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EDITORIAL

Are we monitoring enough? Addressing hepatic and renal safety gaps in rheumatologic therapy

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Abstract

The maintenance of rheumatologic diseases is heavily dependent upon pharmacologic interventions that, though effective, pose substantial risks of hepatotoxicity and nephrotoxicity. Though guidelines for monitoring these patients have been established, compliance with these measures in real-world practice is inconsistent. Some studies show that many patients do not get the needed laboratory tests, especially in resource-limited regions. The following editorial points out the shortcomings in the practice of surveillance for these patients, especially in low-income settings including Pakistan.

Keywords: Hepatotoxicity; Nephrotoxicity; Rheumatology; Monitoring; Non-steroidal anti-inflammatory drugs (NSAIDs); Disease-modifying anti-rheumatic drugs (DMARDs)

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Editorial

The safety profile of rheumatologic agents is overshadowed by their efficacy. Although these agents have revolutionized the treatment of chronic inflammatory diseases, the silent hepatotoxicity and nephrotoxicity profile of these agents is a significant yet underappreciated consequence [1, 2]. The issue is no longer whether the adverse effects occur, but rather whether the monitoring is adequate to detect the adverse effects [1, 2]. While there are established guidelines for conducting tests, they are inconsistently adhered to.

Conventional disease-modifying antirheumatic drugs (DMARDs), especially methotrexate, continue to play a crucial role in the treatment of rheumatoid arthritis [3]. However, methotrexate is known to carry well-established risks of hepatotoxicity, which vary from mild increases in transaminases to fibrosis and cirrhosis [3]. Guidelines recommend patients to have their liver function checked every 4–8 weeks initially, followed by less often monitoring when stable. Although there are well-defined indications for periodic tests of liver function, this is not consistently adhered to in clinical practice, mainly because of a lack of access to such facilities.

The other DMARDs, such as leflunomide and sulfasalazine, share the same risk of hepatotoxicity whereas hydroxychloroquine, which poses less harm to the body, needs only a preliminary investigation [4, 5]. In these cases, it is crucial to monitor the medications according to their toxicity levels instead of having a standard monitoring process, as seen in Table 1 below. Conventional DMARDs need liver tests since they are harmful to the liver, non-steroidal anti-inflammatory drugs (NSAIDs) need renal tests, while biologics need a preliminary infection test and laboratory tests.

The widespread use of NSAIDs remains a major threat to renal function [6, 7]. These compounds have been known to induce acute kidney failure, especially in older adults and individuals with pre-existing renal disease [6, 7]. In addition, their long-term use has been shown to hasten the progression of renal disease, although routine monitoring of renal function is often not performed in outpatient settings.

Biologic therapies have taken a step forward in the management of rheumatologic diseases [8]. Although biologics are associated with less direct hepatic or renal toxicity, they are associated with novel risks. Certain biologics, such as rituximab and tumor necrosis factor (TNF) inhibitors, have been associated with reactivation of Hepatitis B while interleukin-6 (IL-6) and Janus kinase (JAK) inhibitors require periodic liver function monitoring [8, 9]. This reinforces the necessity for proper screening prior to commencing treatment.

A major gap persists between guideline recommendations

Table 1. Common rheumatologic drugs and associated hepatic and renal risks.

Drug/Class	Hepatic Risk	Renal Risk	Recommended Hepatorenal Monitoring
Methotrexate	Hepatotoxicity, fibrosis	Rare	LFTs
Leflunomide	Hepatotoxicity (can be severe)	Rare	LFTs
Sulfasalazine	Mild hepatotoxicity	Rare	LFTs
Hydroxychloroquine	Rare	Rare	Baseline labs
Ciclosporin	Mild hepatotoxicity	Nephrotoxicity (dose-dependent, chronic kidney disease)	Serum creatinine, LFTs, drug levels
NSAIDs	Mild enzyme elevation	Acute kidney injury, Analgesic nephropathy	Serum creatinine
TNF inhibitors (*e.g.*, adalimumab, infliximab)	Hepatitis reactivation, rare toxicity	Rare	LFTs, baseline viral screening
Anti-CD20 (*e.g.*, rituximab)	Hepatitis B reactivation	Rare	LFTs, baseline viral screening
IL-6 inhibitors (*e.g.*, tocilizumab)	Elevated liver enzymes	Rare	LFTs
T-cell co-stimulation inhibitor (*e.g.*, abatacept)	Minimal	Rare	Periodic labs
JAK inhibitors (*e.g.*, tofacitinib, upadacitinib)	Elevated liver enzymes, rare hepatotoxicity	Rare (may increase creatinine slightly)	LFTs, serum creatinine
Glucocorticoids	Rare	Fluid retention, electrolyte imbalance	Serum electrolytes (potassium)
Azathioprine	Hepatotoxicity (cholestasis, transaminitis)	Rare	LFTs
Mycophenolate mofetil	Mild transaminitis (rarely significant)	Rare	LFTs
Cyclophosphamide	Rare	Hemorrhagic cystitis	Urinalysis, serum creatinine
IL-1 inhibitors (*e.g.*, anakinra)	Rare	Dose adjustment in renal impairment	Serum creatinine
IL-17 inhibitors (*e.g.*, secukinumab)	Rare	Rare	Periodic labs
IL-12/23 inhibitors (*e.g.*, ustekinumab)	Minimal	Rare	Periodic labs

LFTs: Liver function tests; NSAIDs: Non-steroidal anti-inflammatory drugs; TNF: Tissue necrosis factor; CD: Cluster of differentiation; IL: Interleukin; JAK: Janus kinase.

and their implementation [10, 11]. Studies have indicated that there is suboptimal compliance with monitoring guidelines in different healthcare settings [10, 11]. The problem is more common in low- and middle-income countries including Pakistan due to resource constraints. Possible causes include restricted access to laboratories, financial difficulties, absence of established guidelines for monitoring, and poor understanding and awareness among physicians.

The presence of co-existing conditions such as diabetes, hypertension, and metabolic syndrome also adds to the susceptibility of patients to hepatic and renal complications [12]. In such patients, even standardized methods of follow-up may not be sufficient; rather, a more rigorous and personalized approach to risk assessment and follow-up may be needed compared to those prescribed by monitoring protocols.

The concern behind this issue can be understood by considering a clinical scenario where a patient on long-term methotrexate therapy presents with an asymptomatic rise in liver enzymes, which may not be detected for a long period unless monitored by laboratory tests [13]. Such cases emphasize how easily drug-induced toxicity can go unnoticed in the absence of structured monitoring. Use of standard guidelines, reminder systems, and patient education may help ensure that this happens. Collaborative management including rheumatologists, nephrologists, and hepatologists is crucial for optimizing patient care and safety.

Conclusion

It is essential to enhance the process of surveillance among patients under rheumatologic agents. It is important to reinforce the standardized protocols and emphasize compliance to the established guidelines. Collaboration among rheumatologists, nephrologists, and hepatologists could contribute to the early diagnosis and management of possible complications. Finally, there is a necessity to enhance surveillance practices so that the positive effects of the medication would not come at the expense of liver and kidney damage.

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NIB—Conception and design, literature research, manuscript writing, review and corrections.

Ethics approval and consent to participate

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Conflict of interest

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