

## Alcoholic Hepatitis and TNF- $\alpha$ Antagonists: The Rise and Fall

Indraneil Mukherjee<sup>1\*</sup> and Zhuo-Qian Zhang<sup>2</sup>

<sup>1</sup>Foregut and Hepato-Pancreato-Biliary, Department of Surgery, Staten Island University Hospital - Northwell Health, Staten Island, New York, USA

<sup>2</sup>Touro College of Osteopathic Medicine, New York, USA

**\*Corresponding Author:** Indraneil Mukherjee, Foregut and Hepato-Pancreato-Biliary, Department of Surgery, Staten Island University Hospital - Northwell Health, Staten Island, New York, USA.

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### Abstract

Alcoholic liver disease (ALD) is the most prevalent cause of advanced liver disease. The disease spectrum ranges from mild steatohepatitis to progressive fibrosis and finally hepatocellular carcinoma. In 2015 in the United States liver cirrhosis was the 12<sup>th</sup> leading cause of death. The crude death rate from alcohol-related cirrhosis was 6.6 deaths per 100,000 population.

Inflammatory cytokines have an important role in the pathogenesis of ALD and drugs targeting inflammatory cytokines like tumor necrosis factor alpha (TNF- $\alpha$ ) have been used. Corticosteroid treatment in Alcoholic Hepatitis have been argued for and against many times over the last few decades. Corticosteroids treatment for severe AH as a reference treatment has been established in the last two decades after multiple meta-analyses of randomized controlled trials concluded that corticosteroids improved the short-term survival of patients with severe Alcoholic Hepatitis (AH). Experimental and clinical evidence indicates that TNF- $\alpha$  and its downstream inflammatory cytokines correlate with disease severity and may contribute to the pathogenesis and clinical sequelae of alcoholic hepatitis thereby implicating a possible role for inhibition of TNF- $\alpha$  in the treatment of alcoholic hepatitis.

In the early 21<sup>st</sup> century, an initial pilot study demonstrated the ability of TNF- $\alpha$  Antagonists to augment the treatment of steroid. However further studies have shown TNF- $\alpha$  to not be helpful in Moderate or Severe AH. Newer therapeutic strategies including Pentoxifylline to improve outcomes are being developed and trialed in the population.

**Keywords:** Alcoholic Hepatitis (AH); TNF- $\alpha$  Antagonists

### Introduction

Alcoholic liver disease (ALD) is the most prevalent cause of advanced liver disease. The disease spectrum ranges from mild steatohepatitis to progressive fibrosis and finally hepatocellular carcinoma.

In 2015, liver cirrhosis was the 12<sup>th</sup> leading cause of death in the United States, with a total of 42,443 deaths. The crude death rate from all cirrhosis was 13.2 deaths per 100,000 population. The rate from alcohol-related cirrhosis was 6.6 per 100,000 population. Among all cirrhosis deaths in 2015, 49.5 percent were alcohol related [1].

Inflammatory cytokines have an important role in the pathogenesis of ALD and drugs targeting inflammatory cytokines like TNF- $\alpha$  have been used [2,3]. Corticosteroid treatment in Alcoholic Hepatitis has been argued many times over in last decade of the 20<sup>th</sup> century to the first decade of the 21<sup>st</sup>. Using corticosteroids as a reference for treating severe AH has been established after multiple meta-analyses of randomized controlled trials concluded that corticosteroids improved the short-term survival of patients with severe AH [4-6].

Data obtained from animal experiments have demonstrated that TNF- $\alpha$  increases vascular permeability and causes vasodilation. The antibodies to TNF- $\alpha$  attenuated liver injury and mice lacking TNF- $\alpha$  receptor-1 did not develop alcohol-induced liver injury [7-10]. Experimental and clinical evidence indicates that and the TNF- $\alpha$  downstream cytokines like interleukin-6, correlate with disease severity and may contribute to the pathogenesis and clinical sequelae of alcoholic hepatitis, thereby implicating a possible role for inhibition of TNF- $\alpha$  in the treatment of alcoholic hepatitis [11].

## Methods

A literature search was conducted using Pubmed, up until November 2018. Original articles and reviews were identified using the key words: "anti-TNF- $\alpha$ ", "infliximab", "adalimumab", "etanercept" and "alcoholic hepatitis". Additional articles were identified through a review of the reference lists of selected pertinent articles.

## Results and Discussion

In 2002, Spahr from Geneva published a randomized controlled pilot study of combination of steroids with infliximab or placebo for treatment of severe AH. In this study, 20 patients with severe AH (Maddrey's DF score > 32) received prednisone 40 mg/day for 28 days and randomly received either infliximab 5 mg/kg IV or placebo at onset. Histology, plasma interleukin-6 (IL-6) and interleukin-8 (IL-8) were measured at baseline and at day 10. The authors found that Infliximab was well tolerated. Their results showed no significant changes from baseline. At day 28, Maddrey's score significantly improved in the infliximab receiving group (39 to 12,  $P < 0.05$ ) but not in the prednisone only group (44 to 22,  $P = NS$ ). At day 10, IL-6 ( $P < 0.01$ ) and IL-8 ( $P < 0.05$ ) decreased in infliximab group, while the changes were not significant in the steroid only group. The authors concluded that in severe AH, infliximab was well tolerated and associated with significant improvement in Maddrey's score at day 28. These promising results from Switzerland encouraged many more pilot studies and larger trials assessing the effects of TNF- $\alpha$  antagonists therapy on survival in severe AH [2].

In 2003, a group from London, UK, designed a study to test the hypothesis that TNF- $\alpha$  is an important mediator of the circulatory disturbances in AH. They evaluated the acute and short-term effects of a single infusion of the monoclonal chimeric anti-TNF- $\alpha$  antibody (Infliximab) on portal and systemic hemodynamics in 10 patients with severe biopsy proven AH. Cardiovascular hemodynamics, hepatic venous pressure gradient (HVPG), and hepatic and renal blood flow were measured before and 24 hours after Infliximab infusion, as well as prior to hospital discharge. They found a reduction of Serum bilirubin ( $p < 0.05$ ), C reactive protein ( $p < 0.001$ ), white cell count ( $p < 0.01$ ) and plasma levels of interleukin (IL)-6 and IL-8 after treatment. Mean HVPG decreased significantly at 24 hours from 23.4 to 14.3 mm Hg;  $p < 0.001$ ) with a sustained reduction prior to discharge (12.8 mm Hg;  $p < 0.001$ ). They found a significant increase in Mean arterial pressure ( $p < 0.001$ ) and systemic vascular resistance ( $< 0.01$ ) as well as a reduction in cardiac ( $p < 0.05$ ) prior to discharge. There was an increase in Hepatic blood flow (506.2 (42.9) to 646.3 (49.2) ml/min) ( $p = 0.001$ ) and renal blood flow 424.3 (65.12) to 506.3 (85.7) ml/min ( $p = 0.001$ ), respectively) prior to discharge. Of the 10 patients, nine were alive at 1 month. The authors concluded that in patients with severe AH (DF of > 32), TNF- $\alpha$  antagonist treatment produced a highly significant, early, and sustained reduction in hepatic venous pressure gradient. They suggested that this is due to a combination of reduction in cardiac output and intrahepatic resistance. They also demonstrated a reduction in hepatic inflammation and improved organ blood flow [12].

Tilg from Austria published in 2003 a study on Anti- TNF- $\alpha$  monoclonal antibody therapy in severe AH. The team treated 12 patients with biopsy-confirmed Severe AH (Maddrey DF > 32) with a single infusion of the anti-TNF monoclonal antibody (Infliximab) at a dose of 5 mg/kg body weight. Serial measurements were made for various cytokines using specific enzyme-linked immunoassays (ELISA). At 1 month 2 patients died from sepsis and rest of the 10 patients were alive at a median of 15 months. Serum bilirubin levels, Maddrey DF score, neutrophil count and C-reactive protein fell significantly within the first month. The authors found an early decrease in plasma levels of proinflammatory cytokines (interleukins (IL)-1beta, IL-6, IL-8, interferon-gamma), though it was not statistically significant. The plasma levels of TNF- $\alpha$  remained near the sensitivity limit of the assay throughout the treatment course. While TNF- $\alpha$  mRNA expression in the liver did not change, expression of IL-8, a cytokine regulated mainly by TNF- $\alpha$ , was almost absent on 28<sup>th</sup> day. They concluded that larger studies should be carried out to get significant results [3].

In a pilot study of 13 patients for the safety and tolerability of etanercept in patients with moderate or severe AH (DF > 15), Menon and group from Rochester, USA, administered Etanercept for 2 weeks. On an intention-to-treat basis, the 30-day survival rate of patients receiving etanercept was 92% (12/13). Adverse events encountered included infection, hepatorenal decompensation and GI bleeding, which required premature discontinuation of etanercept in 23% of patients (3/13) [11].

In 2004, Nauveau stated that despite the controversy surrounding corticosteroid treatment, there are many arguments in support of corticosteroids as the reference treatment for severe AH, especially after a meta-analysis of randomized controlled trials concluded that corticosteroids improved the short-term survival of patients with severe AH [4-6]. He set out to see if Infliximab would be able to improve on the established standard. Nauveau's landmark Double-Blind Randomized Controlled Trial published in 2004 evaluated the efficacy of infliximab and prednisolone at reducing the 2-month mortality rate among patients with severe AH. 36 patients with severe AH (Maddrey score > 32) were randomly assigned to either receiving intravenous infusions of infliximab (10 mg/kg) at 0, 2, and 4 weeks; or placebo. All patients received prednisolone (40 mg/day) for 28 days. Seven patients died in 2 months in the immunosuppression group compared to the placebo group. The study was stopped because of the poor outcome of the study group. The immunosuppressed group also had an increased frequency ( $P < .002$ ) of severe infections within 2 months. They concluded that three infusions of 10 mg/kg of infliximab along with prednisolone may be harmful in patients with severe AH because of the high prevalence of severe infections [13].

A study published in 2008 from New Delhi, India, showed that in severe AH, a single dose infliximab was shown to improve survival and reduce the severity of the hepatitis. In the study Patients with severe AH (Maddrey's score > 32) received a single dose of infliximab 5 mg/kg IV. The study with 19 patients had a primary endpoint of survival at 1 and 2 months. The secondary endpoints were reduction of the Maddrey's DF score and development of any bacterial infections. There was a 1-month survival of 89% and 2-month survival of 68%. At the end of one and two months, compared to the baseline, there was significant improvement in median values of Maddrey's DF ( $p < 0.05$ ). Median serum TNF- $\alpha$  levels decreased from 45 (range 11 - 19,880) at baseline to 20 (range 4 - 8600) pg/mL at 4 weeks ( $p = 0.001$ ). CRP levels, MELD score, and absolute neutrophil count decreased significantly as well. 5 patients (26%) developed infection. Three developed pneumonia and two developed pulmonary tuberculosis. Three patients recovered with treatment but two patients (10%) died (one with pneumonia leading to sepsis and the other of disseminated tuberculosis). The authors also found that absence of hepatic encephalopathy at admission and Lille score also predicted 2-month mortality [14].

In a randomized, Double-Blinded, Placebo-Controlled Multi-Center Trial of Etanercept in the treatment of AH conducted by the Boetticher and group, concluded that in patients with moderate to severe AH, etanercept was associated with a significantly higher mortality rate after 6 months. In this study, 48 AH patients with MELD score  $\geq 15$  were randomly placed into groups that were given up to 6 subcutaneous injections of either etanercept or placebo for three weeks. The 1-month mortality rates of patients receiving placebo and etanercept were similar. The 6-month mortality rate was significantly higher in the etanercept group, compared with the placebo group (57.7% versus 22.7%, respectively; OR and 95% CI: 4.6 and 1.3 - 16.4,  $p = 0.017$ ). Rates of infectious serious adverse events were significantly higher in the etanercept group, compared with the placebo group (34.6% versus 9.1%,  $p = 0.04$ ) [15].

Pentoxifylline is being used in Severe AH as a supplement to corticosteroid or in isolation, in the hope of improving the outcome of the present treatment modality of AH. In a randomized clinical trial, Mathurin compared the use of prednisolone with or without pentoxifylline in patients with severe AH. A 4-week treatment with pentoxifylline and prednisolone, compared with prednisolone alone, did not result in improved 6-month survival. They concluded that the study may have been underpowered to detect a significant difference in incidence of hepatorenal syndrome, which was less frequent in the group receiving pentoxifylline [16]. In a systematic review of meta-analysis for the treatment of Severe Alcoholic Hepatitis with Corticosteroid, Pentoxifylline, or Dual Therapy, Lee et al. found that dual therapy was not inferior to corticosteroid monotherapy and could reduce the incidence of hepatorenal syndrome or acute kidney injury and risk of infection. They concluded that dual therapy should be considered in treatment of patients with severe alcoholic hepatitis [17].

In a recent study, Louvet., *et al.* did a Meta-analysis of eleven randomized controlled trials comparing corticosteroids, pentoxifylline, or their combination in patients with severe AH. Individual Data from these controlled trials were examined if corticosteroids reduce risk of death within 28 days for patients with severe AH, compared with pentoxifylline or placebo. The authors found corticosteroid treatment

significantly decreased risk of death within 28 days compared with or to pentoxifylline. In multiple-imputation and complete case analyses, the effect of corticosteroids compared with controls remained significant. When corticosteroids vs pentoxifylline was compared, the corticosteroid effect remained significant in the complete case analysis but not in multiple-imputation analysis. There was no difference in 28-day mortality when patients were given a combination of corticosteroids and pentoxifylline vs corticosteroids alone or between patients given pentoxifylline vs control. The authors did not find significant differences in 6-month mortality in any of the treatment or controls were compared. Corticosteroids were significantly associated with increased response to therapy compared with controls or pentoxifylline. They did not find any difference in response to therapy between patients given a combination of corticosteroids and pentoxifylline vs corticosteroids alone or pentoxifylline vs controls. They concluded that corticosteroid can reduce risk of death within 28 days of treatment, but not in the following 6 months. This loss of efficacy over time indicates a need for new therapeutic strategies to improve medium-term outcomes [18].

## Conclusion

The use of TNF- $\alpha$  antagonists is based on experimental studies showing that TNF- $\alpha$  has an important role in the pathogenesis of ALD, although recent translational studies do not support this hypothesis [19,20]. There have been clinical studies assessing the effect of infliximab or etanercept, anti-TNF- $\alpha$  agents, in patients with AH. A small randomized-controlled pilot study showed improvement in DF and survival, however subsequent larger studies showed increased rates of infection and increased mortality [2,13,15]. Given the high mortality arising from infectious complications with anti-TNF- $\alpha$  therapy despite the stringent selection criteria used in most trials, it seems unlikely that these agents will ever achieve widespread clinical applications, even in severe AH [21,22]. Therefore, we do not recommend anti-TNF- $\alpha$  agents for treatment of AH.

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