Use of Ketoprofen in those chronically infected with Hepatitis C Virus may improve liver histology

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A. Study Purpose and Rationale

Hepatitis C virus (HCV) affects 170 million people worldwide. It is estimated that 74 to 86 percent of those infected will have persistent viremia, which amounts to 2.7 million people in the U.S. (1,2). Cirrhosis develops in 15-20 percent of those infected, making HCV infection the main indication for liver transplantation in this country. The interval between infection and development of cirrhosis can exceed 30 years, but often develops before 20 years in those with HIV or HBV coinfection, male sex, older age at infection, or chronic heavy alcohol use (3).

The complications from cirrhosis often lead to death, and the only definitive treatment available once liver failure develops is organ transplantation. Interventions to slow the progression to cirrhosis can greatly decrease morbidity and mortality from chronic hepatitis C. Interferon and ribavirin therapy is used, but is costly and associated with a high incidence of side effects including depression, and myelosuppression.

Liver fibrosis in HCV infected patients is due to chronic inflammation. It has been shown that inflammatory modulators may have a beneficial effect on fibrosis (4,5). In one study interleukin (IL)-10, a cytokine that down-regulates the proinflammatory response and has a modulatory effect on hepatic fibrogenesis, was shown to decrease inflammation and fibrosis in a group of patients with chronic hepatitis C (4).

We propose that NSAIDs, through its anti-inflammatory properties, can decrease inflammation in those chronically infected with HCV, with the hope that it may ultimately slow the progression to liver fibrosis. NSAIDs have been chosen because of its favorable side effect profile as well as low cost. In particular, ketoprofen will be used. It has been shown to be well tolerated in another study (6), has high bioavailability, and its pharmacokinetics are not influenced by cirrhosis.

B. Study Design and Statistical Analysis

This is a prospective randomized interventional placebo-controlled double-blinded study.

Patients with chronic Hepatitis C infection with recent liver biopsy demonstrating Grade 3 or 4 inflammation will be randomized to receive either ketoprofen 200mg twice daily, or a placebo pill twice daily. Histologic grade of inflammation will be based on a 04 scoring system for necroinflammatory activity and fibrosis in chronic hepatitis (7). There will be no crossover. Liver biopsy will be repeated after one year. Improvement will be defined as a repeat liver biopsy demonstrating Grade 0 or I inflammation.

The Chi Square test was used to determine sample size. There will be a total of 130 patients; 65 each in the intervention group and placebo group. This was based on the assumption that 10% will be expected to demonstrate improvement in the placebo group, and 30% in the intervention group. The percent of those demonstrating improvement in each group will be analyzed using the Chi Square test. All liver biopsies will be read by a single hepatopathologist.

C. Study Procedure

Patients with a liver biopsy demonstrating Grade 3 or 4 inflammation, with demonstrated HCV positive antibody for at least one year, as well as active viremia defined by detectable HCV RNA by PCR will be given either ketoprofen 200mg twice daily or a placebo pill twice daily for one year. Initial liver

biopsy will be reviewed by a single hepatopathologist to confirm Grade 3 or 4 inflammation. Biopsy will be performed again at the end of the study and read by the same hepatopathologist.

D. Study Drugs

Ketoprofen 200mg PO twice daily.

E. Medical Device

N/A.

F. Study Questionnaire

N/A

G. Study Subjects

Patients eligible for the study include those how are HCV antibody positive, with active viremia who demonstrate Grade 3 or 4 inflammation on liver biopsy.

Patients are not elibible for enrollment if they are being treated with interferon or ribavirin, if they have a bleeding disorder, gastrointestinal ulcers, coinfection with Hepatitis B or HIV, or have other chronic liver diseases such as hemochromatosis or Wilson's disease. Informed consent will be obtained ftorn all subjects.

H. Recruitment of Subjects

Physicians in multiple gastroenterology practices throughout the country will be asked to approach those patients eligible for study, who have a liver biopsy within the past 15 days demonstrating Grade 3 inflammation to participate in the study. They will receive the study drug or placebo within 30 days of the last biopsy.

I. Confidentiality of Study Subjects

All study subjects will receive a confidential code to be used on all data. Data will be stored in a secure location, accessible only to the investigators.

J. Potential Conflict of Interest

N/A.

K. Location of the Study

N/A

L. Potential Risks

These include risks involved in ingesting ketoprofen, including gastrointestinal ulcers and bleeding, or gastrointestinal upset. Risks involved in liver biopsy include infection and bleeding, bowel perforation, and pneumothorax.

M. Potential Benefits

Patients receiving ketoprofen may see an improvement in liver histology and potentially decreased rate of progression to liver fibrosis.

N. Alternative Therapies

N/A

O. Compensation to Subjects

Patients will not be required to pay for ketoprofen or placebo pill, or liver biopsy.

P. Costs to Subjects

None.

Q. Minors as Study Subjects

N/A

R. Radiation or Radioactive Substances

N/A

S. References

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