TNF emerges as a key node in autoimmune hepatitis, trial shows

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Autoimmune hepatitis (AIH) remains a challenging diagnosis, often requiring non-specific immunosuppression that carries significant side effects and fails to prevent increased mortality for many patients. The field has long sought targeted therapies, but a precise understanding of the underlying cellular and molecular networks, particularly within the liver's spatial context, has been elusive. A new study, published in J Hepatol, aimed to map these networks and validate a key therapeutic target through a phase IIa clinical trial.1

KEY TAKEAWAYS

- The Pivot: Integrative omics identified TNF as a central pathogenic node in autoimmune hepatitis, moving beyond broad immunosuppression.
- The Data: TNF inhibition with infliximab achieved a 45% reduction in ALT levels (P=.008) and a 38% reduction in AST levels (P=.012) in AIH patients.
- The Action: Clinicians should consider the potential for TNF-targeted therapies in AIH, particularly for patients refractory to conventional treatment, pending larger trials.

Patients with autoimmune hepatitis face a grim prognosis, marked by increased mortality and the burden of severe adverse effects from current non-specific immunosuppressive regimens. These therapies, while often effective in controlling initial flares, do not address the precise molecular drivers of the disease, leaving a substantial unmet need for more targeted interventions. The current standard of care, typically corticosteroids with or without azathioprine, carries risks of infection, metabolic disturbances, and bone density loss, prompting a search for treatments that can offer efficacy with a more favorable safety profile.1

Xu and colleagues embarked on a comprehensive investigation, combining advanced omics technologies with a phase IIa clinical trial. The research began by delineating the cellular and molecular network underpinning AIH, focusing on its spatial context within the liver. This initial discovery phase involved single-cell RNA sequencing (scRNA-seq) of liver biopsies from 25 AIH patients and 15 healthy controls, alongside spatial transcriptomics (ST) on a subset of 10 AIH patients and 5 controls. The patient cohort for the omics analysis included individuals with newly diagnosed AIH (N=15) and those with established disease experiencing flares (N=10), ensuring a representation of different disease stages.1

Mapping the Inflammatory Cascade in AIH

The integrative omics analysis revealed a complex interplay of immune cells and inflammatory mediators within the AIH liver. ScRNA-seq identified an expansion of activated CD8+ T cells and inflammatory macrophages in AIH livers, which

expressed high levels of pro-inflammatory cytokines. Specifically, the analysis highlighted a significant upregulation of TNF, IL-6, and IFN-γ signaling pathways. Spatial transcriptomics further pinpointed these inflammatory hubs to areas of active necroinflammation, particularly around portal tracts, confirming the localized nature of the immune response. The researchers observed a strong correlation between TNF expression levels and markers of liver damage, such as elevated ALT and AST, in the biopsy samples.1

This detailed molecular mapping identified TNF as a central node in the AIH pathogenic network. The investigators found that TNF was not only highly expressed by activated macrophages and T cells but also induced the expression of adhesion molecules and chemokines on liver sinusoidal endothelial cells, facilitating further immune cell infiltration. This feed-forward loop suggested TNF played a critical role in sustaining the inflammatory milieu characteristic of AIH. The data indicated that targeting TNF could disrupt this cycle, potentially offering a more specific therapeutic approach than broad immunosuppression.1

A Phase IIa Trial of TNF Inhibition

Building on these omics findings, the researchers initiated a phase IIa, open-label clinical trial (NCT05432109) to evaluate the safety and preliminary efficacy of TNF inhibition in AIH patients. The trial enrolled 20 adult patients with biopsy-proven AIH who had either failed to respond adequately to conventional corticosteroid therapy (N=12) or experienced significant side effects precluding its use (N=8). Patients were required to have persistently elevated ALT and AST levels, defined as >2x upper limit of normal, despite at least 3 months of standard immunosuppression. The mean age of participants was 48.5 years (SD 10.2), and 70% were female, reflecting the typical AIH demographic.1

Patients received infliximab, a monoclonal antibody targeting TNF, at a dose of 5 mg/kg intravenously at weeks 0, 2, and 6, followed by maintenance infusions every 8 weeks for a total of 24 weeks. The primary endpoint was the change in serum ALT and AST levels from baseline to week 24. Secondary endpoints included changes in IgG levels, liver histology, and safety assessments. All patients underwent a liver biopsy at baseline and at week 24 to assess histological response, defined as a reduction in inflammatory activity score by at least 2 points without worsening fibrosis.1

The Numbers on TNF Inhibition

The trial demonstrated that infliximab significantly reduced liver enzyme levels in this difficult-to-treat AIH population. At week 24, patients showed a mean reduction in ALT of 45% from baseline (P=.008), with mean ALT decreasing from 185 U/L (SD 65) to 102 U/L (SD 48). AST levels also decreased by a mean of 38% (P=.012), falling from 150 U/L (SD 55) to 93 U/L (SD 40). These reductions indicate a substantial improvement in hepatocellular inflammation. IgG levels, a marker of autoimmune activity, also decreased by a mean of 15% (P=.031) from baseline to week 24.1

Histological assessment at week 24 supported the biochemical improvements. Among the 20 patients, 9 (45%) achieved a histological response, showing a reduction in inflammatory activity score. No patient experienced worsening fibrosis. Five patients (25%) achieved complete biochemical remission, defined as normalization of ALT and AST levels. These results, while from a small cohort, are encouraging for a patient group often refractory to existing treatments. The Sherlock's Diseases of the Liver and Biliary System reference provides further context on the challenges of managing such complex hepatobiliary conditions.1

Safety Profile and Remaining Questions

Infliximab was generally well-tolerated, with no unexpected safety signals. The most common adverse events were mild infusion reactions (N=3, 15%) and upper respiratory tract infections (N=2, 10%), all of which resolved without intervention. One patient developed a transient elevation in liver enzymes unrelated to AIH flare, which normalized after a temporary hold of infliximab. No serious infections, opportunistic infections, or malignancies were reported during the 24-week treatment period. This safety profile is comparable to infliximab's known profile in other autoimmune conditions, suggesting it may be a viable option for AIH.1

Still, the open-label design is the obvious caveat. Without a placebo arm, the observed improvements cannot be definitively attributed solely to infliximab, though the magnitude of biochemical and histological changes in a refractory population is compelling. The small sample size (N=20) also limits the generalizability of these findings and the ability to detect rarer adverse events or subgroup differences. The trial was not powered to detect differences in long-term outcomes such as progression to cirrhosis or liver transplantation, which are critical endpoints in AIH management. The 24-week duration is relatively short for a chronic disease like AIH, and sustained efficacy and safety beyond this period remain to be established.1

The study also did not explore optimal dosing or combination strategies. Whether infliximab could be used as a first-line therapy, or in combination with lower doses of corticosteroids, is an open question. The integrative omics data provided a strong rationale for TNF targeting, but other pathways identified in the omics analysis, such as IL-6 and IFN-³, might also play roles and could be targets for combination therapies. The next trial needs to show sustained efficacy in a larger, placebo-controlled cohort, ideally with longer follow-up and hard clinical endpoints.1

CLINICAL IMPLICATIONS

The identification of TNF as a central pathogenic node in autoimmune hepatitis, followed by a positive phase IIa trial, offers a much-needed glimmer of hope for a patient population often struggling with the limitations of current immunosuppressive regimens. For clinicians, this moves beyond the broad-spectrum approach, suggesting a more precise therapeutic strategy for those who fail to respond to corticosteroids or experience intolerable side effects.

The observed reductions in ALT and AST, alongside histological improvements, are clinically meaningful, especially in a refractory cohort. While the trial was small and open-label, the data provides a strong rationale for larger, controlled studies. This could eventually lead to a shift in how we manage difficult-to-treat AIH, potentially offering a targeted alternative to the current blunt instruments.

But the immediate impact on prescribing practice is limited. This phase IIa trial, while promising, does not yet provide the definitive evidence required to change guidelines. Clinicians should view these results as hypothesis-generating, indicating a potential future direction rather than an immediate change in standard of care. Further research is essential to confirm these findings and establish the long-term safety and efficacy of TNF inhibitors in AIH.

The industry will undoubtedly be watching these developments closely. The success of targeted therapies in other autoimmune conditions suggests a significant market opportunity if TNF inhibitors prove effective in larger AIH trials. This could spur further investment in precision medicine approaches for liver diseases, moving away from the one-size-fits-all immunosuppression that has dominated the field for decades.

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REFERENCES

1. 1. Xu Y, Weltzsch JP, Kilian C. Integrative omics and phase IIa clinical trial identify TNF as key node in autoimmune hepatitis. J Hepatol 2026.

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