Perspective

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Epigenetic therapy for alcoholic hepatitis: can larsucosterol change the treatment landscape?

Faiza Fatima, MBBS[a], Mahnoor Fatima, MBBS[b], Ahmed Raza, MBBS[a], Bilal Ahmad, MBBS[c], Aymar Akilimali, MD[d,*]

Abstract

Alcohol-induced liver disease, encompassing steatosis, hepatitis, cirrhosis, and liver failure, is a significant global health burden, affecting 10–35% of individuals with alcohol use disorder. Alcoholic hepatitis, characterized by hepatocyte inflammation due to chronic alcohol consumption, arises from toxic intermediates produced during alcohol metabolism. These intermediates disrupt cellular function, trigger immune responses, and promote fibrosis, leading to cirrhosis and liver failure. Despite current treatments like corticosteroids and liver transplantation, which alleviate symptoms but fail to reverse cellular damage, the rising prevalence of alcoholic hepatitis underscores the urgent need for innovative therapies. Larsucosterol, a novel epigenetic modulator, has emerged as a promising candidate. By inhibiting DNA methyltransferase, larsucosterol reduces DNA hypermethylation and modulates genes involved in inflammation, lipid metabolism, and cell survival, thereby mitigating liver damage. Early-phase clinical trials, including a phase 2a study, demonstrated its safety, tolerability, and improved biochemical parameters in patients. However, the phase 2b AHFIRM trial did not achieve its primary endpoint, though a lower mortality rate in the 30 mg group suggests potential benefits requiring further investigation. Larsucosterol's immunomodulatory and anti-inflammatory properties offer advantages over corticosteroids, particularly in patients unresponsive to standard therapies. Despite its promise, limitations such as the need for larger, more diverse trials, long-term safety data, and exploration of combination therapies remain. In conclusion, larsucosterol represents a groundbreaking approach to treating alcoholic hepatitis, but extensive research is essential to fully establish its therapeutic potential and address existing gaps in knowledge.

Keywords: AHFIRM trial, alcoholic hepatitis, cirrhosis, larsucosterol, treatment

Alcohol-induced liver disease, including steatosis, hepatitis, cirrhosis, and liver failure, is a growing health concern worldwide, affecting 10% to 35% of people with alcohol use disorder[1]. Alcoholic hepatitis is the inflammation of hepatocytes caused by chronic alcohol consumption. Alcohol oxidation in hepatocytes produces toxic intermediates, which cause cellular damage and inflammation, called alcohol-induced hepatitis, which then leads to cirrhosis and liver failure[2]. Alcohol dehydrogenase converts alcohol into aldehydes, which bind to proteins, nucleic acids, and phospholipids, forming adducts that cause cellular damage, immune response, and fibrosis, disrupting the liver's redox potential[2]. This leads to metabolic shifts exacerbated by interactions with enzymes like CYP2E1 and catalase[2].

HIGHLIGHTS

- Alcoholic hepatitis has a 30% 1-year mortality risk, emphasizing the need for better treatments beyond current options.
- Larsucosterol, an epigenetic modulator, reduces DNA hypermethylation, inflammation, and liver damage in alcoholic hepatitis.
- Early trials show promise, but phase 2b results were inconclusive, warranting further research.
- Future studies should explore long-term safety, efficacy, and combination therapies to fully establish larsucosterol's potential.

The prevalence of alcoholic hepatitis and cirrhosis is increasing with rising alcohol consumption worldwide. Symptomatic alcoholic hepatitis causes rapid onset jaundice and a 30% mortality risk within a year after diagnosis[3]. Alcohol-associated cirrhosis has affected 23.6 million people with compensated and 2.46 million people with decompensated cirrhosis[1]. The current treatment options, including abstinence from alcohol, medications like corticosteroids, and liver transplant for advanced stages[3], decrease symptoms and mortality risk but do not warrant complete cellular reversal. This underscores the need for innovative treatment options like Larsucosterol, a potent

[a]Services Institute of Medical Sciences, Lahore, Pakistan, [b]King Edward Medical University, Lahore, Pakistan, [c]Shaikh Khalifa bin Zayed Al Nahyan medical and dental college, Lahore, Pakistan and [d]Department of Research, Medical Research Circle (MedReC), Goma, Congo

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*Corresponding author. Address: Department of Research, Medical Research Circle (MedReC), Kyeshero Lusaka Rue 216-B, Postal code 50 Goma, North Kivu, Congo. Tel.: +243 825177370. E-mail: aymarakilimali@gmail.com (A. Akilimali).

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epigenetic modulator that reduces hepatic lipid accumulation and inflammation and can become an effective treatment option for alcoholic hepatitis[4].

Larsucosterol inhibits DNA methyltransferase, an enzyme involved in hypermethylation in alcohol-induced hepatitis[4], reducing DNA hypermethylation and modulating gene expression related to stress responses, lipid metabolism, cell survival, and inflammation[4]. This reduces inflammation and enhances cell survival, mitigating liver damage associated with alcohol-induced hepatitis. A phase 2a study by Hassanein *et al* showed that larsucosterol was safe and well-tolerated, with promising efficacy signals. Notably, all participants survived the 28-day study period with significantly improved biochemical parameters compared to the standard-of-care treatment[5]. However, the recent phase 2b AHFIRM trial did not find statistically significant reduction in 90-day mortality or liver transplant rates with larsucosterol, although lower mortality was observed in the 30 mg treatment group, suggesting the need for further investigation[6].

Larsucosterol has immunomodulatory and anti-inflammatory properties, which reduce hepatocyte apoptosis and systemic inflammation. Unlike corticosteroids, it prevents complications related to immunosuppression and demonstrates effectiveness in patients unresponsive to abstinence or nutritional support[4]. Despite the promising signals, limitations persist. The failure to achieve primary endpoint in the AHFIRM trial highlights the need for more extensive and diverse clinical trials. Long-term safety and efficacy beyond 90 days also remain unstudied. The evaluation of the drug's efficacy with existing therapies, such as corticosteroids, also remains unexplored.

In conclusion, larsucosterol emerges as a promising therapeutic agent for alcohol-induced hepatitis, offering anti-inflammatory properties and promoting hepatocyte regeneration through epigenetic modulation. While initial clinical trials have provided encouraging results, more extensive research is necessary to confirm these findings and address the existing limitations. Future research should explore long-term outcomes in larger and more diverse populations. Additionally, further studies should focus on combination therapies with existing treatments to fully establish larsucosterol's therapeutic benefit.

Ethical approval

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Consent

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Author's contribution

F.F.: writing – original draft, conceptualization, methodology; M.F.: writing – original draft, methodology, data analysis; A.R.: writing – original draft, data analysis; B.A.: writing – original draft; A.A.: writing – original draft.

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The authors declare that there is no conflict of interest

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