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TOPIC HIGHLIGHT

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Recent and currently emerging medical treatment options for the treatment of alcoholic hepatitis

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Abstract

Patients with severe alcoholic hepatitis (AH) need to be treated with specific treatment for better outcome. Currently available specific treatment modalities are use of corticosteroids or pentoxifylline. However, the response rate to these drugs is only about 50%-60%. Hence, there is an urgent need for better and more effective treatment options. Tumor necrosis factor plays an important role in the pathogenesis of AH. However, agents blocking the action of tumor necrosis factor have not been found to be effective. Rather the randomized studies evaluating these agents showed an adverse effect and more infections in treated patients. Critical role of tumor necrosis factor in hepatic regeneration explaining this contrast is discussed. Oxidative stress and inflammation derived from gut bacteria ate two main components in the pathogenesis of AH laying foundation for the role of antioxidants, probiotics, and antibiotics in the management of AH. This article reviews the current data and status of these newer agents for the treatment of AH. Of the various options available, Vitamin E and N-acetylcysteine (NAC) have shown great promise for clinical use as adjunct to corticosteroids. With these encouraging data, future well designed studies are suggested to assess Vitamin E and NAC before their routine use in clinical practice in the management of AH.

Key words: Alcoholic hepatitis; Tumor necrosis factor-α inhibitors; Infliximab; Etanercept; Antioxidants; Probiotics; Rifaximin; Betaine; Granulocytapheresis

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AGENTS WHICH BLOCK TUMOR NECROSIS FACTOR-α

Tumor necrosis factor-α (TNF-α) is involved with cytotoxicity, leukocyte activation, inflammatory cytokines and other aspects of the immune response[1]. Alcohol-induced stress leads to increased TNF-α production[2]. Therefore, TNF-α was studied as a target for therapeutic intervention. Two currently available TNF-α inhibitors, infliximab and etanercept, have been evaluated as possible treatments for alcoholic hepatitis (AH). A pilot study of infliximab in 2002 examined 20 patients with biopsy-proven, severe AH (Maddrey's discriminant function

score ⩾ 32). Patients were treated with 28 d of prednisone (40 mg/d) and a single dose of either infliximab (5 mg/kg iv) or placebo on day 0. At day 28, Maddrey's score was significantly improved in the infliximab group (39 to 12, $P < 0.05$) but not in the placebo group (44 to 22, $P > 0.05$). Infliximab infusions were well-tolerated[3]. A later open-label trial evaluated 19 patients with severe AH who were treated with infliximab monotherapy (single dose of 5 mg/kg iv). Significant improvement in median values of Maddrey's Discriminant Function at 1 mo (38 *vs* baseline of 66, $P = 0.002$) and at 2 mo (28 *vs* baseline of 66, $P = 0.006$) was shown with 1 and 2 mo survival of 89% and 68%, respectively.

However 5 (26%) patients developed infection and two subsequently died[4]. Another study, a double-blind randomized controlled trial (RCT), compared 3 groups of patients: infliximab, prednisolone and infliximab, prednisolone and placebo. Within 2 mo, 7 patients in the infliximab group and 3 from the placebo group died and the study was stopped prematurely. The frequency of severe infections was higher in the infliximab group. The authors concluded that infliximab may actually be harmful due to the increased infection risk[5].

Etanercept, another anti-TNF agent, was studied in a pilot study on 13 patients with moderate or severe AH. Etanercept was given in a loading dose on day 1 followed by 25 mg subcutaneously on days 4, 8 and 12. The 30 d survival rate was 92% but several significant adverse events were noted (infection, hepatorenal decompensation, gastrointestinal bleeding) which required premature discontinuation of etanercept therapy in 23% of patients[6]. A double-blinded RCT of 48 patients with moderate to severe AH compared a 3 wk course of etanercept (25 mg on days 1, 4, 8, 11, 15 and 18) with placebo. Steroid or pentoxifylline use was not allowed in this study. Mortality rates at 1 mo were similar between etanercept and placebo (36.4% and 22.7%; odds ratio = 1.8, 95% CI: 0.5-6.5). However, mortality at 6 mo was significantly higher for etanercept as compared to placebo (58% *vs* 23%, $P = 0.017$). Worse outcome with the study drug was due to a higher rate of serious infections in the etanercept group (34.6% *vs* 9.1%, $P = 0.04$)[7]. In summary, TNF-α inhibitors are not effective agents for treating AH and pose a risk of serious infections.

ANTIOXIDANTS

Oxidative stress (OS) is a strong component of AH and the existence of OS markers has been consistently shown[8,9]. Antioxidants such as vitamin E, N-acetylcysteine (NAC) have been tried as adjuvant treatment option for patients with severe AH.

An open label RCT by Phillips *et al*[10] examined 101 patients with severe AH, comparing prednisone to an antioxidant cocktail over a 4 wk treatment period. Mortality at 1 mo was lower with steroids compared to antioxidants (30% *vs* 46%, $P = 0.05$). However, mortality was similar at 1 year. More infections occurred with the antioxidant group but culture proven infection was more frequent in the steroid group[10]. In another RCT, 70 patients with severe AH were randomized, based on 4 wk of steroid use, to receive either a combination of antioxidants (including NAC) for 6 mo or no treatment. Survival at 6 mo was similar in the two groups (53% *vs* 56%, $P = 0.7$) and was also independent of the prior steroid use[11]. Another study evaluated 51 patients with AH who received daily supplementation with 1000 mg of vitamin E and showed improvement in serum hyaluronic acid levels, but no effect was seen on liver function or 1 year survival[12]. A recent RCT from France on 174 patients with AH compared steroids alone to steroids with intravenous NAC given over 4 wk. Mortality at 2 mo was lower in the patients who received steroids and NAC (15% *vs* 33%, $P = 0.007$). Similarly, complication rate at 6 mo was lower in the group receiving steroids and NAC (19% *vs* 42%, $P = 0.001$)[13]. In summary, these data indicate that antioxidants show some promise in the treatment of AH; however, further studies are needed to confirm these findings before their routine use in clinical practice.

PROBIOTICS AND ANTIBIOTICS

Several studies have shown that patients with liver disease have abnormal bowel flora overgrowth and thus probiotics, which help to restore normal bowel flora, have been proposed as a possible treatment for alcoholic liver disease[14,15]. A prospective pilot study randomized 66 patients with alcoholic psychosis to receive either a 5 d course of probiotics (Bifidobacterium or Lactobacillus) or placebo. Compared to controls, all subjects initially had decreased levels of Bifidobacterium and Lactobacillus and significantly elevated ALT, AST and GGT levels. After treatment, the subjects who received probiotics had significantly increased levels of Bifidobacterium and Lactobacillus and decreased liver enzyme levels compared to patients receiving placebo[16]. Another open-label study compared 12 alcoholic cirrhotics who received *Lactobacillus* probiotics for 4 wk to healthy controls. Baseline neutrophil phagocytic capacity in the experimental group was significantly lower compared to healthy controls (73% *vs* 98%, $P < 0.05$). This normalized at the end of the study ($P < 0.05$). *Ex vivo* endotoxin-stimulated levels of soluble TNF-receptor-1, soluble TNF-receptor-2 and interleukin-10 were also significantly lower at the end of the study ($P < 0.05$)[17].

Increased bowel permeability and elevated endotoxin levels are also now being considered as a target for antibiotic therapy. Rifaximin, a derivative of rifamycin with low systemic absorption and broad-spectrum activity against gastrointestinal tract micro-organisms that has been previously used to treat hepatic encephalopathy, is now being studied with regards to improving liver function in alcoholic cirrhosis[18]. A recent study evaluated endotoxin levels and hepatic vein portal gradients (HVPG)

in 30 patients who received a 28 d course of rifaximin. Median plasma endotoxin levels decreased significantly after rifaximin administration both in systemic (1.45 *vs* 0.7, $P < 0.0001$) and splanchnic circulation (1.8 *vs* 0.8, $P < 0.0001$). Median HVPG also decreased from 18 mmHg on day 0 to 14.7 mmHg on day 29 ($P < 0.0001$). Overall, the HVPG decreased in 23, remained stable in 2 and increased in 3 after intestinal decontamination with rifaximin[19]. These findings are in contrast to earlier studies on norfloxacin that showed reduction in serum endotoxin concentrations and partial reversal of hyperdynamic circulatory state in cirrhotics with no significant change on HVPG[20,21].

MISCELLANEOUS TREATMENT MODALITIES

Betaine, a naturally-occurring antioxidant and methionine metabolite, was evaluated in a case report of a 40-year-old female who developed recurrent steatohepatitis due to continued alcohol consumption following liver transplantation. The patient was treated with 10 mg of betaine orally twice daily and subsequent liver biopsies at 6 and 12 mo showed a significant improvement in hepatic steatosis as well as normalization of liver function[22]. Further studies are needed to see if this treatment would show some benefit in AH as well.

Another treatment option which has been tried is granulocytapheresis, a technique that uses an extracorporeal absorptive mechanism to remove up to 60% of activated granulocytes and monocytes from circulating blood and thereby reduces levels of circulating proinflammatory cytokines. This is based on the existence of qualitative functional defects of neutrophils in patients with AH[23,24]. In a case series on 6 patients with severe AH (5 of whom were corticosteroid non responders), use of granulocytapheresis did not provide any benefit. All patients tolerated the procedure without hemodynamic compromise or other complications; however, all but one of the patients died within a month of granulocytapheresis treatment. The sole survivor was the corticosteroid responder in the group[25].

In summary, currently corticosteroids and pentoxifylline remain the mainstay for treating AH. However, there is a need for newer, more efficacious agents to improve the outcome of patients who fail to respond to first line agents. Vitamin E and NAC have shown encouraging data in small studies and need to be explored further in larger trials as adjunctive treatment option for treating severe AH.

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