Role of Pentoxifylline and Steroids for Alcoholic Hepatitis – Has the last word been said?

Abstract 1

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Pentoxifylline vs. corticosteroid to treat severe alcoholic hepatitis: a randomised, non-inferiority, open trial.

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BACKGROUND & AIMS: Both corticosteroid and pentoxifylline reduce short-term mortality in severe alcoholic hepatitis. However, few studies have directly compared the efficacy of pentoxifylline and corticosteroid in patients with this condition.

METHODS: In this multicentre, open-labelled, randomised non-inferiority trial, we assigned 121 patients with severe alcoholic hepatitis (Maddrey's discriminant function ~32) to receive either pentoxifylline (400 mg, 3 times daily, in 62 subjects) or prednisolone (40 mg daily, in 59 subjects). The primary end point was non-inferiority in survival at the 1 month time point for the pentoxifylline treatment compared with prednisolone.

RESULTS: The 1-month survival rate of patients receiving pentoxifylline was 75.8% (15 deaths) compared with 88.1% (7 deaths) in those, taking prednisolone, for a treatment difference of 12.3% (95% confidence interval, −4.2%–28.7%; p = 0.08). The 95% confidence interval for the observed difference exceeded the predefined margin of non-inferiority (Δ15%) and included zero. The 6-month survival rate was not significantly different between the pentoxifylline and prednisolone groups (64.5% vs. 72.9%; p = 0.23). At 7 days, the response to therapy assessed by the Lille model was significantly lower in the prednisolone group (n = 58) than in the pentoxifylline group (n = 5 9): 0.35 vs. 0.50 (p = 0.012). Hepatitis complications, including hepatorenal syndrome and side effects, such as infection and gastrointestinal bleeding, were similar in the two groups.

CONCLUSIONS: The findings demonstrate that the efficacy of the pentoxifylline is not statistically equivalent to the efficacy of prednisolone, supporting the use of prednisolone as a preferred treatment option in patients with severe alcoholic hepatitis.

Abstract 2

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Prednisolone or pentoxifylline for alcoholic hepatitis.

Thursz MR, Richardson P, Allison M, Austin A, Bowers M, Day CP, Downs N, Gleeson D, MacGilchrist A, Grant A, Hood S, Masson S, McCune A, Mellor J,O'Grady J, Patch D, Ratcliffe I, Roderick P, Stanton L, Vergis N, Wright M, Ryder S, Forrest EH; STOPAH Trial.

BACKGROUND: Alcoholic hepatitis is a clinical syndrome characterized by jaundice and liver impairment that occurs in patients with a history of heavy and prolonged alcohol use. The short-term mortality among patients with severe disease exceeds 30%. Prednisolone and pentoxifylline are both recommended for the treatment of severe alcoholic hepatitis, but uncertainty about their benefit persists.

METHODS: We conducted a multicenter, double-blind, randomized trial with a 2-by-2 factorial design to evaluate

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the effect of treatment with prednisolone or pentoxifylline. The primary end point was mortality at 28 days. Secondary end points included death or liver transplantation at 90 days and at 1 year. Patients with a clinical diagnosis of alcoholic hepatitis and severe disease were randomly assigned to one of four groups: a group that received a pentoxifylline-matched placebo and a prednisolone-matched placebo, a group that received prednisolone and a pentoxifylline-matched placebo, a group that received pentoxifylline and a prednisolone-matched placebo, or a group that received both prednisolone and pentoxifylline.

RESULTS: A total of 1103 patients underwent randomization, and data from 1053 were available for the primary end-point analysis. Mortality at 28 days was 17% (45 of 269 patients) in the placebo–placebo group, 14% (38 of 266 patients) in the prednisolone-placebo group, 19% (50 of 258 patients) in the pentoxifylline-placebo group, and 13% (35 of 260 patients) in the prednisolone-pentoxifylline group. The odds ratio for 28-day mortality with pentoxifylline was 1.07 (95% confidence interval [CI], 0.77 to 1.49; P = 0.69), and that with prednisolone was 0.72 (95% CI, 0.52 to 1.01; P = 0.06). At 90 days and at 1 year, there were no significant between-group differences. Serious infections occurred in 13% of the patients treated with prednisolone versus 7% of those who did not receive prednisolone (P = 0.002).

CONCLUSIONS: Pentoxifylline did not improve survival in patients with alcoholic hepatitis. Prednisolone was associated with a reduction in 28-day mortality that did not reach significance and with no improvement in outcomes at 90 days or 1 year. (Funded by the National Institute for Health Research Health Technology Assessment program; STOPAH EudraCT number, 2009-013897-42, and Current Controlled Trials number, ISRCTN88782125).

COMMENTS

Alcohol consumption is on the rise across the globe and in India.[1] The disease spectrum of alcohol related injury includes simple steatosis, alcoholic hepatitis (AH) and cirrhosis. AH is the most severe presentation, ranging from asymptomatic to liver failure. Among patients with alcoholic hepatitis who have Maddrey's discriminant function (DF) $\geq$ 32, the 4 weeks mortality is high, ranging between 30% and 50%.[2] The risk increases in the presence of hepatic encephalopathy. In addition, patients with high model for end stage liver disease (MELD) score (>18), or Glasgow alcoholic hepatitis score (GAHS) > 8 are at risk and need to be considered for therapy to improve prognosis.

The current guidelines on the management of alcoholic liver disease from the American Association for the study of the Liver diseases[2] and European Association for the Study of the Liver[3] recommend prednisolone and pentoxifylline as the treatment options. Sepsis, renal failure and gastrointestinal bleed are contraindications for use of steroids. Steroids in turn increase the risk of infections in these patients; therefore, clinicians are usually reluctant to use them. Pentoxifylline is a phosphodiesterase inhibitor, which acts by inhibiting the synthesis of tumour necrosis factors alpha. Pentoxifylline has been shown to prevent the development of hepatorenal syndrome (HRS) and hence a possible reduction in mortality.[4] There is a lot of heterogeneity in the trials evaluating the role of pentoxifylline. A recent meta-analysis concluded that pentoxifylline was superior to placebo in prevention of fatal HRS, but was not associated with survival benefit at 4 weeks. In addition, there was no significant difference in survival between pentoxifylline and steroids - alone or in combination.[5]

The data available regarding the use of steroids has been controversial. A recent meta-analysis which included 5 RCTs showed a beneficial effect of steroids on the 4 week survival in patients with severe alcoholic hepatitis.[6] Whereas, the Cochrane review included 15 trials, with high bias risk, reported an overall mortality rate of 39.5%. There was no significant reduction in mortality with use of steroids as compared with placebo. The authors concluded that the current evidence does not support the use of steroids in AH and large low bias well designed RCTs are required.[7]

Park et al[8] in a multicentre, open labelled non-inferiority trial involving 124 patients with severe AH compared the short term mortality among the patients randomised to steroids or pentoxifylline. Patients were treated with either prednisolone 40 mg per day or pentoxifylline 1200 mg per day for 4 weeks. The authors reported a lower survival with pentoxifylline as compared to prednisolone both at 4 weeks (75.8% vs 88.1%) and 6 months (64.5% vs 72.9%). The authors concluded that pentoxifylline is less effective than prednisolone. The major drawbacks included absence of a placebo group, study was not double blinded and no liver histology was used for the diagnosis.

The study by Thursz et al[9] was designed to answer the question: whether use of prednisolone or pentoxifylline reduces short term (4 weeks) and medium term mortality (at 90 days and 1 year). The study was a multi-centre randomised control trial, with a 2-by-2 factorial design with 4 treatment groups. The 4 arms included pentoxifylline 1200 mg and placebo, prednisolone 40 mg and placebo, pentoxifylline 1200 mg and prednisolone, placebo and placebo. The therapies were given over a period of 4 weeks. The randomisation was done in block sizes of 4 and stratified by geographical area and risk category. The study was double blinded (neither patients nor clinicians knew about the allocation groups) and intention to treat analysis was used. A total of 1103 were included after screening 5234 patients, over a span of 3 years across 65 hospitals in the United Kingdom. The authors included adult patients with a

clinical diagnosis of AH with DF > 32. Patients with uncontrolled sepsis, active gastrointestinal bleeding, jaundice more than 3 months, aspartate aminotransferases (AST) > 500 IU/L or alanine transaminase (ALT) levels > 300 IU/L were excluded. Of the cohort included, two-thirds were males and the mean daily alcohol consumption was 195–210 g in males and 142–157 g in females. The mean time from admission to start of treatment was 6 days.

The primary outcome included mortality at 4 weeks. The mortality in the prednisolone group was 13.9% and in the pentoxifylline or placebo group was 18.0%. In contrast, there was no difference in the mortality rate between patients receiving pentoxifylline and those who did not (16.4% vs 15.5%). In an unadjusted analysis, the odds ratio (OR) for 28-day mortality with prednisolone, compared with no prednisolone, was 0.72, which was of borderline significance ($P = 0.056$). When pentoxifylline was compared with no pentoxifylline, the OR was 1.07 ($P = 0.686$). The factors predictive of 4 week mortality included treatment with prednisolone, INR, age, total leucocyte count, blood urea, creatinine, serum bilirubin and presence of hepatic encephalopathy. The 90 day and 1 year mortality in patients receiving prednisolone, pentoxifylline or placebo was similar (30% and 57% respectively). In addition, infections were seen significantly more in patients with steroids than who did not receive steroids (3% vs 7%).

The overall mortality rate in the current trial was much lower than the high mortality reported in the initial trials, which possibly suggests these were probably less severe patients. Moreover, only 27% had hepatic encephalopathy, and, among these, advanced HE was present in only 2% of patients, which is a poor prognostic sign in these patients. Nutritional status might be another factor which impacted the mortality in the current cohort.

One of the highlights of the study was the large number of centres involved in the collation of data. Moreover, the factorial design allowed comparison of the 2 different arms with large sample sizes and high statistical power. The authors, in addition to the short term mortality, assessed the medium term outcome with good follow up. In addition, the eligibility of patients was based on the clinical parameters rather than liver biopsy, which is the policy followed in clinical practice at most centres.

Limitations include the absence of liver biopsy, which has been suggested by experts to be included as a diagnostic criterion for AH in clinical trials. Also, financial limitations didn't allow all patients to be followed up completely, and the study was terminated after last patient recruited was followed up for 4 weeks. The difference in the actual and estimated mortality of 20% reduced the effective power of the study and could have affected the conclusions of the study.

To conclude, these 2 studies show that the pentoxifylline for 4 weeks has no role in the management of severe alcoholic hepatitis, whereas steroids are associated with a 4 weeks beneficial effect and there is no effect on the medium term survival at 90 days and 1 year of treatment. Alcohol abstinence is the best option to improve both short term and long term survival in these patients. However, we are still far from the ideal treatment of severe AH, and there is an urgent need to identify new targets for development of more specific and effective therapies.

CONFLICTS OF INTEREST

The author has none to declare.

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