Case report / *Prikaz primera*

Leflunomide hepatotoxicity in rheumatoid arthritis case report and literature review

Okvara jeter pri bolniku z revmaoidnim artritisom zdravljenim z leflunomidom; Prikaz primera in pregled literature

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***Ključne besede**: revmatoidni artritis, leflunomid, poškodba jeter, hepatotoksičnost*

ABSTRACT

Leflunomide (LEF) is a disease-modifying antirheumatic drug that induces hepatotoxicity ranging from mild to severe and can present as acute or chronic liver injury. We described a case of hepatotoxicity from our clinical practice and reviewed the literature that includes the terms 'hepatotoxicity' and 'leflunomide'.

A 70-year-old female patient with seropositive rheumatoid arthritis presented for a regular check-up after 45 days of being introduced to LEF in therapy. The initial elevated laboratory findings are aspartate aminotransferase, alanine aminotransferase and gamma-glutamyl transferase.

IZVLEČEK

Leflunomid (LEF) je antirevmatsko zdravilo, ki lahko povzroči blago do hudo okvaro jeter, ki se lahko kaže kot akutna ali kronična okvara jeter. Opisali smo primer jetrne okvare zaradi leflunomida in pregledali literaturo, ki vključuje izraza 'hepatotoksičnost' in 'leflunomid'.

70-letna bolnica s seropozitivnim revmatoidnim artritisom je prišla na redno kontrolo po 45 dneh po uvedbi LEF v terapijo. Ugotovili smo povišane laboratorijske vrednosti za aspartat aminotransferazo, alanin aminotransferazo in gama-glutamil transferaza.

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Serological, immunological and radiographic findings were without significant deviation. LEF was immediately excluded from therapy and the patient was hydrated and treated with hepatoprotective agents during hospitalisation. Liver function test results decreased and normalized over time without any severe manifestation of liver injury. This case report highlights the importance of monitoring liver function tests during leflunomide therapy. Prompt recognition and treatment of leflunomide-induced hepatotoxicity can lead to a good clinical outcome.

Serološki, imunološki in radiografski izvidi so bili brez pomembnega odstopanja. LEF je bil takoj izključen iz terapije, bolnica je bila med hospitalizacijo hidrirana in zdravljena s hepatoprotektivnimi učinkovinami. Jetrni testi so se sčasoma zmanjšali in normalizirali. Resnih znakov poškodbe jeter nismo potrdili. Prikaz primera kaže na pomen spremljanja jetrnih testov med zdravljenjem z leflunomidom. Hitro prepoznavanje in zdravljenje hepatotoksičnosti, ki jo povzroča leflunomid, vodi do dobrega kliničnega izida.

Abbreviations used in this paper: *LEF – leflunomide; DMARD – disease-modifying antirheumatic drug; RA – rheumatoid arthritis; LTs – liver tests; AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase; ALP – alkaline phosphatase; INR – international normalised ratio; COVID – Coronavirus disease; HSV – herpes simplex virus; CMV – Cytomegalovirus; EBV – Epstein–Barr virus (EBV); AMA – Anti-mitochondrial M2 antibody; cANCA – Antineutrophil cytoplasmic antibody; pANCA – Perinuclear anti-neutrophil cytoplasmic antibodies; RUCAM – Roussel Uclaf Causality Assessment Method*

INTRODUCTION

Leflunomide (LEF) is a disease-modifying antirheumatic drug (DMARD) used to treat rheumatoid arthritis (RA) since 1998. Current guidelines recommend LEF as monotherapy or in combination with other DMARDs, and even as a first-line therapy (1). Although LEF is generally well-tolerated, it is a prodrug converted into its active metabolite, teriflunomide, which inhibits the production of pyrimidine synthesis and affects the immune system, reducing inflammation and joint damage in RA patients (2).

Despite its efficacy in treating RA, leflunomide has been associated with hepatotoxicity, which is the most common adverse effect of the drug. Leflunomide-induced hepatotoxicity can range from mild to severe and can present as acute or chronic liver injury, including liver failure, requiring liver transplantation (3, 4).

The mechanism of leflunomide-induced hepatotoxicity is not fully understood, but it is believed to be related to the drug's metabolite teriflunomide. The long half-life of teriflunomide may contribute to the prolonged hepatotoxic effect, even after stopping the use of the drug. Additionally, other factors such as alcohol consumption, pre-existing liver disease, and concomitant medication use may increase the risk of developing leflunomide-induced hepatotoxicity (5, 6).

In recent years, several cases of leflunomide-induced hepatotoxicity have been reported in the literature. Understanding the risk factors and clinical features of this adverse effect is important for timely diagnosis and appropriately managing this adverse effect.

CASE REPORT

A 70-year-old female patient with seropositive rheumatoid arthritis presented for a regular check-up after 45 days of being introduced to LEF in therapy, a new therapeutic modality. The patient denied any complaints, but laboratory findings revealed elevated values of the serum biochemical liver tests (LTs). The patient was admitted to the Department of Rheumatology, where a normal clinical examination was performed, initially laboratory findings showed elevated values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl trans-

ferase (GGT), alkaline phosphatase (ALP), Direct and Total Bilirubin while albumin and international normal ratio (INR) were within the reference range. Coronavirus disease (COVID), Influenza A and B tests were negative. Abdominal ultrasound and computed tomography scan of the abdomen have not shown any changes in the hepatic and biliary system. Markers for hepatitis, the herpes simplex virus (HSV), Cytomegalovirus (CMV), and Epstein–Barr virus (EBV), copper, ceruloplasmin, antinuclear antibody, liver-kidney microsomal antibody, Anti-mitochondrial M2 antibody (AMA-M2), Antineutrophil cytoplasmic antibody (cANCA), Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), Immunoglobulin G levels were normal. Leflunomide was immediately excluded from therapy, and the patient was hydrated and treated with hepatoprotective agents during hospitalisation. The liver function test results decreased and normalised over time, and it was concluded that the patient had liver damage caused by leflunomide. Table 1 presents the initial laboratory findings. Figure 1 and Table 2 show the trend of the liver function test results. The patient was then switched to other disease-modifying antirheumatic drugs (DMARDs).

Table 1. Initial laboratory findings

ANALYTE	VALUE	NORMAL RANGE
AST	384	< 50 U/l
ALT	1 338	< 50 U/l
GGT	918	8–61 U/l
ALP	144	30–120 U/l
TOTAL BILIRUBIN	37,6	5–21 µmol/l
DIRECT BILIRUBIN	25	0–5 µmol/l

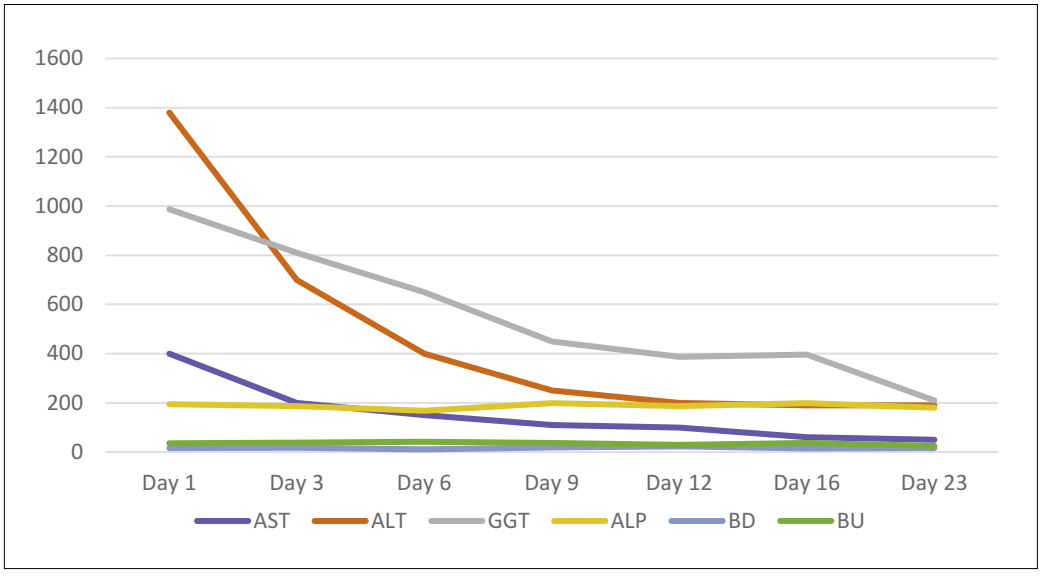

Figure 1. Trend of LTs

DISCUSSION

LEF therapy rarely leads to an increase in transaminases and is most often in the form of a transient slight increase in transaminases. The Roussel Uclaf Causality Assessment Method (RUCAM) is used to consider the probability of the existence of a hepatic lesion, as well as the type of damage: hepatocellular, cholestatic and mixed type (7, 8). In our study, about 45 days passed from the introduction of therapy to the verification of elevated transaminases, and the R factor calculated using the RUCAM calculator was 15.1, which means that it was a hepatocellular type of damage.

According to the data from the register, the median occurrence of liver damage in patients treated with LEF therapy is 49 days, with hepatocellular damage being the most frequent type (9). Our case study supports previous research by confirming that LEF-induced hepatotoxicity is typically characterised by transient hepatocellular damage, aligning with the overall findings in the literature on LEF therapy.

Alves et al. reported no significant difference in the percentages of aminotransferase elevations between

patients treated with methotrexate (MTX) alone and those treated with a combination of MTX and leflunomide (LEF) (10). Xuan et al. suggested that mitochondrial dysfunction is the primary cause of leflunomide-induced hepatotoxicity (11), providing a biochemical basis for the hepatocellular damage we observed. Our study contributes to this understanding by confirming the hepatocellular nature of the damage in our patients.

Van Roon et al. followed 101 patients undergoing leflunomide therapy and noted the severity of liver lesions. Based on liver enzyme determinations, they found that 8.9% of patients experienced grade 2 or

Table 2. Trend of LTs

	AST (U/L)	**ALT** (U/L)	**GGT** (U/L)	**ALP** (U/L)	**Direct Bilirubin** (µmol/L)	**Total Bilirubin** (µmol/L)
Day 1	400	1380	987	195	16	36
Day 3	200	700	810	187	18	38
Day 6	150	400	650	168	11	42
Day 9	110	250	450	199	19	37
Day 12	100	200	387	187	23	29
Day 16	60	190	396	199	15	37
Day 23	50	190	210	180	16	25

Table 3. Comparative analysis of studies on Leflunomide (LEF) Therapy-Induced Hepatotoxicity

Study	**Key findings**	**Type of liver damage**	**Time to onset of damage**	**Additional notes**
Gupta et al. (9)	LEF + other DMARDs in RA treatment can lead to increased liver enzyme levels, though no patients displayed clinical signs of liver damage.	Hepatocellular	Within a month of starting the therapy	Highlights the importance of ongoing monitoring rather than immediate discontinuation of therapy.
Alves et al. (10)	No significant difference in aminotransferase elevations with MTX alone vs. MTX + LEF.	Hepatocellular	Not specified	Indicates no added risk with combination therapy.
Xuan et al. (11)	Mitochondrial dysfunction as the primary cause of LEF-induced hepatotoxicity.	Hepatocellular	Not specified	Provides biochemical basis for hepatocellular damage.
Van Roon et al. (12)	LEF treatment generally leads to mild to moderate liver enzyme elevations, with occasional severe cases, but no life-threatening hepatotoxicity was observed.	Hepatocellular	During the initial six months of treatment	Under continued monitoring of liver functions hepatotoxicity during leflunomide use does not seem to be a major problem in our population.
Current study	Confirms LEF-induced hepatotoxicity with transient hepatocellular damage.	Hepatocellular	~45 days	Highlights the importance of monitoring liver function tests during LEF therapy.

3 hepatotoxicity within the first year of therapy. In most patients, liver enzyme elevations occurred within the first 6 months of treatment and resolved during continued follow-up. None of the patients showed clinical signs of hepatotoxicity (12). This aligns with our findings where the elevation was noted after 45 days and supports the observation that LEF-induced liver enzyme elevations are typically transient and resolve over time. Table 3 offers a comparative overview of research on hepatotoxicity induced by leflunomide therapy.

CONCLUSION

This study underscores that although leflunomide-induced hepatotoxicity is infrequent, it represents a significant concern requiring meticulous oversight. The results indicate that leflunomide therapy can lead to elevated liver enzyme levels, predominantly presenting as mild to moderate hepatocellular damage, with significant enzyme elevations typically occurring within the initial six months of treatment. This highlights the necessity for rigorous monitoring of liver function throughout leflunomide therapy, especially in individuals with pre-existing hepatic conditions. Regular liver function assessments are essential for the early detection of hepatotoxicity, enabling prompt intervention and adjusting the needed therapy. Consequently, while leflunomide is an effective medication for managing rheumatoid arthritis, its potential for liver toxicity demands careful patient evaluation and ongoing surveillance to ensure safety and therapeutic efficacy.

Conflicts of Interest: The authors declare no conflict of interest.

Institutional Review Board Statement: The Ethical Board of the University Clinical Centre of the Republic of Srpska approved this study.

Informed Consent Statement: The patient signed the informed consent.

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