F1000 FACULTY CRITIQUE

Alcoholic hepatitis: Yes to prednisolone and no to pentoxifylline [version 1; referees: not peer reviewed]

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Abstract

An evaluation of a recent study by Thursz MR, Richardson P, Allison M *et al*. "**Prednisolone or Pentoxifylline for Alcoholic Hepatitis**". N Engl J Med 2015;372:1619-28. PubMed PMID: 25901427. EudraCT number, 2009-013897-42. Current Controlled Trials number ISRCTN88782125.

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Critique of:
Citation
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. "Prednisolone or Pentoxifylline for Alcoholic Hepatitis". N Engl J Med 2015;372(17):1619–28. PubMed PMID: 25901427. EudraCT number: 2009-013897-42. Current Controlled Trials number: ISRCTN88782125.

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.

Objective
To determine whether corticosteroids or pentoxifylline reduce the mortality associated with severe alcoholic hepatitis at 28 days, 90 days and 1 year.

Design
Multicenter, double-blind, randomized trial with a 2-by-2 factorial.

Setting
Patients were recruited from January 2011 through February 2014 at 65 hospitals across the United Kingdom.

Subjects
All patients admitted with suspected severe alcoholic hepatitis were evaluated for eligibility. A clinical diagnosis that was based on a history of recent excess alcohol consumption and the absence of other causes of liver disease was used for trial recruitment.

Intervention
Patients were randomly assigned to one of four groups: 1) a group that received a double placebo, 2) a group that received active prednisolone and a pentoxifylline-matched placebo, 3) a group that received active pentoxifylline and a prednisolone-matched placebo, or 4) a group that received both active prednisolone and pentoxifylline.

Outcomes and follow up
1 year follow up with primary outcome of 28-day mortality and secondary outcomes of liver transplantation or mortality at 90 days and 1 year.

Results
A total of 1103 patients underwent randomization, and data from 1053 were available for the primary end-point analysis (28-day mortality). 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). Combined pentoxyfylline-prednisolone therapy did not improve 28-day mortality. 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 (P=0.002). In a prespecified secondary analysis, in which a multivariate backward stepwise (not prespecified) logistic-regression was used to adjust for variables associated with prognosis in univariate analysis, the odds ratio for 28-day mortality among the patients who received prednisolone, as compared with those who did not, was 0.61 (95% CI, 0.41 to 0.91; P=0.02). However, the effect of prednisolone on mortality at 90 days (odds ratio, 1.00; 95% CI, 0.73 to 1.36; P=0.98) and at 1 year (odds ratio, 1.01; 95% CI, 0.74 to 1.39; P=0.94) was not significant.

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.)

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Commentary
Despite decades of research on its management, alcoholic hepatitis (AH) remained a significant cause of morbidity and mortality; Twenty eight day mortality rates were as high as 35% for individuals with a Maddrey's Discriminant Function (MDF) score of at least 32[1]. In 2008 A Cochrane meta-analysis of RCTs comparing glucorticoid therapy to placebo or no intervention, was published[2]. A total of only 721 patients were included. The results showed that glucocorticoids did not reduce mortality compared to placebo but in a subgroup analysis done for patients with MDF of at least 32 there was a significant mortality reduction. The included studies were mostly very small and there was a risk for bias in 12 of 15. In 2011, another meta-analysis was published that combined the results of only the most recent RCTs on glucocorticoids vs other therapy in patients with MDF greater than 32[3]. A total of 418 patients were enrolled and the results showed a survival benefit for steroid use: 28-day mortality rate of ~20% in the steroid group compared to ~35% in the placebo or other therapy group, p=0.0005. Pentoxifylline has been less well studied than glucocorticoids in AH. The key study that showed a significant benefit for pentoxifylline was published in 2000 by Akriviadis *et al.*[4]. It was a double blind randomized trial enrolling 101 patients that showed a 24.5% in-hospital mortality rate in the pentoxifylline group as compared to a 46% mortality rate in the placebo group resulting in a relative risk of 0.59 for death (p = 0.037). However in 2009, Cochrane published a meta-analysis of 5 RCTS with a total of 336 patients[5]. This showed that pentoxifylline reduced mortality compared with

control (RR 0.64; 95% CI 0.46 to 0.89). However, this result was not supported by trial sequential analysis, which adjusts for multiple testing on accumulating data. Of the five included trials, four (80%) had a high risk of bias. As a result of the poor quality of most of the studies, the authors concluded that no conclusions could be drawn regarding whether pentoxifylline had a positive, negative, or neutral effect on participants with alcoholic hepatitis. Mathurin *et al.*[6] found no evidence of an additive effect when pentoxifylline was added to prednisolone confirming the findings of the COPE trial[7]. Based on these published randomized controlled trials (RCT) and meta-analyses, prednisolone and pentoxifylline were incorporated in the past 5 years into guidelines of the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL)[8,9] but these recommendations remained controversial due to the quality of the data upon which they were based.

The STOPAH trial had 90% power to detect a reduction in 28-day mortality from 30% to 21% based on its sample size of 1026 patients. Analyses were on an intention-to-treat basis. Logistic regression was used to compare 28-day, 90-day and 1 year mortality, and liver transplantation rates after adjustments for risk category. Cox proportional-hazards regression was used to compare 1-year survival among the groups, and Kaplan–Meier curves for 1-year survival were plotted. All P values were two-sided. As part of a pre-specified analysis, individual and treatment variables that were found to be significant in univariate analyses were used in multivariate logistic-regression analysis, and backward elimination (which was not prespecified) was applied at a 5% significance level. From Jan 2011, for 3yrs, 5234 potential patients were screened and 4131 were excluded after the various eligibility criteria were applied. 1103 patients were randomized for the trial in nearly even groups. The four groups had similar baseline characteristics and laboratory values.

In unadjusted analysis, prednisolone showed a strong trend towards reduced 28 day mortality (P=0.06) whereas pentoxifylline did not (P=0.69). Neither drug influenced mortality, or the need for liver transplantation at 90 days or 1 year - though one could argue that long term improvement in outcomes for AH is mostly determined by alcohol cessation not the acute treatment of the hepatitis. The dramatic increase in mortality or transplantation from 16% (28 days) to 29% (90 days) to 56% (1 year) underscores the chronic severity of this condition and argues against the meaningfulness of longer term outcomes without alcohol cessation. There was no significant interaction between prednisolone and pentoxifylline (P=0.41). In a secondary analysis that adjusted prognostically important variables, prednisolone improved 28-day mortality (OR = 0.61, p = 0.02) but not 90 day or 1 year outcomes. Infection was higher in the prednisolone group but mortality from infection was similar across groups. Thus the study supports a short term benefit of prednisolone in AH but no benefit from pentoxifylline or the combination.

The study had a number of strengths. Firstly, it had a wide catchment area cutting across 65 hospitals in the UK and increasing the generalizability of the results. Secondly, the use of a 2×2 factorial design was appropriate and well executed. It allowed for the concomitant testing of more than one hypothesis in an efficient manner, whilst monitoring for possible interaction effects. Thirdly, it appropriately adjusted for important prognostic variables such as age, encephalopathy, WBC count, PT, Bilirubin, creatinine and urea levels. An adjusted analysis protects against chance imbalance that can occur in a randomized controlled trial, particularly in smaller trials such as these. In addition, they had pre-specified which variables would be examined for inclusion in this analysis, which reduces bias and makes it more reliable. It was also probably reasonable to use backward stepwise regression as it allowed for the fine-tuning of prior selected variables to get the variables that were of most statistical significance.

The study had a number of limitations. Self-reported alcohol consumption was used for inclusion which unfortunately is not reliable, particularly amongst heavy drinkers[10] associated with severe AH. Although it is difficult to envision a more accurate method and the use of biopsy criteria would violate the usual standard of care. No data were reported on resultant morbidity and quality of life measures which are important patient centered outcomes. The lower than expected placebo/placebo mortality rate could have resulted in an underpowering hence the trend in the prednisolone effect though the pentoxifylline effect was certainly nil.

The STOPAH study is the most comprehensive study to date, looking at the effectiveness of prednisolone and pentoxifylline in treating severe alcoholic hepatitis. When these results are taken in context of the prior studies, there is definitely a suggestion of benefit with steroid therapy. This benefit comes at the cost of more infections. Like many diseases, mortality due to AH has steadily decreased making sample size calculations challenging, and resulting in, an inadvertently underpowered study.

Recommendation
Prednisolone in addition to supportive modalities should be the main stay of therapy for patients with severe AH whereas pentoxifylline has no role in this disease. We should not lose sight of the fact that at 1yr, over 50% of the patients had either died or received liver transplantation underscoring the need to pursue sustained alcohol abstinence as the key for improved medium to long term survival.

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