Deferoxamine Along With Interferon/Ribavirin Versus Repeat Interferon/Ribavirin Alone For Viral End Of Therapy Response Failures

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A. Study Purpose And Rationale

This study will evaluate the ability of the iron chelator deferoxamine mesylate to produce sustained non-detectable hepatitis C (HCV) levels when used in conjunction with a 48 wk course of interferon alpha 2b/ribavirin in patients who previously failed to clear the virus after a 48 wk treatment of interferon/ribavirin alone.

As it stands, the most effective therapy for sustained virologic response (no detectable virus 24 weeks after terminating treatment) against HCV is a 48 week treatment of interferon alpha 2b and ribavirin. In a recent study, 50% of patients receiving such a course of treatment had no detectable HCV RNA at the end of therapy and 48 weeks after therapy 38% of patients sustained this status.[1] With interferon therapy alone, detectable virus at the end of treatment period is considered such a poor prognostic sign for inducing sustained virologic response with interferon that these patients should not be considered

candidates for interferon alone at any dosing schedule.[2] Adding ribavirin to interferon for end of treatment non-responders has demonstrated a less than 10% response rate in several studies.[3] On the other hand, patients who had a end of treatment virologic response to interferon and then recurrence have a reasonable chance of sustained response with interferon alone and even better prognosis if retreated with interferon and ribavirin.[4]

Several small studies have demonstrated that iron reducing individuals with chronic HCV through phlebotomy or chelators, irrespective of liver iron status, makes interferon more effective treatment when following chemical parameters (normalizing ALT's).[5] A single, small study demonstrated a statistical increase in end of treatment virologic response secondary to iron reduction.[5] Therefore, it is reasonable to attempt to induce sustained virologic response in patients who failed to even achieve end of treatment response by using iron reduction along with interferon/ribavirin.

Individuals who respond to interferon have statistically less iron in their livers than non-responders, though the mean of hepatic iron content (HIC) in the non-responders is far below that of iron overload.[5] Ribavirin has been shown to increase the amount of hepatic iron content in the liver, probably secondary to an induced hemolytic anemia. In one study, the HIC increased 1500 (/g per year.[6] Interestingly, this increase is far greater than the mean HIC differences between interferon responders and non-responders. Perhaps ribavirin will be made all the more effective by reversing this possible harmful side effect of iron deposition.

Besides sustained virologic response other important endpoints we will compare between the two treatment groups are: normalization of the ALT, change in hepatic inflammation and change in hepatic iron stores during treatment. These endpoints may then be correlated to presence or absence of complete viral response.

B. Study Design And Statistical Analysis

Four hundred and eighty subjects will be equally and randomly assigned into one of two treatment groups. The groups will be balanced for the presence or absence of cirrhosis, HCV genotype and hepatic iron concentrations. We have determined that this is an adequate level of subjects based on the number necessary to determine a 10% difference between the two treatment groups assuming a 10%

rate of sustained virologic response for ribavirin and interferon alone. We also have assumed a dropout rate for both therapies similar to that of a previous large trial (20%).

C. Study Procedures

Once accepted in the study, patients will undergo a liver biopsy. Most patients involved in this study will not have had a biopsy in the previous year. Some physicians feel this is and important tool before initiating a new therapeutic trial but certainly cannot be considered standard of care. The most common serious adverse effect is significant bleeding, which occurs with less than 1% of biopsies. Deaths occur in less than 1 in 10,000 biopsies.[7] The biopsy is evaluated by an established inflammation score and fibrosis score, stained for iron pattern and hepatic iron quantity measured. Patients are then randomized. One group receives subcutaneous recombinant interferon alpha-2b, three million units three times a week plus oral ribavirin 1000 mg twice a week if under 75 kg and 1200 mg if above 75 kg plus subcutaneous desferoxamine mesyalte 0.5 g three times a week. The second treatment group receives equal amounts of interferon and ribavirin but subcutaneous saline rather than ribavirin. Both the subject and the evaluating physician will be blinded to the variable drug. Treatment for both groups will last 48 weeks.

Subjects from both groups will have outpatient visits wk 1,2,4,6,8 and then every 4 weeks. Blood will be sampled every two weeks until after wk 8 when it will occur every four weeks. A CBC, reticulocyte count, ferritin level and ALT will be measured from each sample. If HgB drops below 10 g/dl, the ribavirin dose will be halved, with a level less than 8 g/dl ribavirin will be discontinued. The deferoxamine schedule will remain unaltered until ferritin is below 30 ng/ml, at that point saline injections are given until the level rises above 30 ng/ml and then deferoxamine will be distributed to the subject again. Deferoxamine injections will be discontinued if the reticulocyte value decreases significantly below the post-hemolysis plateau and accompanies other signs of iron depletion. The HgB, ALT and reticulocytes will all be available to the physician evaluating the subject each visit. Routine ferritin levels are available only to the researcher distributing deferoxamine versus saline. The evaluating physician may order whatever tests he feels necessary to determine if he wishes to stop possible chelation but will not be evaluating ferritin on a scheduled basis.

At the end of the treatment period ALT, ferritin, transferrin saturation, serum iron and HVC RNA level will be measured. The patients will have a repeat liver biopsy to reasses inflammation, fibrosis and iron parameters. This is not standard of care. The risks of liver biopsy were stated above.

Patients will return 24 weeks after end of treatment to measure serum ALT, ferritin and HCV RNA level.

D. Study Drugs

a. Recombinant interferon alpha 2b

This medicine is FDA approved for the treatment of chronic hepatitis C. Its therapeutic class is a biologic response modulator. The most common side effects are: dizziness, tiredness, depression, fatigue, malaise, fever, chills, rash, nausea/vomitting, diarrhea, abdominal cramps. Mild myelosuppression can occurs but usually only in doses higher than used in this study. Other adverse reactions relating to every system can occur but are reported to have an incident of less than 1%

b. Ribavirin

this medicine is considered standard of care in combination with interferon since the 11/98 NEJM article. It is known to inhibit replication of RNA and DNA in various viruses. In the influenza virus it inhibits an RNA polymerase. Adverse effects that have a 1% to 10% incidence are: fatigue, headache, nausea, hemolytic anemia. There is a reported less than 1% incidence of hypotension, cardiac arrest, rash and bronchospasm. These more serious events primarily occur in critically ill patients receiving the aerolisized drug.

c. Deferroxamine mesylate

an iron chelator. Adverse reactions with chronic treatment include irritation at the injection site, occasional and transient arthropathies and at doses much higher than will be given in this study, ototoxicity and retinopathy. Researchers have found that by staying below a threshold these complications are exceedingly rare. At best, when patients receive these medicines near these thresholds they need annual eye/ear exams. Our subjects will be receiving the medicine for less than a year and greater than five times below the safety threshold.[8]

E. Study Subjects

All subjects must have documented HCV antibody, be HCV RNA PCR positive for greater than 6 months and have elevated ALT for greater than six mo. These subjects must have received 48 weeks of interferon/ribavirin with HCV RNA still detectable at the end of treatment. All subjects should be greater than eighteen years of age and less than sixty-five. Patients are excluded if they have received additional courses of interferon or ribavirin beyond the previously mentioned treatment, currently consume more than 10 g of alcohol each day or are an active IDU. Also individuals with decompansated cirrohsis, serum alpha-fetoprotien > 50 ng/ml, HIV infection, a psychiatric diagnosis, seizure disorder, cardiovascular disease, hemophilia, thallasemia, hemolytic anemia, diabetes mellitus, an autoimmune disorder or renal insufficiency are excluded. Women with a baseline hemoglobin less than 12 g/dl and men with a baseline less than 13 g/dl are excluded. Women must also have a negative urinary pregnancy test.

F. Recruitment Of Subjects

Advertisements will be placed in the various participating medical centers. Liver specialists, gastroenterologists and internists will be contacted through the mail and by telephone regarding study eligibility and given the name and number of an individual responsible for enrollment.

G. Potential Risks

Both treatment groups will receive the treatment known to be the most efficacious for this disease. The experimental medicine may cause the anemia induced by the ribavirin to worsen. Adequate monitoring in order to avoid a serious level of anemia has been included in the study. At worst, a patient may require a blood transfusion.

Risk regarding liver biopsy is stated above.

Ribavirin is an assumed human teratogen and so female subjects must be warned and adequately counselled on birth control.

H. Potential Benefits

Patients randomized into the chelation group may have a higher rate of non-recurrence of HCV viremia. If this occurs this aspect of treatment may be offered to all individuals with this disease.

I. Alternative Therapies

For those who do not choose to participate, the alternative therapy is standard interferon and ribavirin versus no treatment.

J. Compensation To Subjects

None will be provided.

K. Cost To Subjects

Any treatment cost within the protocol not covered by the subject's insurance will be covered by the study sponsor. Any medical costs resulting from complications of the treatment not covered by the subject's medical insurance will be covered by the study sponsor.

L. References

[1] McHutchinson JG, Gordon SC, Schiff ER, et al. Interferon Alpha-2b Alone or in Combination with Ribavirin as Initial Treatment for Chronic Hepatitis C. NEJM 1998; 21:1485-9.
[2] Alberti A, Chemello L, Noventa F, et al. Therapy of Hepatits C: Re-Treatment with Alpha Interferon. Hepatology 1997;26(Suppl 1): 137s-142s.
[3] Reichard O, Schvarz R, Weiland O. Therapy of Hepatitis C: Alpha Interferon and Ribavirin. Hepatology 1997;26(Suppl 1)108s-111s.
[4] Davis G, Estaban-Mur R, Rustugi V, et al. Interferon Alpha-2b or in Combination with Ribavirin for the Treatment of Relapse of Chronic Hepatitis C.NEJM 1998;339:1493-9.
[5] Bonkovsky, HL. Therapy of Hepatitis C: Other Options. Hepatology 1997;26(Suppl 1): 143s-151s.
[6] Di Bisceglie AM, Bacon BR, Kleiner DE, et al. Increase in Hepatic Iron Stores Following Prolonged Therapy with Ribavirin in Patients with Hepatitis C. J Hepato 1994;21:1109-12.
[7] Perrillo RP. The Role of Liver Biopsy in Hepatitis C. Hepatology 1997;26(Suppl 1):57s-61s.
[8] Porter J. A Risk-Benefit Assessment of Iron-Chelation Therapy. Drug Safety 1997; 17(6): 407-21.