

# Treatment of Patients With Hepatitis C and Normal Serum Aminotransferase Levels

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**Approximately 30% of patients with chronic hepatitis C have normal serum alanine aminotransferase (ALT) levels and another 40% have ALT levels that are less than twice the upper limit of the normal range. Most patients with normal ALT levels have mild degrees of inflammation with mild or no fibrosis, and the rate of disease progression is reduced compared with that in patients with elevated ALT levels. Some patients with normal ALT levels have advanced fibrosis and cirrhosis on liver biopsy. Treatment of patients with normal ALT levels with either interferon monotherapy or interferon/ribavirin combination therapy has shown sustained virological response (SVR) rates that are equivalent to those achieved for patients with elevated ALT levels. Thus, patients with chronic hepatitis C should not be excluded from therapy based on ALT levels alone. The decision to initiate therapy with interferon and ribavirin should be based on a combination of factors independent of ALT levels including amount of fibrosis on liver biopsy, hepatitis C virus (HCV) genotype and viral level, patient age and motivation, and co-morbid illness, and the presence of other complicating conditions. (HEPATOLOGY 2002;36:S179-S184.)**

**A**t the 1997 National Institutes of Health Consensus Development Conference on "Management of Hepatitis C," the Consensus Panel concluded that alpha interferon treatment could not be recommended for patients with persistently normal alanine aminotransferase (ALT) levels and that therapy might actually worsen the course of disease.<sup>1</sup> This recommendation led to exclusion of patients with normal ALT levels from routine therapy, and helped support the continued exclusion of these patients from the pivotal trials of evolving therapy for this disease. Since that time there has been progress in the understanding of the clinical significance of normal ALT levels in chronic hepatitis C,<sup>2-6</sup> and the completion of several small clinical trials of newer ap-

proaches to therapy in this group of patients. With the advent of combination therapy using interferon and ribavirin and more recently using pegylated interferon (peginterferon) and ribavirin, sustained virological response (SVR) rates have improved dramatically.<sup>7,8</sup> These improvements in SVR rates have resulted in a new risk-to-benefit ratio to be used when considering antiviral treatment for patients with mild or slowly progressive disease. This summary/review will discuss the basis for using ALT levels as a criterion to recommend for or against therapy and the available data on treatment responses for patients with normal ALT levels or with mild disease.

## Treatment With Interferon Monotherapy

Monotherapy with alpha interferon is no longer used in the treatment of chronic hepatitis C, but the results of interferon monotherapy in patients with normal ALT levels were the basis for the conclusions of the 1997 Consensus Conference that these patients should not be treated. The results of 7 studies, including a total of 87 patients, were available for review at the time of that conference.<sup>1</sup> Most patients were treated for 24 weeks, but some for 48 weeks. The overall SVR rate was only 19%. For comparison, the SVR for patients with elevated ALT levels treated with interferon monotherapy for 24 weeks was only 12%. Thus, the SVR for these patients with normal ALT levels was comparable to or even higher than that for patients with elevated ALT levels, although no single

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*Abbreviations: ALT, alanine aminotransferase; SVR, sustained virological response; HCV, hepatitis C virus; AST, aspartate aminotransferase.*

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study had matched these 2 groups for other important variables such as hepatitis C virus (HCV) genotype, patient age, or underlying disease severity in assessing SVR rates. Of most concern, however, was the fact that 30 of 52 treated patients for whom data were available had *de novo* elevations of ALT levels during therapy and some patients continued to have ALT elevations after interferon was discontinued. These findings raised the question of whether interferon therapy in patients with normal ALT levels could worsen the underlying disease by either a direct toxic effect or by inducing immunologic responses to HCV. Understandably, based on the information available at that time, it was concluded that "current studies suggest treatment of patients with persistently normal ALT is not beneficial and may actually induce liver enzyme abnormalities," and that "these patients should not receive therapy outside of controlled clinical trials."<sup>1</sup> Accordingly, many clinicians were hesitant to treat patients with normal ALT levels and reimbursement was often refused for medication for these patients.

Continuing the recommendation that patients with hepatitis C and normal ALT levels should not be treated has been based predominantly on 4 factors: (1) the lack of adequate data on response rates in this group of patients, (2) concerns about safety of therapy, (3) the lack of data on the long-term benefit of sustained responses in patients with mild disease, and (4) the continued improvements in therapy for hepatitis C that continue to promise better and safer regimens in the near future. New information is available on each of these issues.

### Use of ALT Levels as an Enrollment Criterion in Clinical Trials

The lack of adequate data on response rates to antiviral therapy in patients with chronic hepatitis C and normal ALT levels is due to the fact that these patients have been regularly excluded from trials of therapy. Virtually all of the large registration trials of new therapies for hepatitis C have required that patients have elevations in ALT levels. The rationale for this enrollment criterion has not been well defined, but this requirement is probably a residual of the design of studies that were begun before the availability of reliable assays for HCV RNA in which the diagnosis of hepatitis C (or non-A, non-B hepatitis) depended on clinical and histological features or the presence of anti-HCV. With the availability of reliable tests for HCV RNA that could separate patients who had recovered from hepatitis C from those with persistent infection, the criterion for abnormal ALT levels could have been discarded. This criterion was retained at that point, probably to exclude patients with very mild disease. Because the registration trials were required to show improvement in

**Table 1. Treatment of Chronic Hepatitis C With Normal or Near Normal ALT Levels Using Interferon and Ribavirin Combination Therapy**

Study	No. of Patients	ALT Level	Genotype 1	Fibrosis 0 or 1+	SVR
Gordon et al. <sup>10*</sup>	44	<1.3 ULN	65%	89%	36%
Lee and Sherman <sup>11</sup>	19	<1.5 ULN	84%	84%	47%
Di Bisceglie et al. <sup>12†</sup>	24	Normal	80%	50%	25%
Jacobson et al. <sup>13</sup>	56	Normal	75%	64%	32%
Sponseller et al. <sup>14</sup>	24	Normal	64%	71%	50%

Abbreviations: ALT, alanine aminotransferase; SVR, sustained virological response rate; ULN, upper limit of normal range.

\*Among 105 patients evaluated, 44 received interferon and ribavirin for 48 weeks.

†All patients were non-responders to a previous course of interferon monotherapy.

liver histology with treatment, it was convenient to exclude patients with mild disease who would therefore be less likely to show significant improvement with treatment. However, the continued exclusion of patients with normal ALT levels makes it difficult to acquire adequate information on response rates in this group of patients.

### Efficacy and Safety of Combination Therapy in Patients With Normal ALT Levels

Shortly after the 1997 Consensus Conference guidelines were disseminated, results of trials of the combination of interferon and ribavirin were published, and this regimen was approved by the U. S. Food and Drug Administration, initially for patients who had relapsed<sup>9</sup> but subsequently for treatment-naïve patients as well.<sup>7</sup> Combination therapy with interferon and ribavirin soon became the standard of care, and the issue of whether or not to treat patients with normal ALT levels was re-evaluated. The exclusion of patients with normal ALT levels from the registration trials of combination therapy meant that there was little information on response rates in this group. Subsequently, there have been 5 studies of combination therapy in patients with normal or minimally elevated aminotransferase levels (Table 1).

Gordon and colleagues<sup>7,10</sup> performed a *post-hoc* analysis of one of the large registration trials of combination therapy in which 1,744 patients with chronic hepatitis C received interferon alfa-2b (3 mU thrice weekly) and either placebo or ribavirin (1,000 to 1,200 mg/d based on body weight below or above 75 kg) for 24 or 48 weeks. A total of 105 individuals (6%) had minimally elevated ALT levels, defined as an ALT of  $\leq 1.3$  times the upper limit of the normal range at study entry. Histology activity index and fibrosis scores were lower among patients with minimally elevated ALT levels than in those with

greater ALT elevations. Stages 3 or 4 fibrosis were present in 11% of patients with minimal ALT elevations and 25% of patients with more elevated levels ( $P < .001$ ). Nevertheless, the overall rates of SVR were the same in the 2 groups, being 24.7% (26/105; 95% CI = 17.5% to 33.9%) in patients with minimally elevated ALT levels and 27% (440/1639; 95% CI = 24.7% to 29.0%) in those with more elevated levels. Among the 505 patients treated with combination therapy for 48 weeks, SVR rates were 36.3% (16/44; 95% CI = 23.8% to 51.3%) for patients with minimal ALT elevations and 41.0% (189/461; 95% CI = 36.6% to 45.6%) for those with greater elevations ( $P = ns$ ).

In a pilot, uncontrolled prospective study, Lee and Sherman<sup>11</sup> treated patients with chronic hepatitis C and ALT levels that were either normal ( $n = 15$ ) or less than 1.5 times the upper limit of the normal range ( $n = 4$ ). Fourteen patients were women and 16 had genotype 1. Most patients had mild disease histologically, with either no fibrosis ( $n = 7$ ) or stage 1 ( $n = 9$ ) or 2 ( $n = 3$ ) portal fibrosis only. Patients received interferon alfa-2b in a dose of 5 mU daily for 4 weeks followed by 3 mU thrice weekly for 44 weeks combined with ribavirin in a dose of 1,000 or 1,200 mg daily. The overall SVR rate was 47%. No patient developed worsening of ALT levels during or after treatment. These investigators concluded that sustained response rates were excellent in this group of patients.

In a study of retreatment using combination therapy, Di Bisceglie et al.<sup>12</sup> treated 124 patients who had failed to respond to a previous course of interferon monotherapy with the combination of interferon alfa-2b (3 mU thrice weekly) and ribavirin (1,000 or 1,200 mg/d) for either 24 or 48 weeks. Twenty-four patients had normal serum ALT levels before treatment, of whom half had stage 3 or 4 fibrosis. During treatment, 9 of the 24 patients became HCV RNA negative and 6 had an SVR (25%; 95% CI = 12% to 45%), which was similar to the SVR rate of patients with elevated ALT levels (32%; 95% CI = 24% to 42%). The ALT levels in the sustained responders with initially normal ALT levels became more normal with therapy, falling from a mean of 42 U/L before therapy to 19 U/L after treatment. Six patients (25%) had at least 1 elevation in serum ALT during and 6 patients had elevations after therapy, but elevations were transient in all.

Jacobson et al.<sup>13</sup> have reported interim results of a large multicenter trial of therapy in patients with normal ALT levels conducted in the New York metropolitan area. All patients had normal ALT values on 2 or more occasions at least 3 months apart before enrollment. A total of 56 patients were randomized to receive interferon alfa-2b in a dose of either 3 or 5 mU thrice weekly in combination with ribavirin in standard doses of 1,000 to 1,200 mg

daily. At 24 weeks, patients were tested for HCV RNA; therapy was stopped in those who were still positive, but was continued for a full 48 weeks in those who were negative. Initial ALT levels averaged 33 IU/L, 75% of patients had genotype 1, and 36% had stage 2, 3, or 4 fibrosis. The SVR rate for all patients was 32% and was similar with both doses of interferon. The SVR rate was 24% in patients with genotype 1 and 80% in those with genotypes 2 or 3. None of 4 patients with genotype 4 had a sustained response. Five patients had ALT elevations during therapy, but all were transient and no value was greater than twice the upper limit of normal.

Finally, Sponseller et al.<sup>14</sup> have reported preliminary results from a multicenter trial of combination therapy among 116 patients with normal ALT levels. Patients received interferon alfa-2b (3 mU thrice weekly) and ribavirin (1,000 to 1,200 mg/d) for 48 weeks.<sup>13</sup> All patients had persistently normal ALT levels before therapy, with a mean ALT level before treatment of 65% of the upper limit of the normal range. The patient population included 56% women, 71% had stage 0 or 1 fibrosis, and 64% had HCV genotype 1. Twenty-four patients have completed treatment and 24 weeks of follow-up and 12 patients (50%) achieved an SVR; 43% of patients with HCV genotype 1 and 60% of those with non-1 genotypes.

The standard therapy for patients with chronic hepatitis C changed once again in the Fall of 2001 with the introduction of combination therapy using peginterferon alfa-2b and ribavirin.<sup>8</sup> This combination has yielded overall response rates of greater than 50%. No studies have been performed using peginterferon and ribavirin in patients with normal ALT levels. However, in the registration trial for this combination, Manns et al.<sup>8</sup> compared results of therapy in patients with minimal or no fibrosis (stages 0 or 1) with those with bridging fibrosis or cirrhosis (stages 3 and 4). The SVR rates with the combination of peginterferon/ribavirin were significantly higher in patients with mild histology (57%) than in those with more advanced histology (44%). Studies of patients with normal ALT levels using the combination of peginterferon/ribavirin are currently underway.

Thus, in all studies of patients with chronic hepatitis C and normal or near normal ALT levels, SVR rates with the combination of alpha interferon/ribavirin have been similar to rates reported in patients with abnormal ALT levels (Table 1). Furthermore, ALT elevations during and after therapy have been uncommon. While there have been no prospective studies on the use of peginterferon/ribavirin in patients with normal ALT levels, virtually all large studies of combination therapy to date have shown no correlation between initial ALT levels and likelihood of an

**Table 2. Rationale for Therapy of Patients With Chronic Hepatitis C and Normal Serum Aminotransferase Levels**

1. Presence of significant disease activity or fibrosis on liver biopsy
2. Evidence of significant liver disease based on other abnormal findings (e.g., elevated AST level, low platelet count, abnormal imaging studies)
3. Presence of extrahepatic manifestations
4. Presence of symptoms of hepatitis C
5. Major concerns over infectivity
6. Concerns of occupational status and infectivity
7. Motivation and desire for therapy
8. Comorbid conditions (HIV infection, renal disease)
9. Other factors (genotype, viral level, duration of infection)

SVR. Indeed, response rates have usually been highest in patients with lesser degrees of fibrosis compatible with earlier stage disease.

### Rationale of Therapy for Patients With Chronic Hepatitis C and Normal ALT Levels

Approximately 30% of patients with chronic hepatitis C have normal ALT levels and another 40% have ALT levels that are less than twice the upper limit of the normal range.<sup>5</sup> Case series and natural history studies have shown that patients with normal ALT levels usually have mild necroinflammatory changes on liver biopsy and minimal disease progression over time.<sup>2-6</sup> Data are lacking on the safety and efficacy of current therapies for patients with normal ALT levels, but the major reason for not recommending treatment of hepatitis C for these patients is that the normal ALT level is a surrogate marker for mild and nonprogressive disease. However, several issues are worth discussing that are important in making a recommendation for or against therapy in this group of patients (Table 2).

**What Is Meant by Normal ALT Levels?** In most treatment trials, patients defined as having normal ALT levels were required to have 2 or 3 normal values obtained on separate occasions at least 1 month apart during the 6 months before therapy. These same criteria have not been used in all natural history or cross-sectional liver biopsy studies. Serum ALT levels can fluctuate spontaneously in chronic hepatitis C, and a single normal value is unlikely to be representative. In addition, ALT levels in chronic hepatitis C can be influenced by other factors, such as excess alcohol consumption, intercurrent viral illnesses, medications, and presence of other liver diseases such as nonalcoholic fatty liver disease. Furthermore, different laboratories have different upper limits of normal ranges for ALT levels. Finally, body weight can influence ALT levels and normal ranges have not been separately evaluated in patients with different body sizes. Normal values for women and children, for instance, may be lower than those for men and older individuals. Thus, several factors

play a role in determining ALT levels and reliance on a single value to determine whether treatment is warranted is clearly subject to error.

**Is the Presence of Normal ALT Levels a Reliable Marker for Mild Hepatitis?** In analyses of large case series, between 1% and 29% of patients with normal ALT levels have stage 3 or 4 fibrosis on liver biopsy. Indeed, as patients develop cirrhosis, serum ALT levels tend to decrease (as does the ratio of ALT to aspartate aminotransferase [AST]).<sup>15</sup> Thus, patients with normal ALT levels cannot be completely assured that they have mild liver disease, particularly if other liver tests or ancillary studies suggest the presence of significant liver injury. Other tests that can suggest more significant liver disease include elevations in AST, gammaglutamyl transpeptidase, alkaline phosphatase, bilirubin, immunoglobulins, alpha-fetoprotein, and prothrombin time, as well as decreases in platelet counts and serum albumin levels.<sup>5</sup> Given that all tests are normal and that ALT levels are persistently normal, the possibility of significant and progressive liver disease is low.

**Is Prevention of Disease Progression the Only Goal of Therapy?** Recommending that patients with normal ALT levels not receive therapy because normal levels are a marker for mild and nonprogressive liver disease assumes that the only goal of therapy for hepatitis C is to prevent progression of liver disease to cirrhosis and hepatic failure. While prevention of cirrhosis may be the primary and most important goal of therapy, there are certainly other important reasons to treat hepatitis C, such as prevention of transmission, improvement in symptoms and quality of life, amelioration of extrahepatic manifestations, and purely personal or psychological reasons. Thus, for some patients a major concern is the possibility of transmitting hepatitis C to a loved one or child. Currently, there are no reliable means of prevention of sexual or maternal-infant transmission of hepatitis C, but the sustained loss of HCV RNA as a result of treatment is highly likely to prevent such transmission.<sup>16,17</sup> Health care providers with hepatitis C may request therapy despite normal ALT levels because of concerns over transmission of disease to their patient contacts. While such spread is uncommon,<sup>18</sup> excessive concerns over the possibility of transmission may lead to restrictions in professional activities. Extrahepatic manifestations of hepatitis C are also important reasons for treatment, and many patients with cryoglobulinemia or renal disease caused by hepatitis C have normal or near normal ALT levels.<sup>19</sup> Finally, for some patients, knowledge that they have hepatitis C is a persistent cause of anxiety and depression. The use of ALT levels as a surrogate for mild disease and the caveat that patients with mild disease need not receive treatment violates one of the

fundamental principles of ethics in medicine – patient autonomy. Patients themselves should participate in decisions on the management of their disease.

***Does the Presence of Comorbid Conditions Affect Recommendations for Therapy?*** Certain comorbid conditions may provide a strong rationale for early therapy for hepatitis C, regardless of ALT levels or disease severity at the time. Thus, chronic hepatitis C is more rapidly progressive in patients with human immunodeficiency virus infection, and therapy is probably more likely to be effective and better tolerated during early stages of both the hepatitis C and the human immunodeficiency virus infection.<sup>20,21</sup> These factors weigh strongly for early treatment of patients with human immunodeficiency virus coinfection. Similarly, patients with renal disease who are likely to eventually require renal transplantation might be considered for early treatment, before renal failure prevents use of ribavirin and makes therapy more difficult to tolerate.<sup>22,23</sup> Finally, ALT levels may be unreliable in patients who are immunosuppressed or who have renal insufficiency.

***Should Liver Biopsy Be Used to Decide on Therapy in Patients With Normal ALT Levels?*** If normal ALT level is a poor surrogate marker for disease severity, liver biopsy might be recommended to help decide whether therapy is appropriate. Liver histology is considered the “gold standard” for assessing severity and stage of disease. But even liver biopsy has serious shortcomings. Liver biopsy can yield varying results, based on sampling errors and the varying expertise of the hepatic pathologist reviewing the liver histology. Most registration trials of antiviral therapy for hepatitis C have used world expert hepatic pathologists; whereas the average patient undergoing liver biopsy will depend on a local pathologist who may have little or no experience in interpretation of histology in hepatitis C. Liver biopsy is also an invasive procedure that is not without costs and serious complications. These considerations make it unreasonable to require all patients with normal ALT levels who wish to receive therapy to undergo liver biopsy and then require a certain level of disease activity or fibrosis to warrant therapy. Indeed, in the many registration trials of therapy for hepatitis C, liver biopsy was usually required before treatment, but the severity of the findings on liver biopsy were not used as inclusion or exclusion criteria.

***Should All Persons With Chronic HCV Infection Receive Therapy Regardless of Disease Severity?*** The corollary to withholding therapy in patients with mild and nonprogressive disease is to recommend that all patients with chronic HCV infection be treated. Such a recommendation would be acceptable if therapy were highly effective and safe (and reasonably priced). Unfor-

tunately, “highly effective and safe” does not describe current optimal therapy for hepatitis C. The combination of peginterferon and ribavirin given for 24 to 48 weeks is effective in only 50% to 60% of patients and is neither well tolerated nor inexpensive. Side effects can be severe and even life threatening. Most treated patients have significant amounts of fatigue and irritability or depression for the period of therapy. For these reasons, an important rationale for deferring therapy for patients with mild disease is that the treatment of hepatitis C has been steadily evolving and is likely to be more effective, and possibly safer and better tolerated, in 5 to 10 years. The promise of future improvements in therapy is, indeed, the major reason to recommend that patients with persistently normal serum ALT levels not undergo therapy at the present time. However, this recommendation should be accompanied by the recommendation that these patients be followed at regular intervals and be kept abreast of changes in therapy for this disease.

***Are There Other Factors That Weigh Towards Treatment Now Rather Than Waiting?*** For patients with normal ALT levels and mild disease who, nevertheless, still wish to be treated with current therapies, considerations of other factors, such as patient age, suspected duration of treatment, presence of symptoms or extrahepatic manifestations, psychological factors, viral genotype, HCV RNA level, and concerns over infectivity should be used to guide treatment of this disease. Thus, recommending therapy is certainly easier when dealing with a young adult patient with normal ALT levels who is infected with genotype 2 or 3, has a normal body weight, and no comorbidities or personal factors that would make therapy difficult. Such a recommendation is more difficult for the older patient with normal ALT levels who is infected with genotype 1 and is overweight and has had other medical problems. In these patients, liver biopsy can be used to judge whether or not to wait for future improvements in therapy.

## Summary and Recommendations

Approximately 30% of patients with chronic hepatitis C have normal ALT levels and another 40% have ALT levels that are less than 2 times the upper limit of the normal range. The majority of these patients have mild disease histologically, with stage 0 or 1 fibrosis. Nevertheless, these patients can have progressive liver disease and develop advanced fibrosis or cirrhosis. Sustained response rates for patients with normal ALT levels are equivalent to those of patients with elevated ALT levels and degree of elevation of ALT levels has not correlated with overall response rates to antiviral therapy for hepatitis C. The safety of treatment of patients with normal ALT levels,

which was a concern with interferon monotherapy, has not been a problem with combination therapy. The presence of normal ALT levels has been used as a surrogate marker for the presence of mild and nonprogressive liver disease. It should be stressed that the use of ALT levels to assess severity of hepatitis C is not always reliable. Furthermore, patients with mild disease may have other indications for therapy including presence of symptoms, extrahepatic manifestations, serious comorbid conditions, or major concerns regarding infectivity. Patient autonomy dictates that the desires of patients be weighed in any decision for or against treatment. The continuing advances in therapy for hepatitis C argue for deferring therapy in patients with mild disease to a time when treatments are more effective and better tolerated. Nevertheless, patient motivation along with factors of patient age, duration of infection, viral genotype, and HCV RNA levels should be used in deciding on therapy for patients with chronic hepatitis C with or without elevations in serum ALT levels.

## Future Research Needs

Clearly, prospective studies of therapy should include patients with normal serum ALT levels and focus on safety and efficacy in this cohort. Future registration trials of new therapies should include patients with normal ALT levels as a subgroup for analysis. Large clinical trials should also include accurate measures of symptoms, with quality of life and psychological well being as secondary endpoints for careful analysis. Better natural history studies are needed to assess the significance of normal ALT levels in predicting outcome of disease and to identify factors that predict progression in this group of patients. Finally, studies of patients with normal ALT levels are important to elucidate the reasons for the great variability in clinical and histological severity of hepatitis C.

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