CASE REPORT

10.2478/AMB-2026-0019

CHOLESTATIC DRUG-INDUCED LIVER INJURY IN A RHEUMATOID ARTHRITIS PATIENT RECEIVING LEFLUNOMIDE: A CLINICAL CASE REPORT

M. Mihaylova[1,2], B. Zhelezarova[3, 4]

[1]Department of Nephrology, Hematology, and Gastroenterology, Faculty of Medicine, Medical University – Pleven, Bulgaria
[2]Clinic of Gastroenterology, University Hospital „Georgi Stranski" – Pleven, Bulgaria
[3]Department of Cardiology, Pulmonology, Endocrinology and Rheumatology, Faculty of Medicine, Medical University – Pleven, Bulgaria
[4]Clinic of Rheumatology, University Hospital „Georgi Stranski" – Pleven, Bulgaria

Abstract. *Drug-induced liver injury (DILI) is a significant clinical challenge due to its variable presentation and lack of specific biomarkers. Leflunomide, an immunomodulatory agent commonly used in rheumatoid arthritis, carries a known risk of hepatotoxicity, typically presenting with a hepatocellular pattern. We report a clinical case of a 59-year-old male patient with seropositive rheumatoid arthritis who developed cholestatic DILI following combined therapy with leflunomide and aceclofenac. Diagnosis was established based on clinical presentation, laboratory findings, exclusion of alternative causes, and a high Roussel Uclaf Causality Assessment Method (RUCAM) score. Cholestatic DILI associated with leflunomide is relatively rare, making this case a valuable contribution to understanding atypical presentations of hepatotoxicity in rheumatoid arthritis patients. Discontinuation of the implicated agents and initiation of supportive therapy, including corticosteroids and hepatoprotective agents, resulted in gradual clinical and biochemical recovery. This case emphasises the importance of careful monitoring for liver toxicity during combined immunomodulatory and nonsteroidal anti-inflammatory therapy and illustrates the challenges in diagnosing cholestatic DILI, a less common but clinically significant pattern of liver injury.*

Key words: *drug-induced liver injury, immunomodulatory agents, hepatotoxicity, rheumatoid arthritis, nonsteroidal anti-inflammatory drugs*

Corresponding author: *Miroslava Mihaylova, Department of Nephrology, Hematology, and Gastroenterology, Faculty of Medicine, Medical University – Pleven, Bulgaria; Clinic of Gastroenterology, University Hospital „Georgi Stranski", Pleven, Bulgaria, email: mihailova75.md@gmail.com*

ORCID: *0000-0001-7960-4373*

Received: *01 September 2025;* ***Accepted:*** *10 October 2025*

INTRODUCTION

According to the FDA (U.S. Food and Drug Administration) and the EMA (European Medicines Agency), medicines are substances used for the treatment and/or prevention of disease conditions by influencing various functions in the body or altering its structure through different mechanisms of action. Their use is legally regulated and includes activities related to the prevention, registration, and monitoring of adverse events and side effects [1]. Drug-induced liver injury (DILI) represents

unintended damage to liver structure and function following exposure to medications, biologics, or dietary supplements. The clinical manifestations vary widely, from mild, asymptomatic alterations in liver enzymes to severe, acute liver failure [2, 3]. The pathogenesis of DILI includes direct dose-dependent hepatotoxicity, unpredictable, and dose-independent idiosyncratic reactions, and indirect injury mediated through altered drug metabolism or immune dysregulation [2]. Central mechanisms involve increased oxidative stress, mitochondrial impairment, disruptions in hepatic metabolic pathways, and immune-mediated hepatocyte injury, all of which are especially relevant in patients with polypharmacy or autoimmune disorders [4]. The global incidence of DILI appears to be increasing, with a recent meta-analysis reporting an overall incidence rate of 4.94 cases per 100,000 individuals, reaching up to 17.82 per 100,000 in Asian populations [5]. Leflunomide, a synthetic immunosuppressive agent widely used for the management of rheumatoid arthritis (RA), carries a known risk of hepatotoxicity through its active metabolite, teriflunomide [6, 7]. In 2011, the FDA added a 'black box' warning to the label of leflunomide due to the risk of severe liver injury [7]. Approximately 15% of patients treated with leflunomide experience transient, asymptomatic elevations in liver enzymes, while clinically significant liver injury occurs in 1-4% of cases [7]. Across studies involving heterogeneous patient populations, the incidence of severe DILI with jaundice has varied between 0.5% and 0.8% [8]. Despite its generally favourable safety profile, premature discontinuation of leflunomide due to adverse events has been documented in 43.4% [9] and up to 52% of patients [10]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly employed for chronic pain management in rheumatology practice but are also associated with hepatotoxicity [11]. Approximately 10% of cases of drug-induced hepatotoxicity are attributed to NSAIDs due to their widespread use, and it is most commonly observed with diclofenac [12]. Aceclofenac is structurally related to diclofenac, and after oral administration, part of it is metabolised by CYP2C9 to diclofenac [13]. Combined therapy with leflunomide and NSAIDs may increase hepatotoxic risk due to pharmacokinetic and pharmacodynamic interactions that exacerbate oxidative stress and impair hepatic metabolism [6, 7, 14]. Diagnosis of DILI remains challenging due to the absence of specific biomarkers and overlapping clinical features with other hepatic diseases [3, 15]. This report presents a case of cholestatic DILI in a 59-year-old male patient with seropositive RA treated with leflunomide and aceclofenac, highlighting diagnostic and therapeutic considerations.

CASE PRESENTATION

A 59-year-old man with seropositive rheumatoid arthritis (RA), diagnosed six years ago, was previously treated with methotrexate for five years. Treatment was discontinued due to disease exacerbation. The patient was evaluated and deemed eligible for initiation of biological therapy. A preliminary screening for hepatitis B and C, chlamydial infection, Lyme disease, and streptococcal infection was performed, all of which were negative. Initial laboratory results revealed elevated markers of inflammation, including CRP at 45 mg/L and fibrinogen at 5.5 g/L. Rheumatoid factor measured 15.9 IU/mL (upper limit of 8 IU/mL). The patient tested strongly positive for anti-cyclic citrullinated peptide (anti-CCP) antibodies, with a value exceeding 500 U/mL (LOINC-coded assay), which is highly specific for RA. Other baseline liver function tests, haematological parameters, and thyroid function tests were within normal limits. He had a history of mild arterial hypertension and minimal hypercholesterolaemia, without any current medications, and reported minimal to moderate alcohol consumption. Leflunomide therapy was initiated at the standard dose as a bridging treatment toward biological therapy. The patient had been regularly taking aceclofenac before and after leflunomide initiation for several weeks, despite the medical prescription indicating a short-term course of 14 days.

Approximately two and a half months after starting leflunomide, the patient developed progressive fatigue, loss of appetite, unintended weight loss, dark urine, and jaundice. He also experienced a single episode of low-grade fever (up to 37.5 °C) and a transient sore throat. Upon admission, significant elevations in liver enzymes and bilirubin levels were observed.

Serological tests for hepatitis A, B, C, and E viruses, as well as the Epstein–Barr virus (EBV), were negative (only EBV IgG was positive). Autoimmune antibodies: antinuclear and antimitochondrial (ANA, AMA) were negative. Immunoglobulin levels (IgA, IgG, IgM) were within normal reference ranges. Serum protein electrophoresis revealed no abnormalities. Abdominal ultrasonography showed hepatic steatosis without evidence of biliary obstruction. Tumour markers: alpha-fetoprotein and CA 19-9, were within normal limits.

The baseline results and their changes during chronological follow-up are presented in Table 1.

Table 1. Laboratory findings during the clinical course of the patient

Parameter	Reference values	Day 0	Day 4	Day 7	Day 15	Day 38
ALT	0-40 (U/L)	107.1	115.0	122.1	73.8	31.1
AST	0-40 (U/L)	63.2	60.6	72.0	30.0	18.5
ALP	45-130 (U/L)	577.9	438.0	569.0	270.0	104.0
GGT	7-50 (U/L)	699.7	664.0	654.0	321.0	79.0
Total Bilirubin	5-21(μmol/L)	114.8	67.5	64.7	32.8	12.7
Direct Bilirubin	0-5 (μmol/L)	99.7	58.0	53.9	20.0	6.1
Albumin	35-50 (g/L)	33.2	–	–	–	38.7
CRP	0-5 (mg/L)	275.8	63.59	–	–	3.25
Fibrinogen	2-4 (g/L)	7.3	–	–	–	2.99
INR	0.8-1.1	0.99	–	–	–	0.84
WBC	3.5-10.5 ($\times 10^9$/L)	10.1	–	–	–	5.0
Plt	150-400 ($\times 10^9$/L)	338	–	–	–	201
Hb	130-180 (g/L)	121	–	–	–	132
MCV	80-95 (fL)	78.7	–	–	–	81.3

Note: ALT – alanine aminotransferase; AST – aspartate aminotransferase; ALP – alkaline phosphatase; GGT – gamma-glutamyl transferase; CRP – C-reactive protein; INR – international normalized ratio; WBC – white blood cells; Plt – platelets; Hb – hemoglobin; MCV – mean corpuscular volume; "–" indicates data not available

Assessment of the liver injury pattern was performed using the R factor (ALT/ULN ÷ ALP/ULN), which in this case was calculated as 0.7, consistent with a cholestatic type of liver injury [2, 3, 16]. Based on the International DILI Expert Working Group guidelines, the case was classified as moderate in severity, given the presence of jaundice and elevated liver enzymes, without indications of liver failure or coagulation abnormalities [2]. The probability of DILI was evaluated using the updated Roussel Uclaf Causality Assessment Method (RUCAM). The total score of 9 indicates a "highly probable" causal relationship between leflunomide and the observed hepatotoxicity [17, 18].

Upon detection of clinically significant hepatic laboratory abnormalities, leflunomide and aceclofenac were immediately discontinued. Empiric therapy was initiated with intravenous methylprednisolone (40 mg daily), ademetionine (1000 mg daily) and vitamin C (500 mg daily). By day 7, clinical and biochemical improvement remained suboptimal, prompting the initiation of adjunctive therapy with ursodeoxycholic acid (1200 mg/day) and oral acetylcysteine (600 mg/day). Serial follow-up demonstrated marked clinical and laboratory improvement by day 14, with near-complete recovery of hepatic parameters by day 38. Corticosteroid therapy was subsequently tapered in a gradual, stepwise manner, resulting in sustained recovery without evidence of relapse. To consolidate hepatic function, the patient was advised to continue maintenance therapy with ursodeoxycholic acid (600 mg/day) for an additional three months.

DISCUSSION

Proper evaluation of DILI in clinical practice requires establishing a temporal relationship between drug exposure and symptom onset, classifying the pattern of liver injury using the R ratio – hepatocellular, cholestatic, or mixed – excluding alternative causes of hepatic damage, and identifying concomitant factors that may influence the development of liver injury [2, 3, 19]. The initial step in diagnosis is the identification of significant liver test abnormalities. ALT > 5× ULN, ALP > 2× ULN, or bilirubin > 2× ULN with ALT > 3× ULN supports the diagnosis, helping to differentiate DILI from other liver diseases [3, 19]. In most cases, leflunomide-associated hepatotoxicity presents with a hepatocellular pattern and is observed more frequently in women. [8, 20]. The time from drug intake to the onset of initial symptoms varies widely, averaging from 1 to 6 months [20], and in our case, it was two and a half months. Cholestatic forms are less common but may be associated with more severe and prolonged clinical courses [8]. Additionally, seropositive RA and coexisting non-alcoholic fatty liver disease (NAFLD) may further increase the risk of leflunomide-induced hepatotoxicity [21].

Treatment starts by stopping the medicine thought to be causing the problem, and in mild cases, this step alone may be enough. In clinically significant forms of liver injury, careful adjustment of the therapeutic regimen is required. The use of corticosteroids as a therapeutic strategy is not routinely established [22].

In our patient, markedly elevated inflammatory markers were initially observed, reflecting severe systemic inflammation associated both with the underlying disease and the subsequent liver injury. Corticosteroids were introduced to control the primary disease process due to the lack of other suitable therapeutic alternatives at the time.

There is evidence that ursodeoxycholic acid may have a beneficial effect on idiopathic and cholestatic forms of DILI, as in our case, and that it may also be used prophylactically to prevent liver injury. The proposed beneficial effects include stabilisation of cellular membranes, inhibition of apoptosis, antioxidant activity, and restoration of endogenous glutathione levels in cholangiocytes, which are particularly susceptible to injury [23]. Nevertheless, the routine use of ursodeoxycholic acid in such cases has not been established, and current clinical guidelines do not provide standardised recommendations for its application. Evidence also supports the potential benefit of ademetionine in cholestatic DILI due to similar mechanisms of action [24]. In our case, N-acetylcysteine was additionally used as a universal antioxidant, well-established as the primary antidote to acetaminophen poisoning.

CONCLUSION

This case highlights the need for increased vigilance when prescribing medications with potential hepatotoxic effects. In this context, strict monitoring of biochemical parameters is recommended, particularly at the beginning of treatment, along with careful assessment in cases of combined drug therapy and individualised evaluation of risk factors prior to therapy initiation. In addition, adequate patient education regarding possible adverse events is essential for early recognition of liver injury and effective management of therapy. Due to the lack of a universally accepted treatment standard applicable to all cases, therapeutic strategies should be personalised.

Ethical statement: *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki. Full anonymity of the patient has been preserved.*

Conflict of interests: *The authors declare no conflicts of interest and no additional funding.*

Funding: *The authors did not receive any financial support for this work.*

Consent for publication: *Consent form for publication was signed by the patient and collected.*

Declaration of AI Use: *Artificial intelligence was used in the preparation of this manuscript for editing, grammatical corrections, and technical formatting. The authors confirm that they take full responsibility for the accuracy and integrity of the presented content.*

REFERENCE

1. Hadzhieva B, Dimitrov M, Petkova V. Pharmaceutical regulation of herbal medicinal products in the countries of the European Union, the USA, Canada and Japan. Acta Medica Bulgarica. 2023;50(3):71-74.
2. CIOMS Working Group. Drug-Induced Liver Injury: Current status and future directions. [Internet]. Geneva: CIOMS; 2020. Available from: https://cioms.ch/wp-content/uploads/2020/06/CIOMS_DILI_Web_16Jun2020.pdf
3. European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol. 2019;70(6):1222–1264.
4. Stavrakeva K, Popova M, Esad M, et al. Drug-induced liver toxicity. Acta Medica Bulgarica. 2025;51(4):77-85.
5. Li J, Zhao W, Wang R, et al. Mapping the incidence of drug-induced liver injury: A systematic review and meta-analysis. Liver Int.2023;43(12):2826–2837.
6. FDA Drug Safety Communication: Risks of liver injury with leflunomide. [Internet]. U.S. Food and Drug Administration (FDA). 2021. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-risk-liver-injury-leflunomide
7. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012–. Leflunomide. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548725/
8. Devarbhavi H, Ghabril M, Barnhart H, et al. Leflunomide-induced liver injury: Differences in characteristics and outcomes in Indian and U.S. registries. Liver Int. 2022;42(6):1323–1329.
9. Mielnik P, Sexton J, Fagerli KM, et al. Discontinuation rate of sulfasalazine, leflunomide and methotrexate due to adverse events in a real-life setting (NOR-DMARD). Rheumatol Adv Pract. 2023;7(2):rkad053.
10. Miladi S, Ben Yacoub S, Boussâa H, et al. Leflunomide in rheumatoid arthritis: Factors associated with therapeutic maintenance. Revmatologia. 2024;32(1):5–11.
11. Nikolov RP. Adverse reactions associated with the use of non-steroidal anti-inflammatory drugs and non-opioid analgesics. Revmatologia. 2010;18(1):18-27.
12. Meunier L, Larrey D. Recent advances in hepatotoxicity of nonsteroidal anti-inflammatory drugs. Ann Hepatol. 2018;17(2):187–191.
13. Kim S, Lee S, Lee J, Yu K. Modeling of aceclofenac metabolism to major metabolites in healthy volunteers. Biopharm Drug Dispos. 2016;37(9):480–491.
14. Drug Interaction Report: diclofenac, leflunomide. [Internet]. Drugs.com. Available from: https://www.drugs.com/interactions-check.php?drug_list = 869-0%2C1440-0&professional = 1
15. Ahmed T, Ahmad J. Recent advances in the diagnosis of drug-induced liver injury. World J Hepatol. 2024;16(2):186–192.
16. Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89(6):806–815.

17. Danan G, Teschke R. RUCAM in drug and herb induced liver injury: The updated version. Int J Mol Sci. 2016;17(1):14.
18. LiverTox: Roussel Uclaf Causality Assessment Method (RUCAM) in Drug Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases. 2012; Updated 2019 May 4. Available from:https://www.ncbi.nlm.nih.gov/books/NBK548272
19. Chalasani N, Younossi Z, Lavine JE, et al. AASLD Practice Guidance: Drug-Induced Liver Injury. Hepatology. 2017;65(6):2036–2094.
20. Bokan G. Leflunomide hepatotoxicity in rheumatoid arthritis: Case report and literature review.Slovenian J Gastroenterol. 2024;2:1–5.
21. Salmi AR, Islahudin F, Shamsuddin AF, Shahril NS. A study on leflunomide-induced liver injury in rheumatoid arthritis patients. Res J Pharm Technol. 2013;6(5):556–561.
22. Chalasani NP, Hayashi PH, Bonkovsky HL, et al. The diagnosis and management of idiosyncratic drug induced liver injury. Am J Gastroenterol. 2014;109(7):950–966.
23. Bessone F, Hillotte GL, Tamagnone N, et al. Ursodeoxycholic acid for the management of drug-induced liver injury: Role of hepatoprotective and anti-cholestatic mechanisms. J Clin Transl Hepatol. 2025;13(2):162–168.
24. Li M, Luo Q, Tao Y, et al. Pharmacotherapies for drug-induced liver injury: A current literature review. Front Pharmacol. 2022;12:806249.