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HEPATIC INVOLVEMENT IN RHEUMATOID ARTHRITIS: CAUSES, COMORBIDITIES, AND CLINICAL IMPLICATIONS

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ABSTRACT

Aim: The aim of the study is to summarize the current knowledge on the causes of liver dysfunction in patients with rheumatoid arthritis (RA), with particular emphasis on viral infections, nonalcoholic fatty liver disease (NAFLD), autoimmune liver diseases, and treatment-related hepatotoxicity.
Methods: A review of the literature published between 2015 and 2025 was conducted using PubMed and Google Scholar. Studies on hepatic complications in patients with RA were analyzed. Additional relevant studies were identified through reference screening, and selection was based on titles and abstracts.
Results: In RA, liver dysfunction mainly reflects comorbid liver disease and metabolic risk rather than drug toxicity. NAFLD is the most frequent hepatic abnormality in RA, with a prevalence exceeding the general population, strongly associated with obesity, insulin resistance, and inflammatory activity. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections remain clinically relevant due to their potential to mimic or modify RA manifestations and the risk of reactivation during immunosuppressive therapy. Autoimmune liver diseases occur less frequently, though primary biliary cholangitis (PBC) is reported more often in RA than in the general population. Methotrexate (MTX) most commonly causes transient, reversible enzyme abnormalities. Biological therapies and Janus kinase (JAK) inhibitors have varied liver safety profiles, with HBV reactivation in patients without adequate prophylaxis remaining a key concern.
Conclusion: Liver dysfunction in RA reflects coexisting liver disease, chronic inflammation or immunogenetic predisposition. Safe long-term management requires regular liver function assessment, mandatory HBV and HCV screening, and identification of metabolic risk factors to minimize hepatic complications.

KEYWORDS

Arthritis, Rheumatoid; Liver Diseases; Nonalcoholic Fatty Liver Disease; Methotrexate; Biological Therapy; Hepatitis

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1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that is a significant global cause of long-term impairment and health burden (Black et al., 2023; Finckh et al., 2022). In 2020, approximately 17.6 million people worldwide lived with rheumatoid arthritis, with the disease occurring significantly more often in women than in men, and the global standardized prevalence rate increased by approximately 14% compared to 1990, indicating a growing population burden of RA. Furthermore, epidemiological predictions indicate that by 2050, the number of people living with RA worldwide could rise to as many as 32 million, representing a further significant increase in the global prevalence of the disease (Black et al., 2023). Advances in the treatment of RA resulted in marked improvements in disease control and prognosis, but at the same time increased the importance of the long-term consequences of both the disease itself and the therapy applied, including organ complications of potentially significant clinical importance (Black et al., 2023; Smolen et al., 2023). The contemporary therapeutic approach is based on early diagnosis and treatment in accordance with the "treat-to-target" strategy, which aims to achieve remission or at least low disease activity using disease-modifying drugs (Smolen et al., 2023). This model of treatment involves long-term exposure to drug therapy and frequent modifications to treatment, making systemic safety assessment an integral part of patient care (Smolen et al., 2023; Taylor et al., 2021). RA is more than just joint involvement - chronic inflammation and immunoregulatory disorders promote the development of extra-articular manifestations and comorbidities that significantly affect patients' quality of life and mortality (Taylor et al., 2021; D. Wu et al., 2022). Comorbidities in RA are not merely a clinical background but rather interact closely with disease activity and treatment profile, determining therapeutic decisions and the risk of adverse events (Smolen et al., 2023; Taylor et al., 2021). The pathogenesis of RA involves complex autoimmune mechanisms, preceded by a prolonged, often asymptomatic phase of immune dysregulation leading to loss of tolerance to self-antigens and the formation of autoantibodies, detectable long before the onset of clinical symptoms (Alivernini et al., 2022; Guo et al., 2018). In the further course, a pathological inflammatory response is consolidated, in which elements of the innate and adaptive immune systems interact, leading to chronic activation of inflammatory cells and stromal cells in the synovial membrane (Alivernini et al., 2022; Guo et al., 2018). These processes drive excessive synovial tissue proliferation, release of inflammatory mediators, and progressive destruction of cartilage and bone. Importantly, they do not occur in isolation, they reflect a broader pattern of systemic immune dysregulation that extends well beyond the joint (Guo et al., 2018). Concepts of RA pathogenesis emphasize that persistent inflammation and permanent immune dysregulation may promote the development of systemic complications, even during periods of clinically low disease activity or remission (Alivernini et al., 2022). The liver plays a key role in the metabolism of many drugs used in RA, and at the same time may be exposed to both the consequences of chronic inflammation and the adverse effects of long-term immunomodulatory therapy (Taylor et al., 2021; D. Wu et al., 2022). Therefore, it holds a special place among the organs at risk in RA patients. Given that a substantial proportion of patients will require decades of continuous therapy, the hepatic consequences of both the disease and its treatment deserve careful clinical attention (Black et al., 2023). Therefore, this review summarizes the main causes of abnormal liver function test results in RA, including viral hepatitis, fatty liver disease, autoimmune liver diseases, and treatment-related liver damage. In addition, practical implications for screening and monitoring are discussed.

2. Methodology

This paper provides a review of the current evidence on hepatic complications in patients with rheumatoid arthritis, focusing on studies published between 2015 and 2025. To identify relevant literature, the PubMed and Google Scholar databases were searched using the following keywords: rheumatoid arthritis, liver diseases, nonalcoholic fatty liver disease, methotrexate, biological therapy, hepatitis. Additional sources were identified by reviewing reference lists and citation networks of key articles. Publications were screened based on title and abstract, and studies deemed relevant were then subjected to full-text analysis.

3. Viral infections

Hepatotropic viruses may induce a wide spectrum of immune disorders and rheumatological manifestations, most commonly during chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, while the relationships concerning hepatitis A virus (HAV) and hepatitis E virus (HEV) are still poorly understood. The authors emphasize that patients with arthritis, vasculitis, kidney involvement, uveitis, or autoimmune liver disease should be routinely tested for viral hepatitis and considered for antiviral treatment if infection is confirmed (Maslennikov et al., 2021).

Hepatotropic viruses also include HAV and HEV, which are usually responsible for self-limiting hepatitis, but can occasionally cause joint symptoms or mimic rheumatic diseases, especially in patients receiving immunosuppressive therapy (Bauer et al., 2015; Di Bartolomeo et al., 2020; Maslennikov et al., 2021). HEV should be considered in the diagnosis of patients with rheumatic diseases and unexplained hepatic enzyme elevation (Bauer et al., 2015).

However, chronic HCV and HBV infections are of considerable clinical significance, as they can lead to cirrhosis, hepatocellular carcinoma, and numerous extrahepatic manifestations, including joint changes and autoimmune disorders (Cacoub et al., 2017; Priora et al., 2021; Y.-L. Wu et al., 2022). In patients with RA, this problem assumes an additional dimension, both because these infections can mimic or modify the course of the disease and because of the risk of reactivation during immunosuppressive treatment (Hong et al., 2023; Hsu et al., 2016; Ko et al., 2024; Matsuzaki et al., 2018).

3.1 Hepatitis C virus infection

Chronic HCV infection affects approximately 3% of the global population and is often associated with extrahepatic symptoms, such as arthralgia, arthritis, myalgia, sicca complaints, and cryoglobulinemic vasculitis (Cacoub et al., 2017; de Oliveira & da Silva, 2019; Sharma & Sharma, 2022). Some patients develop polyarthritis of the small joints of the hands and feet, which clinically resembles early RA, while others develop a milder, often self-limiting oligoarthritis of several large joints of the lower limbs (Sharma & Sharma, 2022; Siloşi et al., 2017). At the same time, population-based studies show that the percentage of diagnosed RA is higher in people infected with HCV than in those infected with HBV, reaching nearly 20% of patients with HCV in some cohorts, which highlights the association of this infection with the development of rheumatic disease, rather than just its imitation (de Oliveira & da Silva, 2019; Su et al., 2014). Diagnosis is further complicated by the serological profile of patients with HCV, as in various studies up to half of patients have at least one immunological abnormality. Rheumatoid factor is very common occurring in 40–80% of cases, while antibodies against citrullinated peptides, although less common, may also be positive (Cacoub et al., 2017; Priora et al., 2021; Siloşi et al., 2017). A significant percentage of antinuclear antibodies (ANA) and other autoantibodies was furthermore reported, which means that both the clinical picture and laboratory test results may suggest primary RA or other systemic autoimmune diseases (de Oliveira & da Silva, 2019; Priora et al., 2021). In some papers, it appears that HCV-related arthritis is more often associated with cryoglobulinemia, peripheral nerve involvement, or kidney involvement, suggesting a vascular manifestation of infection rather than RA (Cacoub et al., 2017; Priora et al., 2021; Sharma & Sharma, 2022). Su et al., in a large Taiwanese cohort study involving nearly 50,000 individuals with viral hepatitis, showed that chronic HCV infection was associated with roughly a twofold higher risk of developing RA, whereas HBV infection did not meaningfully increase this risk. The association persisted even after adjusting for confounders and restricting the analysis to patients receiving disease-modifying antirheumatic drug (DMARD) therapy (Su et al., 2014). Similar findings were found in a nationwide cross-sectional study, in which HCV infection was associated with an approximately twofold increase in the risk of developing RA and a higher percentage of HCV among patients diagnosed with RA than in the control population (Tang et al., 2025). These data consistently indicate that HCV may trigger autoimmune mechanisms that promote the development of symptomatic RA, rather than just temporary arthritis (Priora et al., 2021; Su et al., 2014; Tang et al., 2025). The course of rheumatic diseases in patients with HCV is also influenced by antiviral treatment. In the interferon therapy era, the induction or exacerbation of autoimmune diseases, including joint symptoms, was reported, which complicated treatment in patients with concomitant rheumatic disease (Cacoub et al., 2017; Sharma & Sharma, 2022). At the same time, observations from large cohorts indicated that effective treatment with interferon in some patients was associated with a lower risk of subsequent development of RA and a reduction in the frequency of autoimmune manifestations (Su et al., 2014; Tung et al., 2018). The introduction of direct-acting antiviral agents (DAAs) changed the clinical picture. Currently, most patients achieve sustained viral elimination with favorable tolerability, while the incidence of cryoglobulinemic vasculitis and

other rheumatological complications of HCV infection is reduced (Cacoub et al., 2017; Priora et al., 2021). From a practical point of view, in patients reporting joint pain and edema, especially with RF or other autoantibodies presence, HCV infection should be routinely considered in the differential diagnosis. If infection is confirmed, careful differentiation between HCV-related arthropathy and early RA is necessary (de Oliveira & da Silva, 2019; Sharma & Sharma, 2022; Siloşi et al., 2017). In patients with concurrent RA and HCV, the decision to initiate intensive immunosuppressive therapy requires close collaboration with a hepatologist. On the one hand, this is due to the risk of exacerbating the infection, and on the other, the potential benefit of HCV eradication in controlling rheumatological symptoms (Cacoub et al., 2017; Tang et al., 2025; Tung et al., 2018).

3.2 Hepatitis B virus infection

The role of HBV infection in rheumatology is more complex and is not limited to arthropathy associated with the disease. Population studies show that patients with RA have a slightly higher rate of diagnosed HBV infection and experience newly detected infections more often than the general population, although the magnitude of these differences is not significant (Hsu et al., 2016; Matsuzaki et al., 2018). In a nationwide Taiwanese analysis, patients with RA showed a higher prevalence of diagnosed HBV infection (around 70 vs. 60 per 1,000) and more than double the incidence of newly detected cases (about 17 vs. 7 per 1,000), and after adjustment for confounding factors, the risk remained moderately but significantly elevated (Hsu et al., 2016). Matsuzaki et al. report that in 1,351 RA patients, 3.7% were found to be chronic HBsAg -positive, and nearly 27% showed signs of past infection (Matsuzaki et al., 2018). Several papers suggest that chronic infection itself may modify the course of arthritis. Histopathological studies showed the presence of HBV antigen and viral material in the synovial fluid in some RA patients, which was associated with significantly greater inflammatory infiltration, poorer clinical response, and faster radiological progression (Chen et al., 2018). These observations indicate that in some patients, chronic HBV infection may further exacerbate local inflammation in the joints. Clinically, the most important concern is the risk of HBV reactivation during immunosuppressive treatment. Evidence from large cohort datasets is notably consistent. In hepatitis B surface antigen (HBsAg) positive patients treated with biologics, the reactivation rate reaches up to one-third, and the associated exacerbations of hepatitis can be severe, leading to failure and death (Hsu et al., 2016). Meta-analyses show that anti-CD20 therapy carries a particularly high risk, as well as some other biologics, while tumor necrosis factor-alpha (TNF-α), Janus kinase (JAK), and interleukin-6 (IL-6) inhibitors in patients without HBsAg have a significantly lower reactivation potential (Hong et al., 2023; Y.-L. Wu et al., 2022). In HBsAg-positive patients treated with tocilizumab, the risk of reactivation without prophylaxis was exceptionally high, while concomitant antiviral treatment eliminated this risk (Ko et al., 2024; Kuo et al., 2021). In contrast, in the group of patients with a previous infection (HBsAg−/HBcAb+), although the risk is significantly lower, it is not zero, and studies have reported isolated but clinically significant episodes (Hong et al., 2023; Matsuzaki et al., 2018). Certain risk factors consistently appear across different analyses. Glucocorticosteroids, especially when used chronically and in combination with other drugs, were independently associated with a higher likelihood of reactivation (Hsu et al., 2016; Y.-L. Wu et al., 2022). Another important factor is the status of protective antibodies. The absence of antibodies against hepatitis B surface antigen (anti-HBs) or their low titer was associated with a several times higher risk of HBV replication, even among patients with only trace evidence of past infection (Hong et al., 2023; Ko et al., 2024; Y.-L. Wu et al., 2022). This means that the infection itself is not clinically neutral, and the patient's immune profile is important in assessing the safety of therapy. Before initiating immunosuppression, a full HBV serologic profile should be obtained in all patients with RA. Appropriately selected prophylaxis with nucleoside analogues effectively prevents reactivation in both HBsAg carriers and some patients with a history of infection (Ko et al., 2024; Kuo et al., 2021; Matsuzaki et al., 2018). The absence of prophylaxis in high-risk groups carries the danger of severe complications. Moreover, because autoantibodies are frequently detected even in healthy individuals, they cannot reliably distinguish infection-associated arthritis from true RA (Generali et al., 2021).

4. Nonalcoholic fatty liver disease and fatty liver

Nonalcoholic fatty liver disease (NAFLD) refers to the accumulation of fat in the liver in individuals without significant alcohol consumption and without other causes of steatosis. This condition ranges from simple steatosis, which is usually non-progressive, to inflammatory nonalcoholic steatohepatitis (NASH), which can eventually lead to fibrosis, cirrhosis, and even hepatocellular carcinoma (Chalasani et al., 2018; Loomba et al., 2021). In inflammatory diseases, including RA, NAFLD occurs more frequently because chronic inflammation and metabolic disorders promote fat accumulation in the liver and accelerate its damage (Barbarroja et al., 2022). In epidemiological studies, the prevalence of NAFLD among RA patients is high, although the values vary depending on the diagnostic methods used. In some analyses, it reaches nearly one-third of patients (Mahapatro et al., 2025; Zamani et al., 2023). Zamani et al. analyzed nine studies evaluating 2,178 patients with RA and estimated that NAFLD occurs in approximately 35.3% of patients; the prevalence was 35.2% among men and 22.2% among women. The paper highlighted that each additional BMI point increased the risk of NAFLD by approximately 24%. A meta-analysis by Mahapatro et al. from 2025 indicates that NAFLD/NASH occurs in approximately 22.8% of patients with RA. The frequency varied significantly depending on the method of diagnosis about 33.3% using FibroScan, nearly 43.9% in biopsy-based studies, and 30.5% in analyses using ultrasound. Meta-analyses demonstrate that the use of more sensitive methods, such as elastography or biopsy, reveals a higher prevalence of steatosis than ultrasound, suggesting that NAFLD may be underestimated if based solely on imaging studies with lower sensitivity (Mahapatro et al., 2025; Zamani et al., 2023).

The development of steatosis is most influenced by metabolic factors, especially obesity and insulin resistance, but also by persistent RA inflammatory activity, which intensifies the metabolic processes conducive to NAFLD (Barbarroja et al., 2022; Zhong et al., 2024). Metabolic risk factors, particularly obesity and pre-existing steatosis, significantly increase susceptibility to liver damage during methotrexate (MTX) treatment. Moreover, in some patients, fatty liver disease progresses to NASH with fibrosis (Mori et al., 2020; Shetty et al., 2017). Due to the high prevalence of NAFLD in patients with RA, it should be considered a significant comorbidity requiring regular assessment of liver function, the use of non-invasive diagnostic methods, close cooperation between rheumatologists and hepatologists, and attention to lifestyle modifications to reduce the risk of disease progression (Chehade et al., 2019; Mahapatro et al., 2025; Schäfer & Keyßer, 2022). Beyond its hepatic consequences, steatosis contributes to cardiovascular risk, a burden that is already elevated in RA, making active monitoring particularly relevant in this group (Barbarroja et al., 2022).

5. Autoimmune Liver Diseases

5.1 Primary biliary cholangitis

Primary biliary cholangitis (PBC) is a chronic, autoimmune cholestatic disease resulting in progressive damage to the small intrahepatic bile ducts and ultimately, fibrosis in advanced stages cirrhosis (Kaplan & Gershwin, 2005). PBC is the most frequent autoimmune liver disease in patients with rheumatoid arthritis, with a frequency of occurrence of 3.8–6.3%. The prevalence of RA in the PBC population has been estimated at 1.8% to 13% (Mihai et al., 2024; Wang & Tsai, 2022). In addition, antimitochondrial antibodies (AMA) were detected in 0.9–18% of patients with RA, which further confirms the partial overlap of the immune response in both diseases (Mihai et al., 2024). In many cases, RA is diagnosed several years earlier than PBC, therefore persistently elevated liver enzyme levels should prompt AMA testing and evaluation for PBC, especially when there are no other causes of cholestasis (Mihai et al., 2024; Wang & Tsai, 2022). At the genetic level, overlap of genetic risk factors has been described, including *HLA-DQB1, STAT4, IRF5, MMEL1* and *CTLA4*, indicating shared immune susceptibility rather than coincidental co-occurrence (Smyk et al., 2012). Overall, the available data indicate that the coexistence of PBC and RA results from overlapping immunological and genetic mechanisms, therefore, in patients with RA, persistent abnormalities in liver tests should be an absolute indication for the diagnosis of PBC (Mihai et al., 2024; Radovanović-Dinić et al., 2018; Wang & Tsai, 2022). In addition, in patients with overlapping RA-PBC, potentially hepatotoxic drugs used in RA should be avoided (Radovanović-Dinić et al., 2018).

5.2 Autoimmune hepatitis

Autoimmune hepatitis (AIH) is a chronic immune-mediated inflammatory process leading to progressive damage to the hepatic parenchyma and requiring long-term immunosuppressive treatment (Komori, 2021). Among patients with RA, AIH is found infrequently, approximately 1.3% in individuals with liver dysfunction. While in AIH cohorts, the presence of RA was estimated at 1.6–5.4% and in some analyses at 2–4% (Wang & Tsai, 2022; Wong & Heneghan, 2015). Common genetic variants, including *STAT4* polymorphisms, confirm the overlap in immune susceptibility between AIH and RA (Migita et al., 2013). Overall, AIH in RA is rare but clinically significant due to shared immunological mechanisms, overlapping serological features, and the risk of drug-induced liver injury in patients treated with biologics (Craig & Cappelli, 2018; Wang & Tsai, 2022).

5.3 Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease leading to damage to the intrahepatic or extrahepatic bile ducts, progressive fibrosis, and the development of cirrhosis (Karlsen et al., 2017; Sarcognato et al., 2021). It often coexists with inflammatory bowel disease, especially ulcerative colitis (Karlsen et al., 2017). The association of PSC with RA is less common than in other autoimmune liver diseases, with the prevalence of RA in large PSC cohorts ranging from 1.2% to 3.4% (Mihai et al., 2024; Wang & Tsai, 2022). In patients with concurrent PSC and RA, the presence of *HLA-DR4* was associated with rapid progression to cirrhosis, sometimes as early as 14-48 months after PSC diagnosis, indicating a group at increased risk of disease progression (Gow et al., 2001; Mihai et al., 2024; Wang & Tsai, 2022). In clinical practice, PSC should be considered in patients with RA and persistent cholestasis, especially when more common causes of liver dysfunction have been excluded (Mihai et al., 2024).

Autoimmune liver diseases occur in patients with RA less frequently than NAFLD or drug-induced hepatotoxicity, but their diagnosis requires caution, as the symptoms are often subtle and may overlap with the side effects of treatment. The common denominator for PBC, AIH, and PSC in patients with RA is the overlap of immunogenetic predispositions, the presence of autoantibodies, and chronic immune system stimulation, suggesting that this comorbidity is not coincidental. Therefore, persistent liver function abnormalities in RA patients, especially when combined with an atypical serological profile should lead to diagnosis of autoimmune liver disease, and in cases of concurrent RA and PBC, caution in the use of hepatotoxic DMARDs is crucial (Mihai et al., 2024; Radovanović-Dinić et al., 2018; Wang & Tsai, 2022).

6. Drugs

Early initiation of therapy with the goal of achieving remission or at least low disease activity remains the central principle of current RA management. MTX remains the drug of first choice, often in combination with short-term glucocorticosteroids, which should be discontinued quickly. If the response is insufficient, subsequent decisions, the addition of biologic therapy or a JAK inhibitor, depend on prognostic factors and the safety profile. DMARDs remain the basis of therapy, especially classic synthetic drugs such as MTX, leflunomide, sulfasalazine, and hydroxychloroquine, which remain the starting point and reference for further treatment regimens (Smolen et al., 2023). The drugs used in RA span a broad spectrum, each carrying a distinct hepatic risk profile that depends on both the mechanism of action and patient-specific factors.

6.1 Methotrexate

MTX remains the first-line DMARD in rheumatoid arthritis, recommended at initiation of therapy for the majority of patients due to its well-established efficacy, long-term safety profile, and ability to improve structural and functional outcomes (Smolen et al., 2023). Current clinical trial data indicate that the hepatotoxicity profile of MTX in patients with RA is more complex than historical reports suggested (Di Martino et al., 2023). The most frequent abnormality consists of mild, transient elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) that appear mainly in the early phase of MTX therapy. In randomized trials, liver enzyme abnormalities occurred in 11.2% of MTX-treated patients overall, including 7.9% with elevations ≤3× ULN and 3.3% with elevations >3× ULN (Conway et al., 2015). In long-term clinical monitoring, ALT values above the upper limit of normal (ULN) were found in 7% of 6,288 performed tests, and at the patient level ALT >1.5× ULN, >2× ULN and >3× ULN occurred in 21%, 15% and 6% of individuals, respectively (Sundbaum et al., 2021). In patients with renal impairment, hepatotoxicity defined as ALT/AST ≥3× ULN was observed in 7.5% (9 of 120 cases) (Lee et al., 2020). Contrary to established opinion, it is not confirmed that MTX itself leads to progressive fibrosis or cirrhosis of the liver in

patients with RA. Neither elastography nor non-invasive panels have shown a relationship between cumulative dose and liver damage (Erre et al., 2019; Olsson-White et al., 2022). In studies based on shear-wave elastography, liver stiffness values were similar in patients who never received MTX treatment and those who had been taking the drug for a long time, and the incidence of significant fibrosis remained ≤3% and did not differ from the general population (Erre et al., 2019). Khoroshun et al. found that serious events such as liver failure or cirrhosis were very rare in analyses and most reports concerned only initial, mild liver enzyme abnormalities (Khoroshun et al., 2025). Metabolic background and comorbid liver diseases, especially NAFLD, obesity, diabetes, and factors associated with metabolic syndrome, play a major role in the interpretation of MTX hepatotoxicity. In many studies, these factors, rather than MTX, showed the strongest association with the presence of fibrosis or higher liver stiffness (Di Martino et al., 2023; Erre et al., 2019). Elevated ALT levels before initiating therapy, especially in metabolic conditions, were one of the most important predictors of subsequent enzymatic disorders during treatment (Sundbaum et al., 2021). In contrast, patients with impaired renal function had a significantly higher risk of toxicity, not only hepatic, which was associated with impaired drug elimination (Lee et al., 2020). Importantly, increased ALT/AST activity correlates poorly with the actual presence of fibrosis, as confirmed by both elastography studies and analyses of non-invasive markers. In a considerable number of patients with normal ALT, mild abnormalities were found in imaging studies, or conversely, false-positive fibrosis panel results were due to RA inflammatory activity (Olsson-White et al., 2022). Therefore, some authors suggest that routine monitoring based exclusively on ALT may be of limited value, and that a more individualized approach should be considered for patients with metabolic risk factors (Di Martino et al., 2023; Sundbaum et al., 2021). In summary, current data clearly indicate that MTX hepatotoxicity in RA is mostly acute, reversible, and enzymatic in nature, and that treatment itself rarely leads to continuous progression of liver damage or fibrosis (Conway et al., 2015; Di Martino et al., 2023; Erre et al., 2019). Coexisting factors play a dominant role, especially NAFLD, obesity, metabolic disorders, previous elevated ALT, and impaired renal function, which determine the risk of abnormalities more strongly than the dose or duration of treatment (Lee et al., 2020; Sundbaum et al., 2021). In many studies, MTX did not cause a greater increase in ALT than comparative therapies, and some meta-analyses showed no significant effect on liver enzyme levels (Jiang et al., 2021). In clinical practice, the safest and most appropriate approach involves assessing risk factors before starting therapy, regular monitoring of ALT in the first few months, and a more individualized approach, especially in patients with metabolic diseases or renal impairment (Di Martino et al., 2023; Sundbaum et al., 2021). Based on current evidence, MTX remains a drug with a favorable hepatic safety profile in most patients with RA, provided that appropriate monitoring is performed and risk groups are identified.

6.2 Other drugs

Among classic synthetic DMARDs, the most clinically significant concern is the hepatotoxicity of leflunomide, which, although less common than older reports suggested, can be severe. In clinical trials, leflunomide and MTX were the most common causes of treatment modification due to abnormal liver tests, with ALT or AST elevations affecting approximately 15% of patients. However, this risk was largely due to metabolic factors such as obesity, diabetes, elevated BMI, or alcohol abuse, which significantly increased the likelihood of needing to change DMARDs (Nandan et al., 2025). Other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including sulfasalazine and hydroxychloroquine, rarely lead to clinically significant liver damage, and reports of severe drug-induced liver injury are exceptional compared to the predominance of mild, reversible increases in transaminases (Smolen et al., 2023). In practice, therefore, the main risk of severe hepatotoxicity is associated with leflunomide, especially in patients with concomitant metabolic disorders.

6.3 Biologics and targeted therapies

In contrast to classic DMARDs, the hepatological profile of biologics and targeted therapies in RA is diverse and depends on both the mechanism of action and concomitant risk factors. In clinical trials with adalimumab, no significant findings in laboratory parameters were observed apart from isolated cases of HBV reactivation, which were considered as rare events and did not exceed the known safety profile (Burmester et al., 2017). Similarly, general safety analyses of tocilizumab revealed that the predominant problem is transient, mainly mild increases in aminotransferase activity, most often during the first year of therapy, with values returning to normal after a few weeks and rarely requiring discontinuation of treatment (Genovese et al., 2017). At the same time, the literature indicates that ALT/AST elevation after IL-6 inhibitors occurs more frequently

with concomitant MTX treatment, although it is usually asymptomatic and does not lead to serious complications (Zhao et al., 2023). The most important consideration regarding liver safety in biological therapies remains the risk of HBV reactivation, which is particularly well documented in the case of tocilizumab. In cohort studies, HBsAg-positive patients who did not receive antiviral prophylaxis experienced reactivation at a rate of up to 100%, with clinical exacerbation and jaundice, which was effectively prevented by the use of nucleoside analogues (Kuo et al., 2021). Data from meta-analyses support that in HBsAg-positive patients, the risk of reactivation is very high, while prophylaxis eradicates it almost completely (Ko et al., 2024). In the HBsAg-negative and anti-HBc-positive population, the risk exists but is significantly lower, usually without the development of overt hepatitis, and the absence of anti-HBs antibodies increases the likelihood of reactivation (Ko et al., 2024; Kuo et al., 2021). An individual approach to monitoring is necessary, especially since IL-6 inhibitors may impair the physiological inhibition of HBV replication, which explains the observed susceptibility to reactivation (Kuo et al., 2021). In the case of TNF-α inhibitors, the nature of potential liver toxicity is different. The described liver damage is rare, but when it occurs, it often resembles autoimmune hepatitis, with a predominance of the hepatocellular type, the presence of autoantibodies, and a typical histological picture (French et al., 2016). Most cases involve infliximab, which appears to carry a higher risk than other drugs in this class, although both adalimumab and etanercept can also lead to aminotransferase abnormalities, usually transient (Burmester et al., 2017; French et al., 2016; Zhao et al., 2023). Notably, hepatotoxic reactions are not a class effect, many patients tolerate another TNF-α inhibitor despite a previous episode of liver damage after receiving a drug from the same group (French et al., 2016). The papers also emphasize that in the case of TNF-α inhibitors, comorbidities, especially HBV infection or NAFLD, can significantly modify the risk and course of adverse hepatic reactions (French et al., 2016; Zhao et al., 2023). Overall, the hepatological safety profile of biologic therapies in RA is highly variable, ranging from mild, reversible enzymatic disorders - adalimumab, tocilizumab, JAK inhibitors, to rare, immunologically mediated damage resembling autoimmune hepatitis - infliximab, and a high risk of HBV reactivation in the absence of prophylaxis - tocilizumab. At the same time, all studies consistently emphasize that most adverse events are potentially reversible, and their prevention, especially through appropriate HBV screening, autoantibody assessment, and ALT/AST monitoring allows for safe treatment (Burmester et al., 2017; French et al., 2016; Genovese et al., 2017; Ko et al., 2024; Kuo et al., 2021; Zhao et al., 2023).

6.4 Janus kinase inhibitors

JAK inhibitors represent an important group of drugs used in patients with rheumatoid arthritis, offering an oral and effective therapeutic option for patients who respond inadequately to conventional or biological disease-modifying drugs (Smolen et al., 2023).

Available safety analyses of JAK inhibitors repeatedly show that this class of drugs can lead to aminotransferase activity increases, usually mild to moderate in severity (Cohen et al., 2020; Hall et al., 2018; Rocha et al., 2021; Taylor et al., 2022).

Systematic reviews emphasize that the increases in liver enzymes observed with JAK inhibitors, including tofacitinib and baricitinib, are consistent with the typical profile of mild laboratory abnormalities characteristic of this class of drugs, and their mild severity and predictable course allow for effective control with routine monitoring and rarely lead to discontinuation of treatment (Cohen et al., 2020; Rocha et al., 2021; Taylor et al., 2022). Data on HBsAg−/HBcAb+ patients show that the risk of HBV reactivation during JAK inhibitor therapy is very low (<1%), and regular monitoring of ALT, HBsAg, and HBV-DNA is considered sufficient without the need for routine antiviral prophylaxis (Hong et al., 2023). The results from clinical trials, long-term analyses, and systematic reviews therefore indicate a repeatable and relatively predictable hepatic profile for JAK inhibitors, typical, mild increases in ALT/AST, rare severe hepatotoxicity, and a very low risk of HBV reactivation in patients with a history of infection (Cohen et al., 2020; Hall et al., 2018; Hong et al., 2023; Rocha et al., 2021; Taylor et al., 2022). This requires standard biochemical monitoring but does not constitute a limitation in long-term use in patients with RA. It indicates that JAK inhibitors have a favorable and predictable safety profile, and clinical experience to date suggests that they will remain an important and promising therapeutic option for the RA treatment.

7. Conclusions

Current data clearly indicate that liver dysfunction in patients with RA is multifactorial and results from both comorbidities and the specific nature of the drugs used, with hepatotropic infections, NAFLD, and autoimmune liver diseases playing the most significant role (Maslennikov et al., 2021; Mihai et al., 2024; Zamani et al., 2023).

NAFLD is the most prevalent hepatic comorbidity in this population, with a prevalence that clearly exceeds that found in the general population. This is due to both the intensified inflammatory process and coexisting metabolic disorders such as obesity and insulin resistance (Barbarroja et al., 2022; Zamani et al., 2023). Population analyses indicate that up to one-third of patients fulfill NAFLD criteria, and studies using more sensitive methods such as elastography or biopsy reveal an even higher prevalence of steatosis and its progressive forms (Mahapatro et al., 2025; Zamani et al., 2023). Importantly, metabolic risk factors increase susceptibility to adverse drug reactions, especially MTX, which in some patients may accelerate the development of inflammation with steatosis and fibrosis (Mori et al., 2020; Shetty et al., 2017). The significance of NAFLD in patients with RA extends beyond the organ itself, as steatosis increases cardiovascular burden and requires consistent monitoring and lifestyle modifications (Barbarroja et al., 2022; Chehade et al., 2019). Autoimmune liver diseases, while less common, are overrepresented in RA relative to the general population. The most commonly diagnosed is PBC, which is significantly more common in RA than in the general population, highlighting the common immunogenetic background of both diseases (Mihai et al., 2024; Wang & Tsai, 2022). The high incidence of autoimmune liver diseases in patients with RA means that chronically elevated liver enzymes always require exclusion of PBC, especially when there are no other causes of cholestasis (Mihai et al., 2024; Radovanović-Dinić et al., 2018). AIH is less common, but its presence in patients with RA is clinically significant due to the partially overlapping immune profile and the possibility of worsening the course of the disease under immunosuppressive therapy, including biological drugs (Craig & Cappelli, 2018; Wang & Tsai, 2022). PSC is even less common, but its coexistence with RA may be associated with faster progression, especially in patients with an unfavorable HLA profile, so persistent features of cholestasis should prompt evaluation in this direction (Gow et al., 2001; Mihai et al., 2024).

HBV and HCV infections remain a key clinical problem because they can mimic or modify the clinical picture of RA, while also posing a major safety challenge during immunosuppression, especially in patients receiving biological therapy (Cacoub et al., 2017). Regarding HCV, population data consistently point to an increased risk of developing RA, which confirms the involvement of viral factors in the initiation of autoimmunity and, at the same time, emphasizes the need to differentiate between infectious arthropathy and early RA (Su et al., 2014; Tang et al., 2025). In turn, chronic HBV infection is primarily associated with the risk of reactivation during immunosuppression, and its scale depends on HBsAg status, the presence of protective antibodies, and the use of antiviral prophylaxis (Hong et al., 2023; Matsuzaki et al., 2018). The most significant risk is associated with biological therapies, primarily IL-6 inhibitors. Studies have reported that in the HBsAg-positive group, the lack of prophylaxis almost always led to reactivation, while appropriate antiviral treatment effectively prevented it (Ko et al., 2024; Kuo et al., 2021). Regarding classic DMARDs, the hepatotoxicity of MTX gains the most attention, although contemporary analyses indicate that it mainly causes reversible enzymatic disorders, and metabolic factors such as obesity or NAFLD have a much broader impact on the risk of liver damage than the drug itself (Di Martino et al., 2023; Erre et al., 2019). Leflunomide remains the drug with the highest hepatotoxic potential among conventional therapies, with metabolic factors and additional burdens playing a dominant role here as well, rather than the toxicity of the drug (Nandan et al., 2025). In the case of TNF-α inhibitors, the picture of hepatotoxicity is different, as the rare incidents of liver damage usually have features similar to autoimmune inflammation and mainly concern infliximab, while not constituting a uniform reaction for the entire drug class (French et al., 2016; Zhao et al., 2023). IL-6 inhibitors, although associated with relatively common yet usually mild elevations in liver enzymes, maintain a favorable safety profile as long as regular monitoring and appropriate HBV prophylaxis are ensured, which plays a key role in preventing serious hepatic complications (Genovese et al., 2017; Ko et al., 2024). JAK inhibitors have a consistent, predictable safety profile, with minor enzyme abnormalities and a very low risk of HBV reactivation, making them a valuable treatment option for long-term RA management (Hong et al., 2023; Rocha et al., 2021). At the same time, NAFLD and autoimmune liver diseases are significant comorbidities, often independent of treatment but significantly affecting laboratory interpretation and therapeutic decisions, especially in patients with chronic inflammatory activity and multiple metabolic factors (Wang & Tsai, 2022; Zhong et al., 2024).

Liver dysfunction in patients with RA is rarely incidental, but largely results from existing liver disease, chronic inflammation, or immunogenetic susceptibility (Craig & Cappelli, 2018; Mihai et al., 2024; Wang & Tsai, 2022). The EULAR recommendations consistently emphasize that the hepatological safety of RA therapy depends primarily on the initial assessment of liver status, mandatory HBV/HCV screening, appropriate ALT/AST monitoring, and cooperation with a hepatologist in patients with comorbidities. The recommendations do not differentiate between classes of drugs, emphasizing individualized therapy and control of risk factors such as NAFLD, alcohol, obesity, and prior hepatotropic infections (Smolen et al., 2023). In clinical practice, this demands regular assessment of liver function, comprehensive diagnostic evaluation in case of persistent abnormalities, and cautious use of hepatotoxic therapies, especially in patients with concomitant PBC or other autoimmune liver diseases. Evidence consistently indicates that the hepatological safety of RA treatment depends primarily on thorough pre-treatment assessment, effective management of comorbidities, and individualized monitoring, rather than on a single drug or therapeutic class (Ko et al., 2024; Mihai et al., 2024; Radovanović-Dinić et al., 2018).

Abbreviations:

AIH (Autoimmune Hepatitis), ALT (Alanine Aminotransferase), AMA (Antimitochondrial Antibodies), ANA (Antinuclear Antibodies), anti-HBc (Antibodies against Hepatitis B Core Antigen), anti-HBs (Antibodies against Hepatitis B Surface Antigen), AST (Aspartate Aminotransferase), BMI (Body Mass Index), CTLA4 (Cytotoxic T-Lymphocyte Associated Protein 4), DAA (Direct-Acting Antiviral Agent), DMARD (Disease-Modifying Antirheumatic Drug), csDMARD (Conventional Synthetic Disease-Modifying Antirheumatic Drug), EULAR (European Alliance of Associations for Rheumatology), HAV (Hepatitis A Virus), HBcAb (Hepatitis B Core Antibody), HBsAg (Hepatitis B Surface Antigen), HBV (Hepatitis B Virus), HBV-DNA (Hepatitis B Virus Deoxyribonucleic Acid), HCV (Hepatitis C Virus), HEV (Hepatitis E Virus), HLA (Human Leukocyte Antigen), IL-6 (Interleukin-6), IRF5 (Interferon Regulatory Factor 5), JAK (Janus Kinase), MMEL1 (Membrane Metalloendopeptidase-Like 1), MTX (Methotrexate), NAFLD (Nonalcoholic Fatty Liver Disease), NASH (Nonalcoholic Steatohepatitis), PBC (Primary Biliary Cholangitis), PSC (Primary Sclerosing Cholangitis), RA (Rheumatoid Arthritis), RF (Rheumatoid Factor), STAT4 (Signal Transducer and Activator of Transcription 4), TNF-α (Tumor Necrosis Factor Alpha), ULN (Upper Limit of Normal).

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