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TOPIC HIGHLIGHT

Ashwani K Singal, MD, *Series Editor*

Corticosteroids and pentoxifylline for the treatment of alcoholic hepatitis: Current status

Ashwani K Singal, Ishmeet Walia, Anjna Singal, Roger D Soloway

Ashwani K Singal, Ishmeet Walia, Anjna Singal, Roger D Soloway, Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX 77555-0764, United States
Ashwani K Singal, Roger D Soloway, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN 55905-0001, United States
Author contributions: Singal AK drafted and revised the manuscript; Walia I and Singal A both worked on the tables, figures and references; Soloway RD supervised and reviewed the final version.
Correspondence to: Ashwani K Singal, MD, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN 55905-0001, United States. singal.ashwani@mayo.edu
Telephone: +1-507-2664056 Fax: +1-507-2664056
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Abstract

The treatment of choice for patients with severe alcoholic hepatitis (AH) is use of corticosteroids. Many randomized well designed studies have been reported from all over the world on the use of corticosteroids in the treatment of AH. However, the data on the efficacy of corticosteroids in these patients have been conflicting. Initial meta-analyses also failed to show beneficial effects of corticosteroids. Based on individual data meta-analysis showing clear benefit of corticosteroids amongst patients with severe AH (modified discriminant function of 32 or more), led American College of Gastroenterology to recommend use of corticosteroids as the first line treatment option amongst patients with severe AH. However, corticosteroids are relatively contraindicated amongst patients with severe AH and coexistent sepsis, gastrointestinal bleeding, and acute pancreatitis. These patients may be candidates for second line treatment with pentoxifylline. Further, specific treatment of AH with corticosteroids far from satisfactory with as many as 40%-50% of patients failing to respond to steroids, thus classified as non-responsive to steroids. The management of these patients is a continuing challenge for physicians. Better treatment modalities need to be developed for this group of patients in order to improve the outcome of patients with severe AH. This article describes at length the available trials on use of corticosteroids and pentoxifylline with their current status. Route of administration, dosage, adverse effects, and mechanisms of action of these two drugs are also discussed. Finally, an algorithm with clinical approach to management of patients who present with clinical syndrome of AH is described.

Key words: Corticosteroids; Pentoxifylline; Alcoholic hepatitis

Peer reviewers: Shivendra D Shukla, PhD, Professor, Department of Medical Pharmacology & Physiology, University of Missouri, School of Medicine M517B Medical Sciences Building One Hospital Drive Columbia, Missouri 65212, United States; Henning Grønbæk, MD, PhD, Associate Professor, Medical Department V, Aarhus University Hospital, Norrebrogade 44, DK-8000 Aarhus C, Denmark

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INTRODUCTION

Patients with severe alcoholic hepatitis (AH) have a short-term mortality of about 40%-50%[1]. Therefore, these patients should be identified early and treated appropriately.

Two established specific agents for treating severe AH are corticosteroids and pentoxifylline.

CORTICOSTEROIDS

The choice for treating patients with established and diagnosed cases of severe AH is corticosteroids[1]. There have been 12 randomized placebo controlled trials (RCT) to assess the benefit of corticosteroids in AH patients (Table 1). Results from these RCTs, conducted during the last 40 years, have varied with the sample size, inclusion/exclusion criteria, disease severity, end-points, type of corticosteroid used and treatment duration. These studies have shown conflicting data on the benefit of steroids with only five studies showing a survival benefit (Table 1). Meta-analyses of RCTs provide the best evidence for efficacy. To date, four meta-analyses have been published on the efficacy of steroids in AH[2-5]. The latest Cochrane analysis concluded that there is no clear evidence that steroids are effective in the management of AH. The potential for bias is due to heterogeneous data[5]. However, the same meta-analyses concluded that steroids do have survival benefit for patients with severe AH (discriminant function index, DFI $\geqslant$ 32)[5].

One of the means to tackle the issue of heterogeneity is to perform meta-analysis on the individual patient data from each study[6]. This had been performed earlier by Mathurin and colleagues from France where they analyzed individual patient data from 3 RCTs. The results of this meta-analysis showed that steroids have survival advantage for severe AH with 28 d survival of 85% among treated patients and 65% for patients receiving placebo (P = 0.001). This was also associated with improvement of liver function starting within the first week of starting the steroids[4].

Corticosteroids act by reducing inflammatory cytokines such as tumor necrosis factor-α (TNF-α), intercellular adhesion molecule 1, interlukin (IL)-6 and IL-8[7,8]. Inflammation is a major component of AH pathogenesis. In fact, in one study, peripheral white blood cell count > 5500/cm and the amount of polymorphonuclear leucocytic infiltration on the liver biopsy specimen were independent predictors for response and survival on steroid treatment[9].

Although, many agents have been used across different studies, prednisolone is preferred (but not demonstrated to be better) over prednisone as the latter requires conversion within the liver to its active form, prednisolone. The drug is given orally in a dose of 40-60 mg/d for a total duration of 4 wk. The treatment is then tapered over next 2-3 wk. If the patient is unable to take it orally due to nausea, vomiting or altered sensorium, an intravenous preparation such as methylprednisolone may be used until the patient is capable to take medication by mouth.

It is prudent to screen patients for any contraindication prior to starting steroids. One of the most important contraindications is the presence of infection which is fairly common among patients with severe AH. This used to be considered an absolute contraindication for steroids[10]. However, the latest data from France have shown that if a patient is adequately treated for an established infection, steroids can be safely started and even improve the outcome in these patients. In this study, all 246 patients studied prospectively were treated with steroids. Patients with infection (25% of the group) were treated adequately with antibiotics prior to starting steroids. Survival with steroids at 2 mo was similar, irrespective of the presence of infection prior to starting steroids (71% *vs* 72%, P = 0.99)[11].

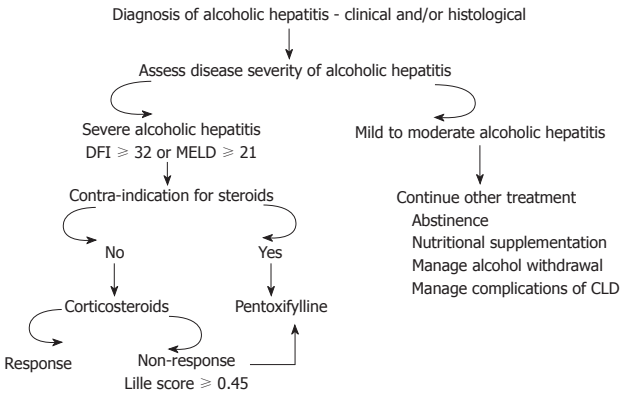

Figure 1 Specific treatment options for management of severe alcoholic hepatitis.

Other contra-indications are an active gastrointestinal bleeding, renal failure, acute pancreatitis, active tuberculosis, uncontrolled diabetes and psychosis. Patients should be assessed for response to steroids. It has been shown that a decrease in bilirubin at 1 wk (early change in bilirubin, ECBL) is a reliable and specific marker for response. Patients who achieved ECBL had a better survival at 6 mo compared to patients who did not achieve ECBL (98.3% *vs* 23%, $P < 0.0001$)[12]. Based on ECBL and other variables, French workers have derived a score (Lille score) based on the patient's age, serum albumin, ECBL, renal insufficiency and prothrombin time. Patients with a Lille score of $\geqslant$ 0.45 are defined as non-responders to steroids (NRS). This score, with a cut off at 0.45, has an accuracy of 75% in predicting death at 3-6 mo[13]. Patients should also be screened for infective complications while on steroids. Occurrence of sepsis and infective complications while the patient is on steroids is a poor prognostic sign. A total of 57 patients developed infection after starting steroids which occurred more frequently among NRS than responders to steroids (42% *vs* 11%, $P < 0.000001$)[11]. Lille score was an independent predictor for the occurrence of infection after starting steroids.

PENTOXIFYLLINE

For patients who have contraindications to steroids, the second option for treatment is oral pentoxifylline (PTX), a phosphodiesterase and a possible TNF-α inhibitor[14] (Figure 1). The drug was first shown to have beneficial effect in AH in a double blind placebo controlled RCT.

Table 1 Randomized studies to assess corticosteroids for treatment of acute alcoholic hepatitis

Ref.	Study design	Sample size	Mean age (yr) males (%)	Drug schedule	Main outcome /findings	Secondary findings	Causes of death
Helman *et al*[19] 1971	Randomized controlled trial: 3 groups: severe, moderate without encephalopathy, and ambulatory	37 (20)	48 (32)	Prednisolone 40 mg/d × 4 wk	Mortality benefit seen only for group I with severe alcoholic hepatitis (1/15 in treated *vs* 6/15 in untreated, $P < 0.01$)	No difference on histology at 4 wk and no effect on prevention to cirrhosis. Improved caloric intake was seen with steroids	Treated: ($n = 1$): liver failure. Untreated: ($n = 6$): hepatorenal syndrome (4), lower gastrointestinal bleed (1), variceal bleed (1)
Porter *et al*[20] 1971	Double blind Randomized controlled trial	20 (11)	45 (64)	6-Methylprednisolone 40 mg/d in 3 d × 10 d followed by oral if possible	Survival 45% *vs* 22%, P = NS	No effect on biochemical parameters	Treated: ($n = 1$): tuberculosis
Campra *et al*[21] 1973	Prospective controlled trial	45 (20)	43 (75)	Prednisone 0.5 mg/kg per day × 3 wk then 0.25 mg/kg per day × 3 wk	Survival was no different (36% *vs* 35%). Trend for improved survival with encephalopathy ($P = 0.2$)	No effect on biochemical parameters	Treated: ($n = 7$): hepatic failure. Untreated ($n = 9$): hepatic failure, GIB (5), renal failure (4)
Blitzer *et al*[22] 1977	Prospective double blind	28 (16)	48.4 (not reported)	Prednisolone 40 mg × 14 d then tapering × 2 wk	Overall mortality higher in the treated group	No effect on biochemical parameters. Prothrombin time higher in non-survivors	Treated: ($n = 11$): GIB, Hepatorenal syndrome, spontaneous bacterial peritonitis fungal infections (33% cases): disseminated aspergillosis, candidemia disclosed on autopsy; Untreated (31%): GIB, hepatorenal syndrome, spontaneous bacterial peritonitis, fungal infections
Shumaker *et al*[23] 1978	Randomized controlled trial	27 (12)	44 (75)	6 -methyl prednisolone 80 mg/d × 4-7 d *po*	No change in survival (50% *vs* 53%)	Patients with contraindication to steroids had higher mortality. Causes of death in the two groups were similar with > 50% dying from GIB	Treated: ($n = 3$): GIB, ($n = 2$): hepatic failure, ($n = 1$): acute pancreatitis. Untreated: ($n = 3$): GIB, ($n = 2$): sepsis, ($n = 1$): not reported
Maddrey *et al*[24] 1978	Randomized controlled trial	55	40 (60)	prednisolone 40 mg/d × 28-32 d	Improved short-term mortality but no effect on development of portal hypertension even in short term	Serum bilirubin > 20, prothrombin time > 8 s, prolonged and encephalopathy predicted mortality	Treated: ($n = 2$): hepatic failure, ($n = 1$): cytomegalic inclusion disease and pneumocystis carinii pneumonia mono-lineal esophagitis, ($n = 2$): severe liver disease. Untreated: ($n = 5$): hepatic failure, coma and hepatorenal syndrome
Lesesne *et al*[25] 1978	Randomized controlled trial	14 (7)	49 (not reported)	Prednisolone 40 mg/d × 30 d then 2 wk of tapering	Improved survival of the treated group. Improved nutrition alone is not a factor for better survival	Infrequent complications from steroids could be cause of death	Treated: ($n = 2$): hepatic failure and hepatorenal syndrome, ($n = 1$): hemorrhagic pancreatitis, ($n = 1$): pneumococcal pneumonia. Untreated: ($n = 7$): hepatic failure, ($n = 4$): GIB, ($n = 3$): hepatorenal syndrome, ($n = 1$): aspiration pneumonia, ($n = 1$): klebsiella bacteremia
Depew *et al*[26] 1980	Randomized controlled trial	28 (15)	49 (66)	Prednisolone 40 mg/d × 28 d then taper × 14 d	Mortality in both groups similar (53% *vs* 54%). LOS: 66 d with prednisolone and 56 d with placebo	No effect on biochemical parameters and complications higher with steroids	Treated: ($n = 7$): urinary tract infection, ($n = 3$) pneumonia, ($n = 2$) septicemia, ($n = 1$) perinephric abscess. Untreated: ($n = 6$): urinary tract infection, ($n = 1$) pneumonia

Ramond *et al*[27] 1992	Randomized controlled trial	61 (32)	48 (not reported)	prednisolone 40 mg/d × 28 d (IV if unable to take orally)	Improved survival at 6 mo (84% *vs* 45%, *P* = 0.002) irrespective of encephalopathy for patients with discriminant function > 32 (21/23 *vs* 10/19, *P* < 0.001)	Death in steroids group occurred early. Patients should be started on steroids while awaiting biopsy results	Treated: (*n* = 2): gastritis and GIB, (*n* = 2): septicemia lung. Untreated: (*n* = 16): GIB, ascites, variceal rupture, pancreatitis, (*n* = 1 each): septicemia
Theodossi *et al*[28] 1982	Randomized controlled trial	55 (27)	Not reported, 70% (treatment group), 30% (control group)	Methylprednisolone 1 g/d × 3 d	Patients survival predicted by: encephalopathy, discriminant function > 93, bilirubin 20 mg/dL, creatinine 3 mg/dL, and histological evidence of cirrhosis	Not reported	Treated: (*n* = 7): septicemia, (*n* = 2): pancreatitis. Untreated: (*n* = 6): septicemia, (*n* = 2): pancreatitis % mortality in patients of hepatic encephalopathy: 94% (treatment group) 69% (control group)
Richardet *et al*[29] 1993[1]	Randomized controlled trial	23 (12)	Not reported	Prednisolone 40 mg/d × 8 d	Tumor necrosis factor, interleukin-6, interleukin-8 decreased in treated group significantly at Day 8 from their baseline Day 0 levels	Not reported	Not reported

[1]Abstract publication. NS: Not significant; GIB: Gastrointestinal bleeding.

Table 2 Randomized controlled trial controlled trial studies to assess pentoxifylline for treatment of acute alcoholic hepatitis

Ref.	Sample size	Mean age (yr) males (%)	Drug schedule	Main outcome/findings	Secondary findings	Causes of death
McHutchison *et al*[30] 1991[1]	22 (12 pentoxifylline)	Not reported	Pentoxifylline 400 mg *tid* × 10 d	Renal impairment more with placebo (mean creatinine change -0.3 *vs* +2.1	No difference on other biochemical parameters. Plasma tumor necrosis factor increased in controls only. Survival trend better with pentoxifylline (3 deaths *vs* 1 death)	Not reported
Akriviadis *et al*[15] 2000	101 (49 pentoxifylline)	42 (71% males)	Pentoxifylline 400 mg *tid* × 28 d	Mortality during the admission 25% *vs* 46% (*P* = 0.037)	Age, creatinine at randomization, and pentoxifylline treatment predicted survival. Tumor necrosis factor levels were no different with pentoxifylline and placebo. However, among non-survivors tumor necrosis factor levels decreased more in pentoxifylline group	Hepatorenal syndrome: treated *vs* untreated (50% *vs* 92%, *P* = 0.009)
Paladugu *et al*[31] 2006[1]	30 (14)	50 (100%)	Pentoxifylline	Mortality at 28 d: 29% *vs* 46% (*P* = 0.09). Time to death 21 d *vs* 18 d (*P* = 0.041)	Tumor necrosis factor levels unchanged in both groups	Hepatorenal syndrome: treated *vs* untreated (50% *vs* 86%, *P* = 0.1)
Sidhu *et al*[32] 2006[1]	50	Not reported	Pentoxifylline 400 mg *tid* × 28 d	Mortality at 28 d (24% *vs* 40%, *P* = NS)	Pentoxifylline reduced creatinine, tumor necrosis factor, discriminant function index, prothrombin time	Hepatorenal syndrome: treated *vs* untreated (83% *vs* 60%)
Lebrec *et al*[33] 2007[1]	132	Not reported	Pentoxifylline	Mortality at 2 mo (14% *vs* 16%, *P* = 0.77) and at 6 mo (27% *vs* 31%, *P* = 0.3) were similar	No difference for serious adverse effects between the 2 groups. Subgroup with renal dysfunction also did not get benefit with pentoxifylline	Not reported

[1]Abstract publication.

The study showed survival benefit at 1 mo with the use of PTX compared to placebo (76% *vs* 54%)[15]. This benefit was attributed mainly to the prevention of the hepatorenal syndrome (HRS) among patients treated with PTX as compared to placebo (50% *vs* 92%, *P* < 0.05)[15]. Later, many studies (reported as abstracts) confirmed this observation of beneficial effect of PTX in the prevention of HRS (Table 2). A study published recently comparing steroids to PTX showed superiority of PTX in the treatment of AH patients with better survival rate at 3 mo (85% *vs* 65%, *P* = 0.04)[16]. This was again mainly due to prevention of HRS by PTX (6 of 34 patients receiving steroids developed HRS compared to none of 34 receiving PTX)[16]. However, the latest Cochrane systematic review of 5 RCTs (4 reported as abstracts) concluded that there is not enough evidence for survival benefit of PTX in the treatment of AH. However, the problem with these studies is a small sample size. Further, four of these

five studies are reported as abstracts[17].

The question of whether PTX is a salvage option for patients with NRS was answered by a study in which patients were identified as NRS at 1 wk (Lille score ⩾ 0.45) and randomized to PTX or placebo. Steroids were continued in both the groups for 28 d[18]. The use of additional PTX failed to demonstrate survival advantage at 2 mo (36% *vs* 31%, $P > 0.05$). Further, there was no benefit shown on the biochemical parameters. Clearly, PTX was not shown to be an option for patients with NRS[18]. However, the drug has not been studied in patients with NRS without additional steroids. Since patients with NRS are prone to develop infectious complications, this might have abrogated the benefit of PTX. Occurrence of infective complications and/or sepsis as cause of death was not reported in this study. Although the evidence for efficacy of PTX for severe AH is weak, this drug may be a second line option and is worth considering until newer and more effective agents are developed.

PTX is given orally at a dose of 400 mg three times a day for a total duration of 28 d. Although an anti-TNF agent, the TNF levels were not shown to be different among patients receiving PTX and those receiving placebo[15]. The exact mechanism of action of PTX is not entirely clear. Neutralization of TNF-α by PTX may explain the protective effect of this drug on HRS although the exact mechanism is not clear.

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