The Impact Of Interferon And Ribavirin Therapy On Quality Of Life In Patients With Chronic Hepatitis C And Normal Alanine Transaminase

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A. Background

Almost 3 million people in the US are chronically infected with hepatitis C virus (HCV) It is the most common cause of chronic liver disease and the leading reason for liver transplant in the US. Chronic hepatitis C (CHC) is variable in its course, as well as its signs and symptoms. For example, a person with chronic hepatitis C may be asymptomatic, have normal liver enzymes and minimal signs of inflammation on liver b~ppsy. In contrast, they could experience fatigue and nausea, have elevated liver prfzymes, and have fibrosis or even cirrhosis on liver biopsy. However, only 20% of individuals with CHC progress to cirrhosis. And, on average the time course from infection to cirrhosis is 20 to 30 years.

Currently, standard of care for treating chronic hepatitis C is combination therapy with Interferon-alpha and Ribavirin. Randomized controlled studies show that overall there is a 40% response rate to combination therapy, meaning suppression of HCV RNA to undetectable levels. Response rates are lower for HCV-genotype 1, estimated around 30%. This genotype is most prevalent, accounting for approximately 65% of HCV infections. Normalization of liver enzymes, specifically alanine transaminase (ALT) and improvement in inflammation and fibrosis on liver biopsy are also measures of effective therapy. These virologic, biochemical and histologic end-points are substitutes for long term end-points, such as progression to cirrhosis, hepatocellular carcinoma and death secondary to end-stage liver disease. Whether or not treating chronic hepatitis C reduces the incidence of these distant end-points is unknown.

For the most part, clinical trials have focused on the patient population with elevated liver enzymes and abnormal liver biopsies. However, a significant number of people with chronic hepatitis C have a normal ALT level. This group has been dubbed "healthy HCV carriers". They are estimated to represent 20% on the chronic hepatitis C population. This group has been uncovered on account of blood donor screening for HCV. On average, individuals with normal ALT have mild to moderate liver disease and a progression rate of liver fibrosis twice as slow as those with abnormal ALT. Studies with monotherapy, IFN alone, indicate that these patients have the same rates of virologic response but little or no histologic improvement. In addition, approximately 40%, of those treated develop elevated liver enzymes. The significance of ALT elevation with therapy is unknown. Given their slow progression of disease and that therapy causes possibly undesirable effects, there exists debate whether or not to treat the "healthy HCV carrier." A 1997 concensus statement by the NIH states that "current studies suggest that treatment of patients with persistently normal ALT is not beneficial .... Therefore, these patients should not receive therapy outside of controlled clinical trials."

Since the effect of therapy on the incidence cirrhosis, HCC and death are unknown, studies have looked at more immediate endpoints other than viral titer, ALT and liver histology. Quality of life scales have been added to treatment trials as an addition means of measuring the "efficacy" of therapy. This measurement assesses whether patients benefit from therapy in a way that may be more meaningful and tangible to them than viral suppression. Also, quality of life measurements can be factored into cost-analysis models to determine a therapy's cost-effectiveness. Studies have shown that CHC carriers have a lower quality of life compared with a healthy population or people with other chronic diseases. And, treatment resulting in viral suppression is associated with a significant improvement in their quality of life.

As discussed, HCV treatment trials frequently exclude individuals with CHC and normal ALT. Similarly, studies on HCV and quality of life have overlooked this population. Therefore, there is a dearth

of data on how CHC affects their lives and if treatment has a beneficial or adverse effect on quality of life. Considering the debate over whether or not to treat, understanding how quality of life changes with therapy would be valuable information to weigh in the decision process.

This study will investigate the effect of combination therapy, IFN and Ribavirin, on quality of life of individuals with chronic hepatitis C - genotype I and normal ALT. Also, this study will determine whether significant changes in quality of life are associated with virologic response to therapy.

B. Subject selection

Patients will be recruited from various medical centers' Internal Medicine, Gastroenterology and Liver clinics and by referral from blood transfusion centers after being identified as HCV positive following blood donation.

a. Eligible patients

- Ages 18 to 60
- HCV antibody positive (by enzyme-linked immunosorbent assay)
- HCV-RNA positive (by RT-PCR)
- Genotype I (a or b)
- Normal serum alanine transaminase (<40 IU/L) x 3 during the previous 6 months
- Liver biopsy in the past year.

b. Exclusion criteria

- decompensated cirrhosis, history of alcohol abuse, HIV positive, HBV positive, psychiatric conditions, anemia (Females - Hgb>12, Mates - Hgb<13), severe cardiovascular disease, prior organ transplant, autoimmune diseases, exposure to interferon or ribavirin in the past.

C. Methods

a. Study Design

This will be a multi-center, prospective double-blinded, randomized, placebo-controlled trial. After an initial 6 month screening period, during which HCV Ab, HCV RNA, HCV genotype, persistence of normal range ALT, and HBV & HIV status will be confirmed, eligible patients will be randomized to treatment or placebo arm. Patients will be assigned to receive either recombinant IFN oc2b 3 million units subcutaneously three times a week and Ribavirin (I 000mg if <75 kg or 1200mg) orally everyday or placebo injections and placebo tablets for 48 weeks. At the start of the study, patients will complete an HQLQ and HCV-RNA titer will be measured. During therapy, patients will be monitored with monthly appointments for tolerance of side effects with interview and blood tests. After treatment, patients will be seen at a 6-month follow-up appointment for repeat HQLQ and HCV-RNA titer. The study will last a total of 72 weeks.

b. Outcomes

1) Qualily of life will be measured by the Hepatitis Quality of Life Questionnaire (VQLQ). The HQLQ consists of the generic Short Form-36 health survey, two additional generic scales (sleep somnolence and health distress) believed to address the experience of having chronic hepatitis C and two hepatitis-specific scales (health distress and limitations). HQLQ is a previously validated self-administered survey. The SF-36 measures eight areas of quality of life: physical functioning, physical role disability, general health, bodily pain, vitality, social functioning, general mental health, emotional role disability. The HQLQ will be administered at the start of the study and 6 months after therapy is completed.
2) Virologic Response is defined as undetectable viral titer (<100 copies) at the end of therapy and at 6-month follow-up. Viral titer is quantified by RT-PCR.

3) A central laboratory will perform Biochemical testing measuring alanine transaminase (ALT). Normal ALT is defined as <40 (IU/L). Participants must have had 3 normal ALT within 6 months.

c. Statistical Analysis

To assess treatment effect on quality of life, paired t-test will be used to compare HQLQ changes from baseline to 6 month follow-up within all groups (IFN/Ribavirin group, placebo group, virologic responders, virologic non-responders). Comparison of HQLQ between groups at 6-month follow-up will be by Analysis of Covariance (ANCOVA), in order to control for baseline scores.

d. Sample Size

For 80% power, testing at p=.05, the number of subjects needed was calculated in below mentioned formulas using effect and standard deviation reported in prior HQLQ employing study. SD=standard deviation, SE=standard error

Paired t-test:
$n=1+8(SD/effect)^2$

Mean change in HQLQ from baseline to follow-up in Virologic Responder group
Effect=2.25
SD = SE* sqrt(N) = 1.1 sqrt(67) = 9
$n=1+8*(9/2.25)^2$
n=129

129 patients are needed in the virologic responder group. Since response is anticipated in 30% of treated patients, total number of patients needed in the treatment (IFN/Ribavirin) group is 430. Total number of patients needed for this study is around 900.

D. Issues:

a. Bias

1) Motivation for participation Patients recruited from the medical center setting may represent a skewed sample of highly motivated individuals. This could be balanced by active recruiting of individuals identified as HCV positive through blood donation.
2) Living with the disease Because they receive care at a medical center suggests two areas of potential bias. First, there exists the possibility that their disease is different than the chronic HCV individual with normal ALT, who is unaware of the diagnosis and has never sought medical attention. Second, being cognizant of the diagnosis could have an emotional and subsequently physical toll. This would affect quality of He assessment on both physical and mental health scales. Without the naive-to-own-diagnosis chronic HCV individual, this study may result in lower HQLQ scores than exist in reality in this population.

b. RiskslSide effects

Both interferon and ribavirin commonly cause side effects: *InterLeron* causes flu-like symptoms (headache, myalgia, fatigue) in 60% of patients, gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea) in 10-30%, and psychiatric symptoms (irritability, depression, insomnia) in 30% of patients. *Ribavirin* causes dermatological symptoms (10-30%) and anemia (10%).

In clinical trials with IFN and Ribavirin given for 48 weeks, discontinuation of treatment due to adverse events reached a rate of 20%. In a NEJM study, the most frequent reason for discontinuation was "emotional disturbance, mainly depression."

For this reason it is necessary to monitor participants closely for side effects and follow standards set by prior trials. In previous studies side effects were rated mild to life threatening. Drug doses were reduced if side effects were rated severe and discontinued if side effects were rated life threatening.

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HEPATITIS QUALITY OF LIFE QUESTIONNAIRE©

Your Health in General

1. In general would you say your health is:

Excellent? | Very good? | Good? | Fair? | Poor?

2. Compared to one year ago, how would you rate in health in general now?

Much better than one year ago? | Somewhat better than one year ago? | About the same as one year ago? | Somewhat worse than one year ago? | Much worse than one year ago?

3. The following items are about activities you might do during a typical day. Does you health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a) Vigorous activities such as running, lifting heavy objects, participating in strenuous sports	?	?	?
b) Moderate activities such as moving a table, pushing a vacuum cleaner, bowling or playing golf	?	?	?
c) Lifting or carry groceries	?	?	?
d) Climbing several flights of stairs	?	?	?
e) Climbing one flight of stairs	?	?	?
f) Bending, kneeling or stooping	?	?	?
g) Walking more than a mile	?	?	?
h) Walking several blocks	?	?	?
i) Walking one block	?	?	?
j) Bathing or dressing yourself	?	?	?

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a) Cut down on the amount of time your spent on work or other activities	?	?
b) Accomplished less than you would like	?	?
c) Were limited in the kind of work other activities	?	?
d) Had difficulty performing the work or other activities (for example, it took extra time)	?	?
e) Were unable to perform work or other activities at all	?	?

10 During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc)?

All of the time | Most of the time | Some of the time | A little of the time | None of the time

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitly false
a) I seem ot yet sick a little easier than other people	?	?	?	?	?
b) I am as healthy as anybody I know	?	?	?	?	?
c) I expect my health to get worse	?	?	?	?	?
d) My health is excellent	?	?	?	?	?

12. Compared to your usual level of social acitivity, has your social activiity during the past 4 weeks decreased, stayed the same or increased because of a change in your physical or emotional conditions?

Much less socially active than before? | Somewhat less socially active than before? | About as socially active as before? | Somewhat more socially active than before? | Much more socially active than before?

13. Compared to others your age, were your social activities more or less limited because of your physical health or emotional problems during the past 4 weeks?

Much more limited than others? | Somewhat more limited than others? | About the same as others? | Somewhat less limited than others? | Much less limited than others?

14) How much of the time during the past 4 weeks…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a) were you discouraged by your health problems?	?	?	?	?	?	?
b) did you feel weighted down by your health problems?	?	?	?	?	?	?
c) was you health a worry in your life?	?	?	?	?	?	?
d) were you frustrated by your health?	?	?	?	?	?	?

5. During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
a) Cut down the amount of time you spent on work or other activities	?	?
b) Accommplished less than you would like	?	?
c) Don't do work or othe activities as carefully as usual	?	?
d) Were unable ot perform work or other activities	?	?

6. During the past 4 weeks, to what extent has your physical health or emotional problems interferred with your nornal social activities with family, friends, neighbors or groups?

Not at all? | Slightly? | Moderatel? | Quit a lot? | Extremely?

7. How much body pain have you had during the last 4 weeks?

None? | Very mild? | Mild? | Moderate? | Severe? | Very severe?

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all? | A little bit? | Moderately? | Quite a lot? | Extremely?

9. These questions are about how you feel and things have been with you during the past 4 weeks. For each question please give the one answer that comes closest to the way you have been feeling.How much of the time during the past 4 weeks…..

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a) did you feel full of pep?	?	?	?	?	?	?
b) have you been a very nervous person?	?	?	?	?	?	?
c) have you felt so down in the dumps nothing could cheer you up?	?	?	?	?	?	?
d) have felt calm and peaceful?	?	?	?	?	?	?
e) did you have a lot of energy?	?	?	?	?	?	?
f) have you felt downhearted and blue?	?	?	?	?	?	?
g) did you feel worn out?	?	?	?	?	?	?
h) have you been a happy person?	?	?	?	?	?	?
i) did you feel tired?	?	?	?	?	?	?
j) did you have enough energy to do the things you wanted to do?	?	?	?	?	?	?

15. How much of the time during the past 4 weeks…..

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a) have you generaly excepted the things you do?	?	?	?	?	?	?
b) has your daily life been full of things that were interesting to you?	?	?	?	?	?	?
c) have you felt cheerful, lighthearted?	?	?	?	?	?	?
d) has living been a wonderful adventure for you?	?	?	?	?	?	?

16. How much of the time during the past 4 weeks has your hepatitis limited you in….

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a) your everday physical activities such as walking or climbing stairs, carrying groceries or participating in sports?	?	?	?	?	?	?
b) your daily work, both outside the home and housework?	?	?	?	?	?	?
c) your normal social activities with family, friends, neighbors and groups?	?	?	?	?	?	?

17. How much during the past 4 weeks….

	All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time
a) where you discouraged because of your hepatitis?	?	?	?	?	?	?
b) did you feel weighted down because of your hepatitis?	?	?	?	?	?	?
c) was having hepatitis a worry in your life?	?	?	?	?	?	?
d) were you frustrated because of having hepatitis?	?	?	?	?	?	?

Fig. 2 Hepatitis Quality of Life Questionnaire. Reprinted with permission form QualityMetric Inc.

TABLE 1. Summary of Hepatitis Quality of Life Questionnaire Scales

		Interpretation of Scores	
	Items	Lowest Possible (Floor)	Highest Possible (Ceiling)
SF-36 Scales			
Physical functioning	10	Limited a lot in performing all physical activities including bathing or dressing	Performs all types of physicalactivities including the most vigorous without limitations due to health
Role disability: physical	4	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities
Bodily pain	2	Verv severe and extremely limiting pain	No pain or limitations due to pain
General health	5	Evaluuates personal *health as* and believes it is likely to get worse	Evaluates personal health as excellent
Vitality	4	Feels tired and worn out all of the time	Feels full of pep and energy all of the time
Social functioning	2	Extreme and frequent interference with normal social activities due to physical and emotional problems	Performs normal social activities without interference due to physical or emotional problems
Role disability: emotional	3	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities
General mental health	5	Feelings of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time
Additional generic scales			
Sleep somnolence	3	During the day, has trouble staying awake and feels drowsy and sleepy all of the time	Never has trouble staying awake and never fcels drowsy and sleepy during the day
Health distress	4	Feels burdened, worried and discouraged about health all of the time	Never feels burdened, worried or discouraged about health
CHC-Specific scales			
Health distress due to CHC	4	Feels afraid, discouraged, weary and hopeless, due to CHC, all of the time	Never feels afraid. discouraged, wearry and hopeless due to CHC
Limitations due to CHC	3	Limited a lot in everyday physical activities by CHC, problems with work due to CHC and extreme interference in social activities due to CHC	Performs everyday physical activities without any limitations due to CHC, has no problems with work or housework due to CHC and performs normal social activities without limitations due to CHC

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TABLE 5. RATES OF DISCONTINUATION OF TREATMENT, DOSE REDUCTIONS, AND OTHER ADVERSE EVENTS DURING TREATMENT*

ADVERSE EVENT	INTERFERON		INTERFERON And RiaAVIRIN	
	24 WK (N=231)	48 WK (N=225)	24 WK (N=228)	48 WK (N=228)
	percent			
Discontinuation of treatment for any sevcre event	9	14	8	21
Dose reduction				
Due to anerniat	0	0	7	9
Due to other adverse events	12	9	13	17
Influcnza-likc symptoms				
Headache	63	67	63	66
Fatigue	62	72	68	70
Nialaise	7	5	4	11
Xlyalgia	57	63	61	64
Axthralgia	27	36	30	33
Niusculoskeletal pain	26	32	20	28
Fever	35	40	37	41
Gastrointestinal symptoms				
Anorexia	16	19	27	25
Dyspepsia	6	9	14	16
Vomiting	10	13	11	9
Nausca	35	33	38	46
Diarrhea	22	26	18	22
Abdominal pain	17	20	15	14
Psychiatric symptoms				
Anxiety	9	13	10	18
Impaired concentration	14	14	11	14
Depression	25	37	32	36
Emotional lability	6	8	7	11
Insomnia	27	30	39	39
Irritability	19	27	23	32
Respiratory tracck symptoms				
Cough	5	9	15	14
Dyspnea	9	10	19	18
Pharyngitis	9	10	11	20
Sinusitis	7	14	9	10
Dermatologic symptoms				
Alopecia	27	28	28	32
Pruritus	9	8	21	19
Rash	9	8	20	28
Dry skin	4	8	8	15
Inflammation at injection site	10	14	13	12

*Only events that occurred in at least 10 percent of patients arc included.
tThc daily dose of ribavirin was reduced to 600 mg for patients with hemoglobin values below 10 g per deciliter, and treatment with ribavirin was discontinued in patients with hemoglobin values below 8.5 g per decilitcr.
In the case of other severe events, the dose of interferon was decreased to 1.5 million units thrce times a week and the dose of ribavirin was decrcased to 600 mg per day