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Rethinking Hepatotoxicity Risk in Oral Psoriasis Therapies

Ryan Quigley:
In patients with psoriasis, clearing the skin is only part of the story. Some therapies leave a quieter mark—on the liver.

Welcome to *AudioAbstracts* on ReachMD. I'm Ryan Quigley, and today, I'll be sharing insights from a comprehensive review of hepatotoxicity risk across oral treatments for moderate-to-severe psoriasis.

For patients and clinicians navigating the challenges of moderate-to-severe psoriasis, oral systemic therapies remain a mainstay—they're often the most accessible and cost-effective route when biologics are either unavailable or unaffordable. But long-standing reliance on agents like methotrexate and acitretin can present a burden that's often underestimated: liver toxicity.

A recent comprehensive review by Elsisi and colleagues puts this trade-off into focus. Their work dives into the efficacy and hepatic safety profiles of four primary oral agents—methotrexate, cyclosporine, acitretin, and apremilast. What emerges is a compelling case for precision in how we choose, monitor, and support these medications in real-world practice.

Methotrexate continues to serve as a cornerstone in psoriasis care. Its dual action on keratinocyte proliferation and systemic inflammation makes it particularly valuable in patients with psoriatic arthritis.

But methotrexate's mechanism—blocking DNA synthesis in rapidly dividing cells—comes with a cost.

Oxidative stress and the buildup of hepatotoxic metabolites converge to produce a pattern of liver injury that requires active monitoring. The risk is magnified in patients with metabolic dysfunction-associated steatotic liver disease or concurrent inflammatory bowel disease, where baseline hepatic vulnerability is already elevated.

Acitretin, a vitamin A derivative often selected for pustular and erythrodermic variants of psoriasis, offers effective disease control but walks its own fine line with hepatic risk. Its conversion into etretinate—especially in the presence of alcohol—may prolong systemic exposure and increases the potential for hepatocellular and cholestatic damage. While many cases involve transient transaminase elevation, there are documented instances of cirrhosis and even fulminant liver failure.

Cyclosporine offers a faster path to skin clearance, making it particularly useful in flare scenarios or as a bridge to slower-acting therapies. Its liver toxicity, while less pronounced than that of methotrexate or acitretin is still nontrivial. Mechanistically, cyclosporine contributes to liver injury through oxidative stress, inflammation, and apoptosis. Its long-term use is limited by additional risks for nephrotoxicity and hypertension.

Then there's apremilast. This PDE4 inhibitor stands apart in both pharmacology and hepatic profile. While its efficacy is modest compared to its counterparts, its hepatic safety record is robust.

Studies consistently report minimal impact on liver enzymes, with most abnormalities resolving without intervention. For patients with preexisting liver disease, or those who experience hepatotoxicity on other systemic agents, apremilast offers a low-risk alternative.

But efficacy and safety data alone don't guide care unless they're paired with thoughtful monitoring.

For methotrexate and acitretin, baseline liver function testing followed by periodic monitoring is necessary, with increasing support for noninvasive tools like transient elastography to assess fibrosis risk over time. Cyclosporine requires vigilance as well, particularly in higher-risk patients. By contrast, apremilast stands out for not requiring routine liver monitoring.

Together, these standards reinforce that hepatotoxicity isn't managed reactively, but anticipated and monitored over time.

Looking ahead, newer therapies may help rebalance efficacy and hepatic safety.

Emerging small-molecule agents, including TYK2 inhibitors and RORγt inhibitors, are designed to target psoriasis pathways with greater specificity, and early data suggest cleaner hepatic profiles. Meanwhile, biologic therapies continue to demonstrate strong efficacy without the same burden of cumulative liver toxicity. Advances in pharmacogenomics, biomarker development, and drug delivery approaches further support a shift toward individualized regimens optimized for both skin clearance and long-term safety.

Overall, managing psoriasis is no longer just about suppressing inflammation. It's about doing so in a way that anticipates and mitigates organ injury, especially in therapies intended for long-term use. Hepatotoxicity may be a silent threat, but with the right tools and vigilance, it doesn't have to be inevitable.

This has been an *AudioAbstract*, and I'm Ryan Quigley. To access this and other episodes in our series, visit ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!

Reference

Elsisi AE, Abu-Risha SES, Alkabbani MA, et al. Balancing efficacy and hepatoxicity: a comprehensive review of oral medications in psoriasis management. *Naunyn-Schmiedeberg's Archives of Pharmacology*. 2025;398:16355-16384. doi:10.1007/s00210-025-04334-1