Etanercept as an adjuvant to pegylated interferon alpha and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a randomized, double-blind, placebo-controlled study

Njeri Thande

A. Study Purpose and Rationale

It has been estimated that 2.2% of the world's population is infected with hepatitis C. Acute infection with hepatitis C (HCV) is followed by chronic infection in 50-80% of those infected.[1,2] Chronic infection with HCV is associated with multiple complications, including possible development of hepatic cirrhosis, hepatic decompensation, and hepatocellular carcinoma.

The current standard of care for chronic HCV with compensated liver disease is weekly subcutaneous pegylated-interferon (PEG-IFN) alpha in combination with twice daily oral ribavirin. PEG-IFN consists of polyethylene glycol attached to interferon alpha – this attachment increases the half-life and duration of therapeutic activity of interferon alpha. Ribavirin is a synthetic guanosine analogue – has been postulated to inhibit viral-dependent RNA polymerase, the capping structure of viral mRNA, and inosine monophosphate dehydrogenase. However, how it works in conjunction with interferon is not well understood. The combination of PEG-IFN and ribavirin results in a sustained virological response (SVR), defined as sustained clearance of HCV RNA from the serum at 6 months after discontinuation of therapy, of 50-60%. HCV genotype 1a and 1b, the most prevalent genotypes in the United States and Western Europe were more resistant to therapy compared with genotypes 2 and 3. Patients with HCV genotypes 2 or 3 achieved an SVR of 75-80%. Patients with HCV genotype 1 achieved an SVR of about 40%.[3-8]

Given the poor response rate to current standard of care for chronic HCV and the wide spectrum of quite severe adverse effects that can be associated with treatment; treatment is not recommended for all infected individuals. Patients who have evidence of progressive disease manifested by persistently elevated levels of serum aminotransferase (ALT) and hepatic fibrosis on biopsy and who have no absolute contraindications to the standard of care are thought to be the most appropriate to undergo anti-viral therapy.[9]

Despite significant improvement over the years in therapy options for patients with chronic hepatitis C, a significant proportion of treated HCV-infected patients still fail to respond to currently used drugs, this is especially true for people with HCV genotype 1.

In an attempt to provide more efficacious therapy options for patients with chronic HCV, a recent small randomized, double-blinded study investigated the efficacy and safety of etanercept as an adjuvant to interferon alpha plus ribavirin compared to interferon alpha plus ribavirin alone (the study was initiated prior to data that revealed the superior efficacy of PEG-IFN compared to interferon in the treatment of chronic HCV). The study showed that the addition of etanercept resulted in doubling of the eradication of HCV RNA in the serum (32% vs. 63%) after 24 weeks of therapy, with no appreciable increase in adverse effects. However, there was no significant difference in sustained virological response between the interferon plus ribavirin group compared to the etanercept, interferon, and ribavirin group.[10] The study was significantly limited by sample size and possible premature termination of treatment with etanercept.

The rationale for using etanercept as therapy for chronic HCV infection, has to do with its effects on tumor necrosis factor α (TNF-α). TNF-α is an inflammatory cytokine. TNF-α is produced by non-parenchymal cells and hepatocytes of the liver and has been implicated as a cofactor in liver injury and a possible mediator of HCV replication. Etanercept is a genetically engineered fusion protein that binds to and inactivates TNF.[10,12,13.] It stands to reason, that etanercept may inhibit HCV viral replication and inhibit liver injury via its effects on TNF-α.

Etanercept has been successfully used to treat rheumatoid arthritis and psoriatic arthritis. Long-term administration of etanercept (up to 18 months) in rheumatoid arthritis patients has been deemed safe and well tolerated.[11]

The purpose of this study is to further investigate the efficacy and safety of etanercept as an adjuvant to the current standard of care for chronic hepatitis C.

B. Study Design and Statistical Analysis

This study will be a randomized, double-blinded, placebo-controlled study.

The subjects will be stratified by HCV genotype (1 or others) and the presence or absence of cirrhosis. The subjects will then be randomly assigned in equal proportions to either receive etanercept, PEG-IFN alpha 2b, and ribavirin or PEG-IFN alpha 2b and ribavirin. Randomization of patients will be done by an independent central randomization center. Each subject will be assigned a unique code that will correlate with treatment assignment. The research team will be fully blinded to treatment assignment.

The primary measure of efficacy will be sustained virological response, defined as undetectable HCV RNA in the serum 6 months after the end of therapy. Secondary outcomes will include undetectable HCV RNA at 48 and 60 weeks, normalization of ALT at 48, 60, and 72 weeks, and histological response at 72 weeks. Histological response will be assessed by the Metavir scoring system that has been specifically designed for patients with hepatitis C. The scoring system consists of an inflammation grading score, which ranges from 0 to 3 and a fibrosis staging score, which ranges from 0 to 4. The Metavir fibrosis scores are 0 (no fibrosis), 1 (stellate enlargement of portal tracts, but no septa), 2 (enlargement of portal tracts with rare septa), 3 (numerous septa without cirrhosis), 4 (cirrhosis). An improvement in fibrosis will be defined as a decrease in 1 or more from the pretreatment to post-treatment Metavir fibrosis score, and a worsening of fibrosis will be defined as an increase in this score of 1 unit or more.

The study will need to have 120 patients per group so as to achieve 90% power to detect a 20% difference in SVR rates (55% vs. 75%), at the 5% level of significance. The treatment comparison is PEG-IFN alpha-2b, ribavirin, plus etanercept against PEF-IFN alpha-2b plus ribavirin. The expected response rate (sustained virological response) for PEG-IFN alpha-2b and ribavirin is 50-60%. It was determined that a 20% improvement in this baseline response would be clinically worthwhile given the risks and benefits of successfully treating chronic hepatitis C.

Continuous data will be analyzed by the Student *t* test if the data are normally distributed or by the Wilcoxon rank-sum test otherwise. Categorical data will be analyzed by the χ^2 or Fisher exact test. All statistical tests will be two sided. All efficacy analyses will be based on all patients who will receive at least one dose of the study medication.

C. Study Procedure

PEG-IFN alpha 2b will be administered at a dose of 1.5 micrograms/kg each week subcutaneously and ribavirin will be administered orally twice per day at a total dose of 1000mg for those who weighed 75kg or less and 1200mg for those who weighed more than 75kg for a total of 48 weeks. Etanercept or placebo (saline) will be administered subcutaneously in a dose of 25mg twice a week for 48 weeks. Sustained viral eradication was measured by testing HCV RNA at 24 weeks after discontinuation of all therapy (week 72).

The patients will self-administer the study medications. They will receive reminder telephone calls on the days they are scheduled to receive the subcutaneous medications. During treatment, patients will be assessed as outpatients at weeks 2, 4, 6, 8, and 12, and then every 6 weeks for the duration of therapy, and also at 4, 12, and 24 weeks after the end of therapy. During these visits biochemical and hematological testing will be done by a central laboratory. Serum HCV RNA will be measured before treatment; during treatment at weeks 4, 12, 24, 36, and 48; and after treatment at weeks 12 and 24, with a quantitative and qualitative PCR assay (COBAS AMPLICOR HCV v2.0, Roche Diagnostics, Branchburg

New Jersey; lower limits of HCV RNA detection of 100 copies/ml). HCV genotyping will be performed at the Mayo Clinical Central Virology laboratory with the use of a genotyping assay. Liver biopsies will be taken at the start of therapy and 24 weeks after the end of therapy. Liver histology will be analyzed by a single pathologist who will be unaware of the patient's identity, treatment regimen, response, or timing of the biopsy relative to treatment.

Adverse effects will be graded according to the modified World Health Organization grades as mild, moderate, severe, or potentially life-threatening. However, on the basis of adverse effect profiles of PEG-IFN alpha-2b, ribavirin, and etanercept, selected hematological and biochemical measurements will be assigned more restricted requirements for reduction or permanent discontinuation of therapy. Therapy will be permanently discontinued for life-threatening events. For severe adverse effects other than anemia, the dose of PEG-IFN alpha-2b will be decreased by 50% and the dose of ribavirin will be lowered to 600mg/day. Full doses can be restarted after the event abates. If the event persists, all drugs will be discontinued. For anemia, the ribavirin dose will be lowered to 600mg/day for falls in hemoglobin of less than 10g/dl, and ribavirin discontinued for falls in hemoglobin of less than 8.5g/dl. Once lowered, the ribavirin dose will remain at 600mg/day for the rest of the study. Etanercept will not be dose-reduced but will be interrupted in the patients with a medically significant infection (defined as requiring IV antibiotics or hospitalization). Etanercept will be restarted after the infection has resolved.

D. Study Drugs

The following drugs will be used in this study:

Peginterferon alpha 2b. This drug is FDA approved for the treatment of chronic hepatitis C alone or in combination with ribavirin for patients with compensated liver disease. Contraindications (when used in combination with ribavirin) include hypersensitivity to peginterferon alfa-2b or any of the components, pregnancy (or men with pregnant partners), and patients with hemoglobinopathies. Precautions include anemia- hemolytic anemia (10%) in patients on ribavirin, autoimmune disease (potential exacerbation), bone marrow depression prior to therapy (exacerbation; normalization of blood counts prior to therapy is indicated), carcinogen- ribavirin has genotoxic and mutagenic properties, cardiovascular disease (peginterferon alfa-2b is capable of producing hypotension and arrhythmias; infarction has occurred rarely), chickenpox, herpes zoster, or other viral infection (worsening and/or spread), chronic hepatitis C coinfected with HIV or hepatitis B (clinical experience lacking), colitis (fatal/nonfatal; discontinue if signs/symptoms develop), endocrine disorders (diabetes mellitus, thyroid disorders, hypertriglyceridemia, and pancreatitis), hypersensitivity reactions, impaired fertility, infectious disorders (may cause or aggravate), liver/organ transplant recipients: safety and efficacy data lacking, patients with a psychiatric history (eg, depression, suicidal behavior, emotional lability) (potential exacerbation; suicide risk), pulmonary disease (potential exacerbation), renal impairment (dose adjustment; potential for exacerbation related to fever/dehydration induced by peginterferon alfa-2b). Common adverse effects include flu-like symptoms, injection site reactions, and ophthalmologic disorders. Serious adverse effects include bone marrow suppression, colitis, pancreatitis, psychiatric adverse effects (aggressive behavior, mental depression, and suicide).

Ribavirin. The oral form of this drug is FDA approved for chronic hepatitis C infection with compensated liver disease, in combination with interferon, Chronic hepatitis C infection with HIV coinfection in patients with compensated liver disease (in combination with peg-interferon alfa-2a (Pegasys(R)). Contraindications include hypersensitivity to ribavirin products, pregnancy or pregnant partner of male patient, autoimmune hepatitis, creatinine clearance less than 50 mL/min, ribavirin as monotherapy for hepatitis C, significant or unstable cardiac disease, patients with hemoglobinopathies. Precautions include adverse effects associated with interferon therapy when using ribavirin in combination for hepatitis C infection, extreme care to avoid pregnancy; must use 2 forms of effective contraception during treatment and the 6-month post treatment period, anemia induced by ribavirin may result in deterioration of cardiac function and/or exacerbation of coronary artery disease (oral), liver or other transplantation recipients, interferon-nonresponders, patients with decompensated liver disease or

co-infected with hepatitis B or HIV; safety and efficacy not established. Common adverse effects include fatigue, headache, anorexia, dyspepsia, nausea, rash, pruritus, conjunctivitis. Serious adverse effects include hemolytic anemia (cardiac and pulmonary events have occurred), pancreatitis (fatal and nonfatal).

Etanercept. This drug is FDA approved for ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis. Contraindications include hypersensitivity to etanercept or components, active infections including chronic or localized infection including sepsis. Precautions include significant exposure to varicella virus, central nervous system demyelinating disorder, history of significant hematological abnormalities, poorly controlled or advanced diabetes (risk of infections), concurrent live vaccination, concurrent immunosuppressive therapy, possible increase in risk of malignancy, possible formation of lupus-like syndrome. Common adverse effects include gastrointestinal effects, abdominal pain, vomiting, injection site reactions (37%), new onset/exacerbation of CNS demyelinating disorders, respiratory tract symptoms, cough, rhinitis. Serious adverse effects include allergic reactions (<2%), anemia, aplastic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, infections including sepsis, optic neuritis (rare), tuberculosis, malignancy.

E. Medical Device

This study will not be testing a medical device.

F. Study Questionnaires

This study will not utilize any questionnaires

G. Study Subjects

The subjects will be treatment-naïve adults with chronic hepatitis C defined as serological evidence of HCV infection, detectable HCV RNA in the serum as measured by PCR, and elevated ALT values for at least 6 months (above the upper limit of normal > 41 UI/L).

Exclusion criteria will be as follows: inability to provide written consent, presence of concomitant causes of liver disease (such as hepatitis B, autoimmune hepatitis, NASH, etc.), presence of HIV, known hypersensitivity to any of the study drugs, evidence of decompensated liver disease, autoimmune disease, cardiac arrhythmias, CAD, anemia (hemoglobin < 12g/dl for women and <13g/dl for men), neutropenia (neutrophil count < 1.5 x 10^9/L), thrombocytopenia (platelet count < 100 x 10^9/L), hemoglobinopathies, renal failure, pregnancy (or men with pregnant partners), inability to use contraception, depression, seizure disorders, demyelinating disease, poorly-controlled diabetes, alcohol use, previous organ transplantation, immunosuppresion of any type, age under 18 and over 70

The study will not include vulnerable populations. The study will not be restricted by gender or race.

H. Recruitment of Subjects

Subjects will be recruited from primary care and liver clinics at CPMC. Information regarding the study will be distributed to physicians in these clinics via mail, email, telephone, or face-to-face meetings. These physicians will in turn approach any patient who seems suitable for the study and ascertain from the patient whether he or she is willing to participate and discuss the study further with the research team. The research team will only approach patients who have first discussed the study with their primary physicians and seemed agreeable to participation.

I. Confidentiality of Study Data

The study data and identity of study subjects will remain confidential. The data will be coded. A unique code number will be generated for each subject. Personal identifier such as social security number, hospital unit numbers, subject initials, phone numbers, or addresses will not be used as coding mechanisms.

J. Potential Conflict of Interest

The investigators or the University do not have proprietary interest in the drugs being tested or the device being used and do not stand to benefit financially from the results of the investigation.

K. Location of the Study

This study will be based at New York Presbyterian, Columbia University Medical Center. Subjects will come to the Irving Center for Clinical Research outpatient unit for follow up visits and to receive blood draws when indicated. Liver biopsies will be performed using existing resources at Columbia University Medical Center.

L. Potential Risks

The medical risks to subjects in this study will be related to potential adverse effects from the study drugs. Peginterferon in combination with ribavirin has been FDA approved for the treatment of chronic hepatitis C in patients with compensated liver disease. However, there are still many potential adverse effects that may result from this therapeutic combination. The addition of etanercept to peginterferon plus ribavirin has not been FDA approved, and the possible adverse effects from this triple-regimen have not been well-documented. One study compared the efficacy and safety of interferon alpha2b plus ribavirin to interferon alpha2b, ribavirin, and etanercept. This study did not show an increased risk of adverse effects in the group receiving etanercept. However, the study had a small sample size and was not adequately powered to detect significant differences in adverse effects.[10] Theoretically, one would expect etanercept to incur an additional risk of the following severe adverse effects: infection, hematological abnormalities, and possibly malignancy.

The risks of a liver biopsy are usually very small. The primary risk of liver biopsy is bleeding from the site of needle entry into the liver, although this occurs in less than 1% of patients. About a third to a half of patients will experience some pain after the biopsy. Other possible complications include the puncture of other organs, such as the kidney, lung, or colon. Puncture of the gallbladder may be associated with leakage of bile into the abdominal cavity, causing peritonitis. There is also a small chance that an infection may occur. Fortunately, the risk of death from liver biopsy is extremely low, ranging from 0.1% to 0.01%.[14]

M. Potential Benefits

The benefits of treatment of chronic hepatitis C with peginterferon plus ribavirin is a 50-60% chance of successful eradication of HCV[3,4] and HCV-associated complications, including cirrhosis, hepatic decompensation, and hepatocellular carcinoma. The addition of etanercept to peginterferon and ribavirin has the potential to increase the chances of successful eradication of HCV. A previous study that compared the efficacy and safety interferon alpha2b plus ribavirin to interferon alpha2b, ribavirin, and etanercept showed a significant increase (32% to 63%) of the sustained virological response (defined as absence of HCV RNA in the serum 6 months after discontinuation of all therapy) with the addition of etanercept.[10]

N. Alternative Therapies

The standard of care for treatment of chronic hepatitis C with compensated liver disease is peginterferon plus ribavirin. This treatment regimen has been shown to result in a 50-60% sustained virological response[3,4]. Half the patients in this study will be randomized to this treatment regimen and the other half will receive peginterferon, ribavirin, and etanercept. The addition of etanercept is experimental but may improve the percentage of patients achieving a sustained virological response. However, there is a risk that the patients receiving etanercept will be at an increased risk of developing adverse effects.

O. Compensation to Subjects

The subjects will not be financially compensated for their participation in the study.

P. Costs to Subjects

The subjects of this study will not incur any additional costs as a result of participating in this study. The expense of all clinic visits, including transportation to and from that visit, will be paid for by the study. The subjects' study drugs will be paid for either through the subjects' prescription drug plan or by the study sponsor.

Q. Minors as Research Subjects

The study does not involve the participation of minors

R. Radiation or Radioactive Substances

The study does not involve any radiation or radioactive substances

S. References

1. Heathcote J, Main J. Treatment of hepatitis C. *Journal of Viral Hepatitis*. 2005; 12: 223-235.
2. Lauer GM, Walker BD. Hepatitis C Virus Infection. *New England Journal of Medicine.* 2001; 345 (1): 41-52.
3. Manns MP, McHutchinson JG, Gordon SC *et al.* Peginterferon alpha-2b plus ribavirin compared with interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized controlled trial. *Lancet.* 2001; 358: 958-965.
4. Fried MW, Shiffman ML, Reddy KR *et al.* Peginterferon alpha-2a plus ribavirin for chronic hepatitis C virus infection. *New England Journal of Medicine.* 2002; 247(13): 975-982.
5. Di Biscegalie AM et al. Recombinant interferon alpha therapy for chronic hepatitis C: a randomized, double-blind, placebo-controlled trial. *New England Journal of Medicine.* 1989; 321:1506-10.
6. Davis GL et al. Treatment of chronic hepatitis C with recombinant interferon alpha: a multicenter randomized, controlled trial. *New England Journal of Medicine.* 1989; 1501-6.
7. Poynard T et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet.* 1998; 352:1426-32.
8. McHutchinson JG et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment of chronic infection with hepatitis C. *New England Journal of Medicine.* 1998; 339: 1485-92.
9. National Institutes of Health. National Institutes of Health consensus development conference statement on management of hepatitis C. *Hepatology* 2002; 36(5 Suppl. 1); S3-S20.
10. Zein NN. Etanercept as an adjuvant to interferon and ribavirin in treatment-naïve patients with chronic hepatitis C virus infection; a phase 2 randomized, double-blind, placebo-controlled study.

Journal of Hepatology. 2005; 42: 315-322.
11. Moreland LW, Baumgartner SW, Tindall EA, Schiff MH, Fleischmann RM, Weaver A, et al. Longterm treatment of DMARD failing rheumatoid arthritis patients TNF receptor p75 Fc fusion protein (TNFR:Fc:ENBRE™) (abstract). *Journal of Investigational Medicine*. 1998. 46:229A.
12. Larrea E et al. Tumor necrosis factor alpha gene expression and the response to interferon in chronic hepatitis C. *Hepatology.* 1996; 23 (2) 210-7.
13. Nelson DR, Lim HL, Marousis CG, Fang JW, Davis GL, Shen L, et al. Activation of tumor necrosis factor-alpha system in chronic hepatitis C virus infection. *Digest of Disease Science.* 1996; 41:315-321.
14. American Liver Foundation. Liver Biopsy Fact sheet. http://www.liverfoundation.org