Tirzepatide is a novel, first-in-class, dual GIP and GLP-1 receptor agonist. It was recently approved by the Food and Drug Administration for T2DM.[1] In a randomized, open-label, parallel-group, phase 3 trial in people with T2DM, inadequately controlled by metformin with or without sodium-glucose transport protein 2 inhibitors, tirzepatide was not only found superior to titrated insulin degludec, with greater reductions in HbA_{1c}, it was also found to significantly reduce weight. In a 15 mg tirzepatide group, 88% of the patients were able to reduce ≥5%, 69% achieved ≥10%, and 43% achieved ≥15% of their total weight.[10] In another large randomized controlled trial in patients with T2DM, tirzepatide was found to be superior to semaglutide with respect to the mean change in glycated hemoglobin, and also induced greater weight loss than semaglutide with a relative difference of 5.5 kg from baseline in 40 weeks. At 40 weeks, the mean reductions in body weight with tirzepatide at a dose of 5 mg, 10 mg, and 15 mg were −7.6 kg, −9.3 kg, and −11.2 kg, respectively, as compared with −5.7 kg with semaglutide.[11]

In the current SURMOUNT-1 trial, it is remarkable that the magnitude of weight loss with tirzepatide was similar to that with bariatric surgery, which raises the potential for alternative medical approaches to the treatment of obesity. The strengths of the trial are the inclusion of a large number of participants, the racial and ethnic balance, and the lack of major off-target side effects. However, long-term studies are needed to study whether the remarkable weight loss achieved by tirzepatide can be sustained even after stopping the drug or will the drug need to be continued for life.

CONFLICTS OF INTEREST

None.

FUNDING

None.

REFERENCES

1. Syed YY. Tirzepatide: first approval. *Drugs*. 2022;82:1213–1220. https://doi.org/10.1007/s40265-022-01746-8.
2. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387:205–216. https://doi.org/10.1056/NEJMoa2206038.
3. Kessler C. Pathophysiology of obesity. *Nurs Clin*. 2021;56:465–478. https://doi.org/10.1016/j.cnur.2021.08.001.
4. Finer N. Medical consequences of obesity. *Medicine (Baltim)*. 2015;43:88–93. https://doi.org/10.1016/j.mpmed.2014.11.003.
5. Grunvald E, Shah R, Hernaez R, et al. AGA clinical practice guideline on pharmacological interventions for adults with obesity. *Gastroenterology*. 2022;163:1198–1225. https://doi.org/10.1053/j.gastro.2022.08.045.
6. Chang SH, Stoll CRT, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. *JAMA Surg*. 2014;149:275–287. https://doi.org/10.1001/jamasurg.2013.3654.
7. Kim W, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. *Pharmacol Rev*. 2008;60:470–512. https://doi.org/10.1124/pr.108.000604.
8. Rosen CJ, Ingelfinger JR. Shifting tides offer New hope for obesity. *N Engl J Med*. 2022;387:271–273. https://doi.org/10.1056/NEJMe2206939.
9. Ard J, Fitch A, Fruh S, Herman L. Weight loss and maintenance related to the mechanism of action of glucagon-like peptide 1 receptor agonists. *Adv Ther*. 2021;38:2821–2839. https://doi.org/10.1007/s12325-021-01710-0.
10. Ludvik B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet Lond Engl*. 2021;398:583–598. https://doi.org/10.1016/S0140-6736(21)01443-4.
11. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med*. 2021;385:503–515. https://doi.org/10.1056/NEJMoa2107519.

Ashish Kumar
Institute of Liver, Gastroenterology, & Pancreatico-Biliary Sciences, Sir Ganga Ram Hospital, New Delhi, India

Address for correspondence: Institute of Liver, Gastroenterology, & Pancreatico-Biliary Sciences, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi, 110 060, India. Fax: +91 11- 25861002.
E-mail: ashishk10@yahoo.com (A. Kumar)

24 November 2022.

A Review on "IL-1 Receptor Antagonist Plus Pentoxifylline and Zinc for Severe Alcohol-Associated Hepatitis"

Abbreviations: AH: Alcoholic hepatitis; ALD: Alcoholic liver disease; COMB: Anakinra, pentoxifylline and zinc; MDF: Maddrey's discriminant function; MELD: Model for End-Stage Liver Disease; PRED: Methylprednisolone

https://dx.doi.org/10.1016/j.jceh.2023.01.011

Szabo G, Mitchell M, McClain CJ, Dasarathy S, Barton B, McCullough AJ, et al. IL-1 receptor antagonist plus pentoxifylline and zinc for severe alcohol-associated hepatitis. Hepatology. 2022; 76: 1058–68.

SUMMARY

Alcoholic hepatitis (AH) is a stage of alcoholic liver disease (ALD), which typically presents as tender hepatomegaly, insidious onset of jaundice, malaise, and fatigue with features of Systemic Inflammatory Response syndrome (SIRS) following prolonged and heavy alcohol consumption.[1,2] A value of 32 or greater as per by Maddrey's discriminant function (MDF) predicts a mortality of 20–30% within 1 month and 30–40% in 6 months[3]. Ever since Thursz *et al.* in 2015[4] reported modest improvement in mortality with the use of corticosteroids, it has been used to reduce the inflammatory damage. As the pathophysiology of the disease implicates pro-inflammatory cytokines IL-beta and TNF-alfa resulting from hepatocyte injury, it becomes natural to investigate the role of anti-interleukin 1 in slowing the progression of the disease.

In a recent study, Szabo *et al.* assessed the superiority of COMB (anakinra, pentoxifylline, and zinc) over PRED (methylprednisolone) in patients with a clinical diagnosis of severe AH (Model for End-Stage Liver Disease [MELD] >20, MDF >32). They were randomized to either receive methylprednisolone for 28 days or a combination of anakinra (14 days) plus pentoxifylline (28 days) plus zinc. After a thorough screening, 104 patients were chosen in which 53 patients were randomized into the COMB and 50 to the PRED treatment. MELD 20–25 and MELD >26 strata showed nonsignificant treatment effects in favor of COMB. The primary endpoint was set to survival at 180 days. Survival at 28 days was similar between the 2 groups. They were no unexpected serious adverse events and a near-comparable incidence of infections was seen. It was concluded that the combination therapy has similar survival benefits compared to corticosteroid therapy in severe AH.

COMMENTARY

Severe alcoholic hepatitis is associated with poor treatment outcomes predominantly due to a limited understanding of the pathophysiology of the disease. As a result, any therapy that is being instituted to reduce the inflammatory damage is proving to be partly beneficial. In their review, Tornai and Szabo[5] had previously discussed the emerging medical therapeutics toward this disease. Monoclonal antibodies like anakinra (IL-1 alfa) and canakinumab (IL-1beta) block the IL receptor antibodies and reduce inflammation. Agents like N-acetylcysteine, S-adenosylmethionine, metadoxine, and so on, alleviate the oxidative stress and prevent excessive liver injury. Akriviadis *et al.* have proven that pentoxifylline improves hepatic and renal functioning in alcoholic hepatitis, albeit short term.[6] After Kim *et al.*[7] established the anti-inflammatory role of sulfated oxysterol (DUR-928) in Non-alcoholic steatohepatitis (NASH) in preclinical models, a trial is currently evaluating the efficacy of DUR-928 in alcoholic hepatitis.

Through this study, with the use of anakinra, Szabo *et al.* have validated the role of IL-1 in the inflammatory cascade. As an anti-inflammatory, anakinra is a better and safer option as compared to tumor necrosis factor (TNF) alfa inhibitors and prednisone. Even though TNF alfa inhibitors are effective in reducing inflammation, the increased risk of infections[8,9] outweighs the benefit. Hmoud *et al.*[10] and many other studies have reported an increased risk for infections (bacterial and fungal) in patients taking corticosteroids[10–10] including this study (10% (PRED) vs. 0% (COMB)). However, in the Indian setting (external validity), the two major reasons which would result in poor compliance toward therapy: (1) cost of anakinra and (2) Parenteral route of administration (SC). Also, as this study revealed nonsuperior outcomes of COMB over PRED (statistically insignificant) for a period over 28 days (as compared to corticosteroids), the rationale of prescribing COMB is weak. There are recent data[11] that have revealed that combination therapy of anakinra and zinc sulfate had a significantly lower 90-day survival than those treated with prednisone. Also, there was a higher incidence of acute kidney injury in the anakinra zinc sulfate group as compared to prednisone group.[11]

The study was underpowered as only 130 patients were involved in randomization. The average BMI in 103 patients was 30.6 ± 8.0 kg/m^2 which could have had a confounding effect on the liver injury. Therefore, a liver biopsy would have confirmed the diagnosis as Severe alcoholic hepatitis (SAH). The study should have elaborated on (a) the presence and severity of infection, (b) acute on chronic liver failure, and (c) other organ damage as these parameters play a crucial role in prognosis and outcomes. Lille's score which is utilized to predict corticosteroid responsiveness at day 7 and is not validated for anakinra or pentoxifylline. Also, in patients with Lille's score >0.45 at day 7, steroids were continued for 28 days. It is not clear whether interleukin 1 (IL-1) suppression causes a compensatory increase in other cytokines something which the authors could have elucidated upon through this study.

Nevertheless, such studies, which assess combination therapy, need to be conducted as they help understand the disease better and as a result improve management strategies. Only through such efforts will be decipher the entire picture and the best outcomes.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Shrihari Anil Anikhindi, Writing of manuscript.
Akshay Anil Anikhindi, Writing of manuscript.
Prof Ashish Kumar, Editing and review.
Prof Anil Arora, Editing and review.

CONFLICTS OF INTEREST

None.

FUNDING

No funding.

REFERENCES

1. Shah NJ, Royer A, John S. Alcoholic Hepatitis. Updated 2022 Jun 11. In: StatPearls Internet. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470217/.
2. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med*. 2009;360:2758–2769.
3. Maddrey WC, Boitnott JK, Bedine MS, Weber Jr FL, Mezey E, White Jr RI. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology*. 1978;75:193–199.
4. Thursz MR, Richardson P, Allison M, et al, STOPAH Trial. Prednisolone or pentoxifylline for alcoholic hepatitis. *N Engl J Med*. 2015 Apr 23;372:1619–1628. https://doi.org/10.1056/NEJMoa1412278. PMID: 25901427.
5. Tornai D, Szabo G. Emerging medical therapies for severe alcoholic hepatitis. *Clin Mol Hepatol*. 2020 Oct;26:686–696. https://doi.org/10.3350/cmh.2020.0145. Epub 2020 Sep 28. PMID: 32981291; PMCID: PMC7641578.
6. Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology*. 2000;119:1637–1648. https://doi.org/10.1053/gast.2000.20189.
7. Kim MJ, Lin WQ. DUR-928, an endogenous regulatory molecule, exhibits anti-inflammatory and antifibrotic activity in a mouse model of NASH. In: *Emerging Trends Conference: Emerging Trends in Non Alcoholic Fatty Liver Disease*. 2017.
8. Tilg H, Jalan R, Kaser A, et al. Anti-tumor necrosis factor-alpha monoclonal antibody therapy in severe alcoholic hepatitis. *J Hepatol*. 2003;38:419–425.
9. Poynard T, Thabut D, Chryssostalis A, Taieb J, Ratziu V. Anti-tumor necrosis factor-alpha therapy in severe alcoholic hepatitis: are large randomized trials still possible? *J Hepatol*. 2003;38:518–520.
10. Hmoud BS, Patel K, Bataller R, Singal AK. Corticosteroids and occurrence of and mortality from infections in severe alcoholic hepatitis: a meta-analysis of randomized trials. *Liver Int*. 2016;36:721–728.
11. Szabo G, Mitchell M, McClain CJ, Dasarathy S, Barton B, McCullough AJ, et al. IL-1 receptor antagonist plus pentoxifylline and zinc for severe alcohol-associated hepatitis. *Hepatology*. 2022;76:1058–1068.

Shrihari Anikhindi, Akshay Anikhindi, Ashish Kumar, Anil Arora

Institute of Liver, Gastroenterology and Pancreatico-biliary Sciences, Sir Ganga Ram Hospital, New Delhi, India

E-mail: dr.anikhindi@gmail.com (S. Anikhindi)

23 November 2022.

Making Sense of the Antisense Therapy for Hepatitis B – Bepirovirsen

SUMMARY OF THE STUDY

Bepirovirsen is a 2′-O-methoxyethyl modified antisense oligonucleotide (ASO) in development for treating chronic hepatitis B virus (HBV) infection. It targets all HBV ribonucleic acid (RNA), including HBV messenger RNA and pregenomic RNA. In the recent issue of the New England Journal of Medicine, Yuen *et al.* reported the results of a phase 2b, randomized trial (the B-Clear Trial)[1] involving patients with chronic hepatitis B (CHB) infection who were receiving or not receiving nucleos(t)ide analogue (NA) therapy. Four hundred and fifty-seven patients (n = 227 stable on NA therapy, n = 230 not on NA therapy) were randomized in a 3:3:3:1 ratio to receive weekly subcutaneous injections of bepirovirsen at a dose of 300 mg for 24 weeks (group 1), bepirovirsen at a dose of 300 mg for 12 weeks then 150 mg for 12 weeks (group 2), bepirovirsen at a dose of 300 mg for 12 weeks then placebo for 12 weeks (group 3), or placebo for 12 weeks then bepirovirsen at a dose of 300 mg for 12 weeks (group 4). The primary composite efficacy outcome was an HBsAg level below the lower limit of detection and an HBV DNA level below the lower limit of quantification maintained for 24 weeks after the end of bepirovirsen treatment. The results indicated that bepirovirsen at a dose of 300 mg per week for 24 weeks (group 1) resulted in 9–10% of participants having HBsAg and HBV DNA loss for 24 weeks after the end of bepirovirsen treatment. Results were similar in participants receiving NA therapy and those not receiving NA therapy. The Baseline HBsAg level predicted the response, and a receiver–operating characteristic analysis suggested that an HBsAg level of 3000 IU per millilitre at baseline was an appropriate cutoff point as a predictor of response. Among participants having hepatitis B e antigen negative (HBeAg-negative) status, the primary outcome occurred in 10% and 14% of those receiving NA therapy and in those not receiving NA therapy, respectively. Among participants having HBeAg-positive status, the primary outcome occurred only in those receiving NA therapy. The adverse events, including injection–site reactions, pyrexia, fatigue and increased alanine aminotransferase levels, were more common with bepirovirsen than with placebo.

https://dx.doi.org/10.1016/j.jceh.2022.12.013