A prospective, multicenter, double-blind, randomized-controlled trial of prednisolone versus prednisolone and pentoxifylline in severe alcoholic hepatitis

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A. Study Purpose and Rationale

The purpose of the study is to evaluate the effect on survival of prednisolone versus prednisolone and pentoxifylline in patients with severe alcoholic hepatitis. Alcoholic hepatitis (AH) is prevalent in about twenty percent of heavy drinkers and while current recommendations favor treating severe AH with corticosteroids, the practice has not been universally accepted. There have been numerous studies involving corticosteroids and AH, and recent studies have shown that patients with Maddrey discriminant function ≥32 have a two-month survival of about 80% after treatment with corticosteroids compared with a spontaneous survival between 50-65%(1-5). Short-term survival in less severe AH with discriminant function less than 32 has been shown to be near 90% (3).

Research seems to suggest an inflammatory process contributes to the pathogenesis of AH, with experimental and clinical data suggesting components of lipopolysaccharide (LPS) and pro-inflammatory cytokines as the effector molecules in alcohol-induced liver injury with activation of Kupffer cells causing production of pro-inflammatory cytokines including TNFα (1, 6). It has been observed that patients with AH have higher serum levels of TNFα and IL-8, which have correlated with severity of liver disease (7). Corticosteroids have anti-inflammatory effects that seem to work at least in part related to the inhibition of polymorphonuclear neutrophil activation, ICAM-1 expression and pro-inflammatory cytokines (1,8). Pentoxifylline is an inhibitor of TNFα synthesis. Pentoxifylline has been evaluated in a double-blind, randomized-controlled trial versus placebo in severe AH (9). One hundred one patients were enrolled with improvement in one-month survival from 53.9% in placebo group to 75.5% in pentoxifylline group.

Although both prednisolone and pentoxifylline have been shown to improve short-term mortality in AH, prednisolone has not been universally accepted as the appropriate treatment modality and pentoxifylline has only one published study showing significant decrease in mortality. These two agents have also been used in combination in clinical practice without evidence showing decreased mortality with dual agent use compared to single agent. This study will attempt to answer whether the combination of prednisolone and pentoxifylline shows improved short-term survival in severe AH compared to prednisolone alone.

B. Study Design and Statistical Analysis

The study will enroll consecutive patients admitted to several large academic urban medical centers with a high prevalence of alcoholic hepatitis. Informed consent will be obtained from all patients, or in the case that the patients are incapacitated consent will be obtained from the designated legal health care proxy. Each patient will have a history of ethanol abuse and an admission diagnosis of acute alcoholic hepatitis. Inclusion criteria will be based on previously published studies of pentoxifylline (9) and will include 1) Maddrey discriminant factor (DF) ≥ 32 2) Jaundice and 3) 1 or more of the following clinical or laboratory findings: palpable tender hepatomegaly, fever, leukocytosis with white blood cell count >12000/mm3 with neutrophilic differentiation, hepatic encephalopathy, and hepatic systolic bruit. Enrollment will be limited to within 10 days of hospitalization.

Biopsy diagnosis will not be required secondary to the risk of biopsy in patients with severe coagulopathy.

Exclusion criteria will include concomitant bacterial or systemic fungal infection and active GI bleeding.

After consent is obtained, patients will be randomized to receive either 28 days of prednisolone 40mg daily by mouth and pentoxifylline 400mg three times a day by mouth or prednisolone 40mg daily by mouth and placebo three times a day by mouth.

Randomization will be stratified by serum creatinine levels equal to or above and below 2.5 mg/dL to balance renal impairment between the two groups. Randomization will be performed at a central randomization location and the study medicine will be delivered by the research pharmacy with both the physician and patient being blinded to medication being administered. In the event of severe gastrointestinal bleeding after enrollment, therapy will be held temporarily until control of hemorrhage. Other medical management will be continued based on the judgment of the physician treating the patient. Patients will be examined at least weekly for possible complications (GI bleed, infection, abdominal pain, dyspepsia, diarrhea, leukopenia, thrombocytopenia, renal impairment, skin rash, and hepatic encephalopathy). At the onset of the study, labs will be drawn measuring presence of antibodies against hepatitis C, hepatitis B surface antigen, cholesterol, α-fetoprotein and IL-8. Complete blood count, liver function panel, electrolytes, serum creatinine, blood urea nitrogen, prothrombin time, and fasting glucose will be measured at least twice a week.

Once the patient can medically be discharged, they will be given capsules to take at home (with extra capsules given to prevent patient from bringing empty bottle at completion of study) and instructed to follow-up weekly until the 4-week study period is over. At the weekly follow-up, capsules remaining in bottle will be counted, labs will be drawn, and physical examination will be performed. At the completion of 4 weeks study period and at 2 months, follow-up exam will be performed with routine laboratories as well as TNF-α levels. Patient or patient's family will be contacted at 6 months and 1 year to assess for survival data.

An independent data safety monitoring board will meet every 6 months to examine preliminary data.

Primary Outcome: 2-month mortality.

Secondary Outcomes: 6-month mortality, 1-year mortality. Change in TNF-α level. Change in liver function tests.

Enrollment: Enrollment goal will be a total of 438 patients based on the chi-squared test on proportions with an estimated survival of 80% at 2 months in the prednisolone group based on prior published studies. This number of patients will have power at the level of .80 with α of 0.05 to show the estimated improvement in survival to 90% at 2 months in the prednisolone plus pentoxifylline group.

Data Analysis: All analysis will be done on an intention-to-treat basis. Primary endpoint survival data will be analyzed by chi squared test on proportions. Kaplan-Meier survival curves will be used to analyze survival over time. Cox-proportional hazard model will be utilized to analyze survival over time with logistic regression. Secondary data that are continuous will be tested using either t tests or repeated measures analysis of variance (ANOVA) as required.

C. Study Procedure

The primary endpoint of the study will be completed in 2 months. Each patient will actively participate for two months, however contact will be maintained with the patients for at least one year to assess survival. The study is expected to run for 4 years

The only procedures done to the patient for the purpose of the study will be blood draws. All other procedures will be done at the discretion of the treating physician in order to ensure the best quality of care for the patient.

D. Study Drugs

Prednisolone is FDA approved for: (10)

- Asthma, uncontrolled
- Endocrine disorders (eg, adrenocortical insufficiency, congenital hyperplasia, thyroiditis, hypercalcemia of cancer)
- Hematologic and Neoplastic disorders (eg, leukemia, lymphoma, thrombocytopenic purpura, anemia)
- Inflammatory conditions
- Multiple sclerosis exacerbations
- Nephrotic syndrome
- Ophthalmic diseases (eg, uveitis, temporal arteritis)

While it is not approved for alcoholic hepatitis, it is the current standard of care for patients with a discriminant function ≥32. The dosage used in this study is consistent with dosages used in prior studies and the standard of care dosing. Contraindications include: systemic fungal infections, hypersensitivity to prednisolone or its components, and use of live attenuated vaccines (immunosuppressive doses).

Adverse effects include: (10)

- **COMMON**
  - euphoria/depression
  - GI distress
  - growth depression
  - impaired skin healing, skin atrophy
  - increased risk of infection
- **SERIOUS**
  - cataracts/glaucoma
  - Cushing's syndrome
  - fluid and electrolyte disturbances
  - HPA axis suppression/adrenal insufficiency
  - hyperglycemia
  - osteoporosis, especially in elderly
  - tuberculosis reactivation

Pentoxifylline is FDA approved for intermittent claudication, but not for alcoholic hepatitis. It is commonly used in patients with alcoholic hepatitis as adjunctive therapy with prednisolone or alone if the patient cannot tolerate corticosteroids. The dosage used in this study is consistent with dosage used in the major study showing survival benefit in AH (9). Contraindications include hypersensitivity to pentoxifylline or methylxanthines, recent cerebral hemorrhage, or recent retinal hemorrhage.

Adverse effects include: (10)

- **COMMON**
  - dyspepsia, nausea, vomiting
  - dizziness, headache
- **SERIOUS**
  - angina (less than 1%), edema (less than 1%), hypotension (less than 1%), arrhythmias (rare)
  - confusion (less than 1%), depression (less than 1%), seizures (less than 1%)

- aplastic anemia (rare), leukopenia (rare), thrombocytopenia (rare)
- hepatitis (rare), jaundice (rare), elevated LFTs (rare)

E. Medical Device

There are no medical devices under investigation in this protocol.

F. Study Questionnaires

There will be a standard questionnaire to assess patient's history of alcohol use.

G. Study Subjects

Inclusion and exclusion criteria are outlined in section B, Study Design and Statistical Analysis.

H. Recruitment of Subjects

Subjects will be recruited from all inpatient admissions with diagnosis of alcoholic hepatitis at participating centers.

I. Confidentiality of Study Data

All patients will have a unique study code, independent from MRN, SSN, name, phone number or address. Identity of study subjects and study data will be safeguarded and only available to unblinded independent Data Safety Monitoring Board. Data will be stored in a secure location, accessible only to the investigators.

J. Potential Conflict of Interest

There are no known potential conflicts of interest.

K. Location of Study

Study will take place at CPMC and four other large, urban medical centers with similar patient demographics to CPMC.

L. Potential Risks

Patients will be informed of all possible side effects of medications as listed above in section D, Study drugs. Patients will be informed that if they are receiving standard of care (prednisolone) with addition of placebo, it may not be as effective as standard of care plus pentoxifylline. Patients will be informed that if they are receiving prednisolone and pentoxifylline together there currently no known benefit compared to receiving prednisolone alone.

M. Potential Therapies

Patients will be informed that they may or may not benefit from inclusion in the study. Patients will be informed of potential benefits to society.

N. Alternate Therapies

Current standard of care therapy will be discussed with all patients as well as the fact that no pharmaceutical agent has been approved for treatment of alcoholic hepatitis.

O. Compensation of Subjects

The subjects will receive the study medicine at no cost and will be reimbursed for expenses related to follow-up appointments.

P. Costs to Subjects

The subjects will not incur any additional costs as a result of participation in the study.

Q. Minors as Research Subjects

No minors will be research subjects.

R. Radiation or Radioactive Substances

The study will not expose patients to radiation or radioactive substances.

S. References:

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9. Akriviadis E, et al. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind placebo-controlled trial. Gastroenterology. 2000, 119 1637-48.
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