirubin and/or INR along with investigations for other possible causes of liver damage in order to define clinically significant DILI. Psychological is also a factor in RA. Depression and anxiety can be associated with chronic pain, loss of function, fatigue and the requirement for prolonged treatment and/or worry about the disease's progression. Recently, a meta-analysis of diagnostic interview studies has been published which reported a combined prevalence of 17.9% for depressive disorders and 13.5% for anxiety disorders in individuals with RA. Incidence rates have been reported in a variety of ways, depending on the population and specific type of diagnostic interview. Psychological symptoms are therefore clinically significant and should be considered in the routine assessment, as well as physical and treatment-related symptoms. Considering hepatic laboratory abnormalities along with psychological symptoms may give a more comprehensive picture of patients taking long-term RA treatment, as this is equally important as treatment safety. The primary objective of this study was to determine the prevalence of liver-function abnormalities among RA patients receiving csDMARDs and tsDMARDs in a tertiary

care setting, to assess the distribution of liver function abnormalities among the most commonly used combination of RA DMARDs and also to determine the burden of depressive and anxiety symptoms according to PHQ-9 and GAD-7 screening questionnaires.

MATERIALS AND METHODS

Study Design and Setting

It is an observational study of prospective design, which was performed in a hospital environment at Adesh Hospital, Bathinda, Punjab, India, in the Outpatient Department of Medicine, among patients with RA. Some demographic, lifestyle, treatment-related, and psychological factors and liver-function abnormalities were examined in conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) groups. Data collection took place for 3 months after 6 months of the project.

Study Population and Eligibility Criteria

Eligible patients were those diagnosed with rheumatoid arthritis (RA) who were taking at least one of the csDMARDs or tsDMARDs and had been advised to undergo liver-function testing. Informed written consent was given by all participants.

Patients were eligible to be included if they were aged 18 years or older and were prescribed csDMARD or tsDMARD therapy and their treating doctor had recommended liver-function testing. Patients with severe psychiatric illness, pregnant/lactating women and those with pre-existing liver disease (except drug-induced) were excluded.

The sample size calculation was initially based on an overall sample size of 113 patients, a population of 158 patients and a significance level of 0.05. Finally, 114 patients were analysed.

Data Collection and Study Variables

Information was gathered via patient interviews, analysis of available clinical records, a structured data-collection form and standardised psychological screening questionnaires. Data recorded were age, sex, BMI, smoking status, alcohol use, DMARD use, liver-function results and psychological symptoms.

The evaluation of DMARD therapy was done both by the general class of the drug and by the specific therapy. Treatment was mainly in the form of csDMARDs, tsDMARDs and combination therapy. The treatments used were

methotrexate and leflunomide (MTX + LFN), tofacitinib (TOF), methotrexate alone (MTX), leflunomide alone (LFN) and others (DMARDs).

Assessment Of Liver Function

All liver-function tests performed throughout the evaluation for the study were deemed normal or abnormal. Furthermore, serum glutamate pyruvate transaminase (alanine aminotransferase (SGPT/ALT) was evaluated as it was an important biochemical parameter in the study data.

The liver-function abnormality is thus reported here rather than as confirmed liver injury due to a drug. This terminology has been selected because there is insufficient patient-level data and/or data on all biochemical thresholds and possible other causes of liver injury and/or formal causality assessment in the thesis dataset to confirm all patients with DILI.

The participants were then split into the following groups:

- Normal liver-function group
- Abnormal liver-function group

The results were then compared according to the treatment with DMARD therapy.

Assessment Of Psychological Symptoms

Patient Health Questionnaire-9 (PHQ-9) and Generalised Anxiety Disorder-7 (GAD-7) questionnaires were used to measure depressive and anxiety symptoms, respectively. The scores of each scale were calculated in the original symptom categories as well as a binary screening outcome, which is clinically more accessible in the present manuscript.

For depressive symptoms:

- PHQ-9 <10: No clinically significant depressive symptoms
- PHQ-9 ≥10: clinically significant depressive symptoms present

For anxiety symptoms:

- GAD-7 < 10: low to moderate symptomology of anxiety
- GAD-7 ≥10: Clinically significant anxiety symptoms present.

This means the psychological effects can be more definitely recorded as presence or absence of symptoms and can be summarized in place of in the main paper in several severity orderings.

Depression and anxiety were considered as separate psychological outcomes. Attempts to

create the following list of combined variables were not made, as summarised thesis data was not available to determine if the same patients were screened positive on both the PHQ-9 and GAD-7 questionnaires.

Statistical Analysis

Data were organised and analysed using MS Excel. Means and frequencies (for categorical variables) were used as descriptive statistics for continuous variables. The descriptive statistics are mean and standard deviation of age, and frequencies and percentages of categorical variables.

The Pearson chi-square test was used to assess the relationship between the broad DMARD class and liver-function status. The SGPT/ALT levels of the patients with normal liver function and abnormal liver function were ranked and compared by the Mann–Whitney U test. Statistical significance was defined as $p < 0.05$.

Ethical Considerations

The study was conducted after obtaining approval from the AIPBS College Research Committee (Letter No. AIPBS/2025/0184) and the Ethics Committee for Biomedical and Health Research, Adesh University, Bathinda (Letter No. AU/EC_BHR/2K25/713). Written informed consent was obtained from all participants. Participation was voluntary, and participants were free to withdraw at any time without penalty. Privacy and confidentiality were maintained through anonymisation and secure handling of patient data.

RESULTS

Baseline Characteristics of the Study Population

In total, there were 114 patients with RA who were included in the analysis. The mean age was 48.46 ± 10.32 years, with an age range of 22–72 years. Most of the subjects were females (76.3%, $n=87$) and males (23.7%, $n=27$).

Regarding BMI, 29 patients (25.4%) were underweight, 38 (33.3%) had normal BMI, 29 (25.4%) were overweight, and 18 (15.8%) were obese. The majority of people were non-smokers (89.5%), and 81.6% reported that they did not drink alcohol. Data on demography and lifestyles are summarised in Table 1.

Table 1. Baseline Demographic and Lifestyle Characteristics of the Study Population

Characteristic	Category	n (%)
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Age, years	Mean ± SD	48.46 ± 10.32
	Range	22–72
Sex	Male	27 (23.7)
	Female	87 (76.3)
BMI	Underweight (<18.5 kg/m ²)	29 (25.4)
	Normal (18.5–24.9 kg/m ²)	38 (33.3)
	Overweight (25.0–29.9 kg/m ²)	29 (25.4)
	Obese (≥30 kg/m ²)	18 (15.8)
Smoking status	Non-smoker	102 (89.5)
	Past smoker	11 (9.6)
	Current smoker	1 (0.9)
Alcohol consumption	Yes	21 (18.4)
	No	93 (81.6)

DMARD Treatment Pattern

The most common treatment class was conventional synthetic DMARDs (n=78; 68.4%) followed by targeted synthetic DMARDs (n=32; 28.1%). Three patients (3.5%) were treated with combination therapy.

The most common individual regimen was MTX+LFN (55 patients, 48.2%). Of these, 32

patients (28.1%) were using the drug tofacitinib, 14 patients (12.3%) were using leflunomide monotherapy, 7 patients (6.1%) were using other DMARDs, and 6 patients (5.3%) were using methotrexate alone. The distribution of the treatments is shown in Table 2 and graphically in Figure 1.

Table 2. Distribution Of DMARD Therapy in the Study Population

Treatment classification	n	%
DMARD class		
csDMARDs	78	68.4
tsDMARDs	32	28.1
Combination	4	3.5
Individual regimen		
MTX + LFN	55	48.2
Tofacitinib	32	28.1
Methotrexate	6	5.3
Leflunomide	14	12.3
Other DMARDs	7	6.1
Total	114	100.0

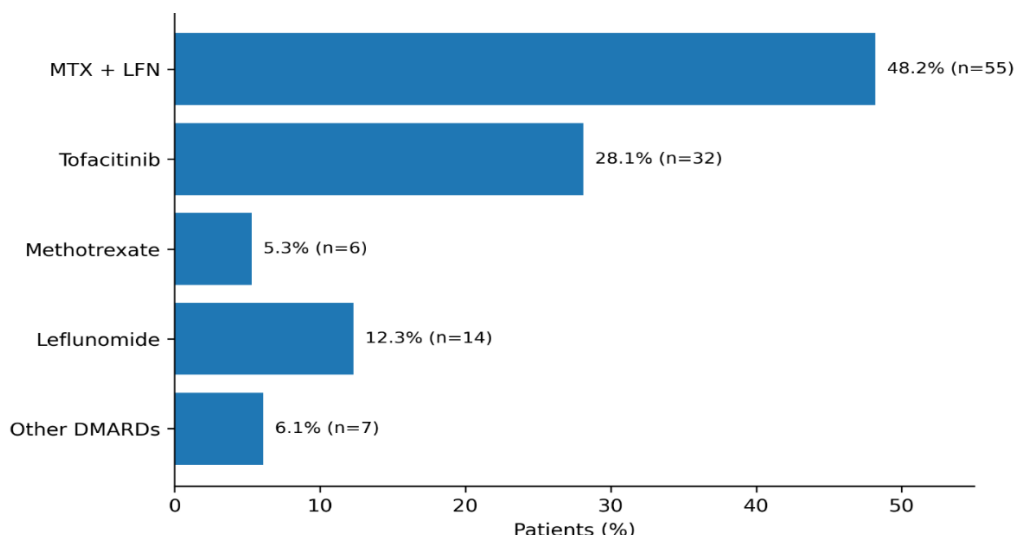


Figure 1. Distribution of Individual DMARD Regimens Among Patients with Rheumatoid Arthritis.

Liver Function Abnormalities According to DMARD Therapy

A total of 96 of 114 patients (84.2%) had normal liver-function tests, and 18 patients (15.8%) had abnormal liver-function tests. Across the broad category of DMARDs, the percentages of patients with abnormal liver-function test findings were 16.7% (13 of 78) for those taking csDMARDs, 12.5% (4 of 32) for those taking tsDMARDs and 25.0% (1 of 4) for those taking combination DMARD therapy. The reported p-value, which was 0.749, was derived from a Pearson chi-square value of $\chi^2=0.579$ with 2 degrees of freedom, and indicated that there was no statistically significant association between broad DMARD class and liver-function status. Abnormal liver-function tests were

observed in 10 of 55 (18.2%) patients receiving MTX+LFN, 4 of 32 (12.5%) patients receiving tofacitinib, 1 of 6 (16.7%) patients receiving methotrexate alone, 2 of 14 (14.3%) patients receiving leflunomide alone, and 1 of 7 (14.3%) patients receiving other DMARD regimens within the individual-regimen group. The results of these are summarised in Table 3 and represented in the graph (Figure 2). Interpretation of these findings should also consider potential contributors to abnormal liver-function tests, including alcohol consumption, obesity, unhealthy dietary habits, physical inactivity, metabolic comorbidities and concomitant medications. These factors may influence liver-function findings independently of DMARD class.

Table 3. Liver-Function Status According to DMARD Treatment

Treatment group	Normal LFT, n (%)	Abnormal LFT, n (%)	Total
DMARD class			
csDMARDs	65 (83.3)	13 (16.7)	78
tsDMARDs	28 (87.5)	4 (12.5)	32
Combination	3 (75.0)	1 (25.0)	4
Individual regimen			
MTX + LFN	45 (81.8)	10 (18.2)	55
Tofacitinib	28 (87.5)	4 (12.5)	32
Methotrexate	5 (83.3)	1 (16.7)	6
Leflunomide	12 (85.7)	2 (14.3)	14
Other DMARDs	6 (85.7)	1 (14.3)	7
Overall	96 (84.2)	18 (15.8)	114

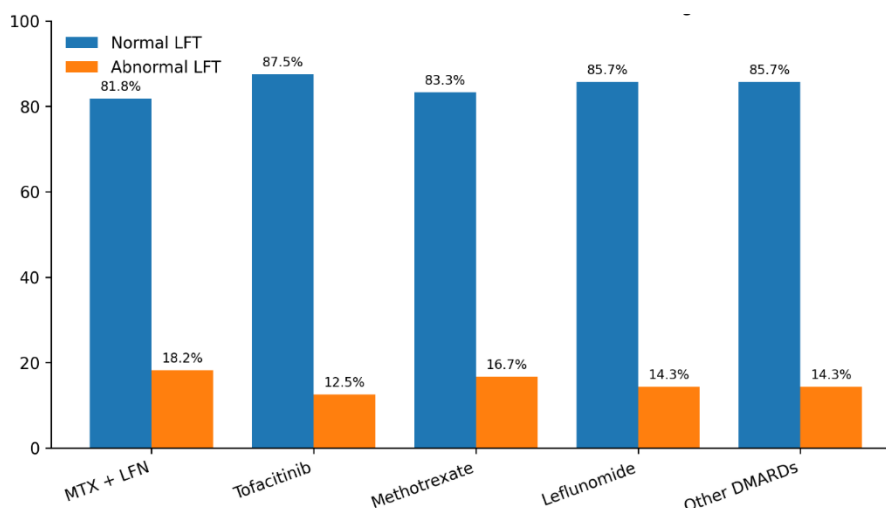


Figure 2. Frequency Of Abnormal Liver-Function Findings According to Individual DMARD Regimen.

Psychological Symptoms Among the Study Population

Psychological screening revealed that 91 of the 114 patients (79.8%) had a PHQ-9 score < 10 (which reflected a mild or less depressive symptomatology) and 23 (20.2%) a PHQ-9 score $\geq$ 10 (which reflected a moderate or greater depressive symptomatology).

In the group of patients with anxiety, 17.5% (20/114) had scores $\geq$ 10 on the GAD-7,

indicating moderate or greater levels of anxiety and 82.5% (94/114) scored below the threshold.

The statistics of who had screen-positive scores for depressive and anxiety symptoms are shown in Table 4 and presented graphically in Figure 3. Data from the thesis were synthesised without specifying by patient, in order to assess these outcomes.

Table 4. Psychological Symptoms Based On PHQ-9 And GAD-7 Screening

Psychological outcome	Symptoms absent, n (%)	Symptoms present, n (%)
Depressive symptoms, PHQ-9 $\geq$ 10	91 (79.8)	23 (20.2)
Anxiety symptoms, GAD-7 $\geq$ 10	94 (82.5)	20 (17.5)

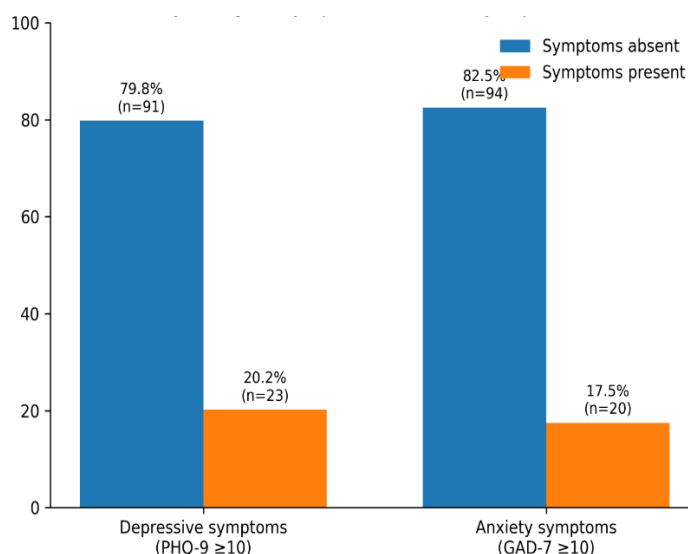


Figure 3. Prevalence of Moderate-Or-Greater Depressive and Anxiety Symptoms Among the Study Population.

DISCUSSION

The aim of this prospective, observational study was to evaluate liver-function abnormalities and psychological symptoms in 114 RA patients receiving conventional or targeted synthetic DMARDs (csDMARDs). Most of the study group were female (mean age 48 years). Most of the patients had normal liver function, 15.8 % abnormal. The percentages of abnormal results varied by treatment group, but there was no significant relationship between the broad level of DMARD and liver function status. The results suggest that liver-function abnormalities are a clinically relevant issue to consider when using DMARDs and should be taken into account when selecting a DMARD, the metabolic status of the patient, co-morbidities and baseline liver function. Similarly, liver disease and co-morbidities are now emphasised in guidelines as a goal for monitoring and consideration of the initiation and use of DMARDs, including methotrexate. In the present study, methotrexate and leflunomide (55 patients) were the most common therapy. 18.2% of the patients receiving this combination had abnormalities in liver function compared to 16.7% of patients receiving methotrexate monotherapy and 14.3% receiving leflunomide monotherapy. The differences in numbers in the treatment groups, however were markedly different and, as therapy was not randomised, these numbers do not prove that a specific therapy causes hepatic injury. Up to now, evidence suggests cautious monitoring of the liver is necessary during methotrexate therapy. Mori et al., in a long-term study of 289 newly treated patients with RA, reported the 5 year cumulative incidence of persistent transaminitis to be ~ 13%. Moderate to severe hepatic fat deposition and obesity were among the most important factors associated with high CHA levels, which were associated with sustained elevation of transaminases. The data indicated that observed defects during therapy with a DMARD could be related to the drug itself, rather than to the class of DMARDs. In our study, numbers presented with MTX+LFN are very similar to previous clinical studies. Curtis et al. reported 22% of RA patients with ALT/AST levels above the upper limits of normal (ULN) on methotrexate, 17% on leflunomide and 31% on MTX+LFN. Also, combination treatment resulted in more severe elevations being more common. They shouldn't be used to compare with our 18.2% frequency, as definitions, monitoring intervals, populations and doses of the studies were all different, but

both say liver enzymes should be monitored routinely during these therapies. Liver-function abnormalities during DMARD therapy may be influenced by alcohol consumption, obesity, metabolic comorbidities and concomitant medications. Lifestyle habits, including physical inactivity and diets high in added sugars, may also contribute indirectly through metabolic dysfunction and hepatic fat accumulation. www.niddk.nih.gov Although patients with previously diagnosed liver disease were excluded, 41.2% of the study population were overweight or obese, and 18.4% reported alcohol consumption. These factors should therefore be considered when interpreting the observed abnormalities. However, the presented analysis did not establish their independent associations with abnormal liver-function tests, and reported alcohol consumption should not be equated with alcohol misuse. Consequently, the abnormalities cannot be attributed solely to DMARD therapy.. This is in keeping with the fact that mild elevations of the aminotransferases are seen during tofacitinib therapy. The majority of patients in the tofacitinib-treated Indian patient subset experienced elevation of ALT levels, with around 11% of patients having levels greater than three times the upper limit of normal, in a subset analysis. A percentage similarity should be used with caution since it is based on our outcome (abnormal LFTs) and not on the same definition based on ALT. Liver function tests (SGPT/ALT) were found to be significantly raised in the present study in the cases with abnormally raised liver function tests. This is a normal result as ALT is an important part of biochemical markers of hepatocellular injury, and should not be the only parameter used to indicate clinically significant DILI. In addition, consideration of treatment changes based on persistence and severity of the liver enzyme abnormality, repeated testing, examination of preexisting abnormalities, and examination of other liver diseases are of particular interest for liver enzyme abnormalities in RA, based on recent clinical data. The second noteworthy finding in the investigation was the psychological burden was observed in the study population. Twenty patients (20.2%) met the screening criteria for moderate or higher depressive symptoms (PHQ-9 ≥ 10) and 17 (17.5%) met the screening criteria for moderate or higher anxiety symptoms (GAD-7 ≥ 10). These are only preliminary findings and should be understood as a screen-positive

psychological symptom and not a diagnosis. The present population of India has been supported by psychometric studies in India for the use of the PHQ-9 and GAD-7. Both instruments had been evaluated by De Man et al. in a population from India, and they found acceptable psychometric properties and measurement stability across the different demographic subgroups, suggesting they can be used to measure depression and anxiety symptom severity. Any psychiatric disorder questionnaire score should continue to be used to help identify psychiatric disorders, and should not be used to supplant the clinical evaluation of a psychiatric disorder when a psychiatric disorder is suspected. Our psychological results are also comparable to the real-world data available about inflammatory arthritis. In a study conducted in 2026, using the PHQ-9 and GAD-7 questionnaires, a significant number of psychological symptoms were detected by simply completing a systematic screening of the questionnaires; some 24.8% of all RA patients had symptoms of depression detected, and around 20% had symptoms of anxiety detected. Our cohort has a screening frequency of depression of ~20.2% and anxiety of ~17.5%, which is very similar to this level. The variation in prevalence rates across the different studies may be due to the use of different screening instruments, the use of different cut-offs, the different study samples, the activity of the disorder, or because symptoms have been reported, but not clinically diagnosed anxiety disorders. There were significant variations across the 47 studies included in the systematic review of more than 11,000 patients in the prevalence and assessment of anxiety in RA. Therefore, care needs to be taken in comparing percentages from different studies. Similarly, in clinical practice, there is recent evidence that the use of the psychiatric history does not necessarily lead to the recognition of psychological symptoms. Ionescu et al. found that, using questionnaire-based screening, they identified a greater number of depressive and anxiety symptoms among RA patients compared to those identified from the patients' medical history and that the questionnaire was correlated with RA disease activity and functional impairment and pain. The results suggest that a brief psychological evaluation may be helpful in the treatment of RA in general. The results are supportive of a patient-centred monitoring approach that incorporates liver-function results and the patient's DMARD

treatment, metabolic profile, alcohol consumption and initial hepatic function. Consideration might be given in patients receiving methotrexate, leflunomide and those with other metabolic risk factors. Pharmacological monitoring can also be done through a psychological evaluation. In the present study, almost 25% of the patients had clinically relevant depression symptoms, and 19.7% of the patients had clinically relevant anxiety symptoms. Screening is not a psychiatric diagnosis, but can be helpful in identifying an individual who may require further clinical evaluation. This is definitely a strength of this study, as the measure of DMARD therapy, the liver-function status and the psychological symptoms were taken in the same population, which was a tertiary-care cohort of patients with RA. The prospective observational approach also enabled collection of clinically relevant data from standardised PHQ-9 and GAD-7 instruments. There are a number of caveats. The study was carried out in one centre, and in some treatment groups the number of patients was relatively small, especially in the largest group (those treated with combination treatment). So, statistical comparisons and conclusions between the DMARD groups are not sound. Non-randomised patient differences in regimens might be related to prescribing or to patient factors. The patients were split into two groups, however: those with normal results of liver function tests and those with abnormal results of liver function tests. Not all participants had completed biochemical thresholds and serial measurements, and did not have all alternative causes ruled out, nor had they completed formal DILI causality assessments. So, the results cannot be interpreted as a rate of liver damage caused by the drug. In addition, both the PHQ-9 and the GAD-7 are screening tools, not diagnostic interviews. There was also no overlap at the patient level between the two questionnaires; therefore, the number of unique patients who had some depressive or anxious symptoms was not calculated. More centres with longer duration and longitudinal monitoring of the liver and with more metabolic risk factors, treatment duration, disease activity and multivariable analysis would provide a more accurate estimate of liver abnormalities and the psychological burden of RA.

CONCLUSION

In this prospective observational study of 114 patients with rheumatoid arthritis, 15.8% had

abnormal liver-function tests, with no statistically significant association between broad DMARD class and liver-function status. Although patients with previously diagnosed liver disease were excluded, the potential contributions of alcohol consumption, obesity and other metabolic or lifestyle factors could not be independently established. Moderate or higher depressive and anxiety symptoms were identified in 20.2% and 17.5% of screened participants, respectively. These findings support comprehensive follow-up incorporating liver-function monitoring, assessment of metabolic and lifestyle factors, and psychological screening. Larger multicentre prospective studies with serial biochemical assessments and adjustment for relevant confounders are needed to clarify factors associated with hepatic abnormalities during DMARD therapy.

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