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Utilization of Virologic Testing in the Treatment of Chronic Hepatitis C

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Slightly fewer than half of patients with chronic hepatitis C fail to eradicate hepatitis C virus (HCV) when treated with the current regimen of combination therapy with pegylated interferon and oral ribavirin (PEG-R).^(1,2) With past treatment regimens including interferon monotherapy or the combination of standard interferon with ribavirin, patients who remained HCV RNA positive by qualitative testing by RT-PCR after 12 or 24 weeks, respectively, had little or no chance of achieving a sustained virologic response (SVR).^(3,4) Preliminary data from one of the PEG-R studies suggested that the most appropriate time point for assessing response with the current regimen was also 24 weeks.⁽¹⁾ Thus, treatment could be discontinued early in viral non-responders, saving them the inconvenience and expense of the latter half of the treatment course. However, several papers also reported that the lack of an even earlier reduction in viral level was predictive of non-response despite continued treatment.^(5,6) Unfortunately, these reports examined small numbers of patients and used quantitative assays for HCV RNA that were neither reliable or commercially available. Recently, several standardized commercial assays for quantitating HCV RNA have become available. The role of these quantitative tests in assessing early virologic response (or non-response) to PEG-R has not been studied.

The goal of the current analysis was to determine whether reduction of the level of HCV RNA during the first weeks of PEG-R treatment predicted response and non-response at the end of treatment and whether this information would be used to formulate early stopping rules before 24 weeks of treatment. Data from two recent large international clinical studies of pegylated interferon plus oral ribavirin was made available by the study sponsors, Schering Plough and Roche Pharmaceuticals, after agreement of the study investigators.^(1,2) Only those treatment groups receiving the optimal regimen were included (PEG-IFNa2a 180 mcg q wk + ribavirin 1000–1200 mg daily; PEG-IFNa2b 1.5 mcg/kg qwk + ribavirin 800 mg daily). Quantitative HCV RNA was measured at baseline, 4 weeks, 12 weeks, and 24 weeks by the NGI method (Schering study) or Amplicor with appropriate dilutions of high titer samples (Roche study).^(7,8) This data was analyzed to answer the following questions: (a) Can serial quantitative HCV RNA testing predict a lack of virologic response to PEG-R? (b) Can serial quantitative HCV RNA testing predict a sustained virologic response to PEG-R? (c) What is the optimal time to determine early virologic response?

The analysis of the 2 data sets with respect to the ability of the week 12 viral response to predict non-response is shown in the table below. The results with the 2 different interferon regimens are nearly identical. Early virologic response (EVR) was best defined as a fall in HCV RNA level after the first 12 weeks of treatment to less than the lower limit of detection (PCR) or by at least 2 logs compared to the pre-treatment level. Overall, 82.7 percent of patients treated with this combination achieved EVR and 68 percent of these cases eventually achieved SVR. SVR was more than 50 percent more likely to occur in patients who were able to receive at least 80 percent of the recommended dose and duration of drugs. Failure to

achieve an early virologic response was highly predictive of non-response; only 2 of 161 (1.2 percent) patients without EVR ultimately achieved SVR. Viral response at 4 weeks was less predictive than the 12 week response; failure to achieve a 4 week EVR was associated with a 4 percent chance of SVR. A quantitative cutoff of more than 2 logs (e.g. 3 logs) missed some patients who ultimately achieved SVR while a less rigorous cutoff (e.g. 1 log) allowed too many non-responders to continue on treatment.

<i>Early Virological Response</i>	<i>Treatment Response</i>	
	<i>SVR</i>	<i>NR</i>
Study #1		
Yes	71.8%	28.2%
No	0.0%	100.0%
Study #2		
Yes	64.9%	35.1%
No	3.2%	96.8%
Combined Data		
Yes	68.3%	31.7%
No	1.2%	98.8%

In summary, most patients who receive treatment with pegylated interferon and ribavirin achieve early virologic response, defined as a fall in HCV RNA level by at least 2 logs or to undetectable by PCR after the first 12 weeks of treatment. About two-thirds of these patients will ultimately achieve SVR, thus providing excellent motivation to continue therapy and not dose reduce unnecessarily. In contrast, those who fail to achieve an early virologic response have only a very small chance of achieving SVR even if therapy is continued for a full year. Discontinuation of therapy is encouraged in these cases.

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The Role of Liver Biopsy in Therapy of Chronic Hepatitis C

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As the efficacy of therapy for chronic hepatitis C improves, as acceptance of such therapy becomes more widespread, and as management of chronic hepatitis C extends from specialist hepatologists to nonspecialists, the role of liver biopsy in the management of chronic hepatitis C is being re-examined. When the role of liver biopsy was considered during the previous NIH Consensus Development Conference in 1997, pretreatment liver biopsy was endorsed as the "gold standard" for assessing the grade of liver injury

and the stage of liver fibrosis in anticipation of antiviral therapy. The same recommendations appear in the consensus statement of the European Association for the Study of Liver Disease; are supported by the Centers for Disease Control, United States Public Health Service; and are implied in the consensus statement on prevention and management of hepatitis C in the Asia-Pacific region. Since that time, a series of reports have appeared either supporting or challenging the role of such histologic assessment in the management of chronic hepatitis C. In reevaluation of the value of liver biopsy, we should consider whether hepatic histology (a) provides prognostic information about the future natural history of chronic hepatitis C, (b) predicts the likelihood of response to antiviral therapy, and (c) remains the gold standard that it represented or can be supplanted by “surrogate” indicators.

Selecting patients for treatment would be easier if available therapy were uncomplicated, highly effective, simple to administer, limited in duration, and well tolerated. In patients with chronic hepatitis C, however, available therapy is far from ideal, and many factors color the decisions of individual patients and their physicians. Antiviral therapy for chronic hepatitis C requires injection therapy; side effects are common and especially difficult to accept in a population of predominantly asymptomatic persons; approximately half of treated patients fail to respond to the best therapy available; for many patients progression is so slow and limited that the decision to treat is readily postponed; and, if the steady progress in efficacy of antiviral therapy over the last decade is an indication of progress to come, many patients might fare just as well to wait until antiviral therapy improves. Perhaps, for patients with HCV genotypes 2 and 3, response to therapy is so likely that the threshold for treatment is achieved in almost all cases; however, because most patients have genotype 1, and because 60 percent of patients in this category fail to respond, pretreatment variables that shed light upon prognosis and likelihood of response to therapy are valuable for decision-making about therapy.

Although much is known about the natural history of chronic hepatitis C in large cohorts of affected persons, predicting the future course of the disease in any individual is difficult. Of the several potential prognostic variables, the most reliable appears to be histologic grade and stage, as assessed by one of several extant histologic classifications systems. Studies relying on serial liver biopsies suggest that patients with mild hepatitis and limited fibrosis progress slowly or not at all over a 10–20 year horizon, while those with moderate to severe inflammation (grade) and fibrosis (stage) progress inevitably to cirrhosis over a 20–10 year horizon, respectively. Therefore, a baseline biopsy is useful for determining the urgency of initiating therapy. Moreover, almost all instances of hepatitis C being discovered in clinical practice now represent hepatitis C virus (HCV) infections acquired one to three decades earlier, originating at a time of life when “risky” behavior occurred, even transiently. Thus, for most patients undergoing liver biopsy for chronic hepatitis C, current biopsy includes an approximate assessment of the impact on inflammation and fibrosis of several decades of HCV infection and virus-associated liver injury. These observations have been invoked as the primary justification for recommending liver biopsy prior to embarking upon a course of antiviral therapy.

Liver biopsy is felt to be helpful in excluding other causes of liver injury that might confound interpretation of the clinical and histologic expression of HCV infection. Because some patients with chronic hepatitis C have other, concomitant causes of liver injury, a pretreatment liver biopsy to exclude such alternative factors as fat, alcohol, iron, etc. may shift clinical focus away from hepatitis C to the alternative process. Moreover, some of these factors, e.g., fat or iron, have been suggested to be cofactors in the progression of fibrosis. Another argument in favor of a pretreatment biopsy in patients with chronic hepatitis C can be made for anyone with any type of liver disorder for which treatment is an option. That is, a baseline biopsy obtained prior to committing a patient to long-term treatment preserves the value of potential subsequent histologic assessment for management decisions made in the future.

Based upon histologic prognostication, many clinicians decline to pursue therapy in patients with mild chronic hepatitis C. From a societal perspective, however, Wong et al. suggested that treatment of mild chronic hepatitis with combination interferon-ribavirin is actually cost-effective, reduces the risk of cirrhosis, and prolongs survival. The comparison strategy for this analysis was watchful waiting, with liver biopsies repeated every three years and therapy introduced for histologic progression; in addition, the calculated

costs of therapy involved the combination of standard interferon with ribavirin. Although sensitivity analyses were included to address uncertainties in the many estimates required for such an analysis, this analysis was based upon costs of a previous generation of therapy, not the increased costs of contemporary therapy with pegylated interferon plus ribavirin. In addition, the benefit identified would be marginal or negligible if only one additional liver biopsy were to be performed in the future, and the analysis could not include the impact of the inevitable introduction of more effective, better tolerated treatments that would justify postponing treatment for several years.

Whether critiques of this analysis are substantial or quibbling, the perspective of individual patients and physicians may be very different and no less valid or compelling than the societal perspective adopted in this analysis. For many patients with mild disease and a likelihood of progression to cirrhosis that may be as low as 20 percent over 20 years, a viable strategy would allow postponing treatment for several years and embracing therapy without an additional liver biopsy when more highly effective treatments become available.

Liver biopsy would be less important were other clinical or laboratory tests available that could predict reliably the grade of inflammatory injury or the stage of fibrosis; however, to date, no such surrogates have been validated. Weighing against liver biopsies are the high costs of the procedure as well as its invasive nature and associated risks. Because most patients referred for evaluation have moderate to severe chronic hepatitis on liver biopsy, and because liver biopsies have been found by some investigators to have a limited impact on decision-making about treatment, the importance of a pretreatment liver biopsy might be questioned. Even the assumption that liver biopsy would be valuable for excluding other diagnoses in patients with chronic hepatitis C could not be confirmed by Saadeh et al. Nevertheless, these investigators marshaled data to support the utility of pretreatment liver biopsy by showing limited sensitivity and specificity of nonhistologic approaches, none of which was adequately predictive of histologic findings in the large majority of patients. Predicting the presence of cirrhosis is especially challenging; cirrhosis can be present in up to half of well compensated patients with chronic hepatitis C, and neither a single test nor a combination of clinical and laboratory features has been shown to have sufficient predictive value for the presence of cirrhosis. Given the implications of cirrhosis for surveillance and management, baseline biopsy takes on special importance.

On the other side of the coin, baseline biopsies have been reported to demonstrate unexpectedly mild liver disease in some patients referred for treatment, including persons with hemophilia and with injection drug use, and the more publicized women who received contaminated anti-D immune globulin in Ireland and Germany. Thus, nonhistologic assessments have neither the sensitivity nor the specificity to replace liver biopsy in the initial assessment of suitability for treatment.

Another area of potential controversy is the subset of patients with chronic hepatitis C but persistently normal aminotransferase activities. Anecdotal reports have appeared to show that some of these patients have histologically very severe or advanced liver disease, suggesting that all such patients require liver biopsy to unearth clinically subtle but advanced liver disease. When group data are evaluated, however, the preponderance of evidence suggests that severe liver injury is the marked exception in such patients. Moreover, among patients with chronic hepatitis C and persistently normal aminotransferase levels, histologic activity, as monitored by sequential liver biopsies over more than half a decade, does not progress. Therefore, and because the last NIH Consensus Development Conference in 1997 failed to identify any benefit of therapy in this subgroup, many authorities are reluctant to pursue liver biopsy in patients with normal aminotransferase activity.

Although other predictors of responsiveness to therapy exist, the degree of fibrosis has also been shown to be an independent inverse predictor of response to therapy. On the other hand, the negative predictive value of fibrosis or cirrhosis is too low to justify withholding therapy, and the need for therapy may be more compelling in this group of patients who have more advanced disease.

For contemporary antiviral therapy of chronic hepatitis C, pretreatment liver biopsy provides important

information about prognosis and the need for early treatment and should be retained. Future research should focus on delineating how broadly histologic assessment should be implemented and whether other clinical features suffice to supplant liver biopsy under certain circumstances. Because liver biopsy is invasive, the search for noninvasive laboratory markers of necroinflammatory activity, fibrosis, and cirrhosis should command a high priority, as should the quest for genetic markers associated with accelerated disease progression.

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Utility of Liver Biopsy in Management of Hepatitis C: A Systematic Review

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Introduction

Liver biopsies are frequently recommended in the management of patients with chronic hepatitis C. Histologic criteria have been established to assess the severity of both inflammation and fibrosis. However, it remains uncertain how this information assists in establishing prognosis or predicting efficacy of treatment.

Objective

We conducted a systematic review of the literature to determine: (1) how the results of initial liver biopsy relate to measures of disease progression and treatment outcome as assessed by histologic and virologic

parameters and (2) the value of serum biochemistry tests and serologic measures of fibrosis in predicting histologic findings.

Methods

Literature Sources

Seven electronic databases were searched through DIALOG for the period from January 1996 to March 2002. Additional articles were identified by searching references in pertinent articles, hand searching relevant journals, and querying technical experts.

Eligibility Criteria

Exclusion criteria for review included: non-English language, articles limited to basic science or non-human data, previously reported data, and meeting abstracts. Inclusion criteria for review were: study designed to address our key question, information pertinent to management of hepatitis C, and 30 or more study subjects with hepatitis C. In addition, for those studies pertaining to how results of initial liver biopsy relate to measures of disease progression and treatment outcome, we required at least six months of followup after initial biopsy and outcomes measured by an appropriate objective standard such as virologic or histologic measures.

Assessment of Study Quality

Each eligible article was reviewed by a pair of reviewers, including at least one team member with relevant clinical training and/or one with training in epidemiology and research methods. Paired reviewers independently rated the quality of each study in terms of the following categories: representativeness of study subjects (5 items); bias and confounding (4 items); description of therapy (4 items); outcomes and follow-up (5 items); statistical quality and interpretation (4 items). Reviewers assigned each response level a score of 0 (criterion not met), 1 (criterion partially met), or 2 (criterion fully met) to each relevant item on the quality form. The score for each category of study quality was the percentage of the total points available in each category and therefore could range from 0–100 percent. The overall quality score was the average of the five categorical scores. We also documented source of funding.

Extraction of Data

The paired reviewers also abstracted data on type of study and geographical location; the study groups; specific aims; the inclusion and exclusion criteria; demographic, social, and clinical characteristics of subjects; and results. Differences between the two reviewers in either quality or content abstraction were resolved by consensus.

Synthesis

Results of Literature Search

We identified 3,104 potentially relevant citations and 1,731 of these were eligible for abstract review. Through the abstract review process we identified 254 articles that could contain data on one of our key questions regarding the utility of liver biopsy in patients with chronic hepatitis C. After reviewing these 254 articles, we found 147 studies that addressed the value of initial or follow-up biopsies predicting treatment outcomes and 107 articles that addressed the relationship between serological markers and histological findings. We subsequently reviewed the full articles to ensure they met our eligibility criteria. We have focused on randomized controlled trials of therapies for which assignment to a treatment was *not* determined by biopsy results. Data from these eligible studies will be presented in a series of evidence tables and figures highlighting their distinguishing characteristics, methodologic strengths and limitations, and key findings.

Children with Hepatitis C

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Less is known about HCV infection in children compared to infection in adults, due to the small proportion of HCV-infected individuals that are children and the lack of manifestations of this infection during childhood. Nonetheless, most HCV-infected children develop chronic hepatitis, and, although rare, cirrhosis and end-stage liver disease have been described. There are differences in modes of acquisition, natural history, complications, and treatment between pediatric and adult HCV infection.

The seroprevalence of anti-HCV is 0.2 percent in children less than 12 years of age, and 0.4 percent in those 12 to 19 years of age. Using these figures, it can be estimated that there are somewhere around 240,000 exposed or infected children in this country. Although there has been a significant decrease in the incidence of new HCV infections in adults, new infections continue to occur in children via perinatal transmission. Because receipt of blood or blood products prior to 1992 was an important mode of transmission of HCV to children, there is a cohort of adolescents who have had HCV for 10–20 years. Perinatal transmission provides a cohort of infected children from newborns through the teenage years. Horizontal transmission, from adult to child in the household, or child-to-child at home or at school, does not seem to be an important factor in the epidemiology. The prevalence of HCV infection in children not currently explained by risk factors, i.e., sporadic or community-acquired HCV, is felt to be low. Many children infected with HCV are yet to be identified.

Acute HCV infection is rarely recognized in children, outside of special circumstances like a transfusion-associated outbreak. Fulminant hepatitis due to HCV has not been described in children. Chronically infected children are asymptomatic or have non-specific fatigue and/or abdominal pain, with normal or mildly abnormal ALT levels. Clinically apparent autoimmune manifestations are rare.

Independent effects of age at acquisition and mode of acquisition on natural history are difficult to separate in pediatric studies. In addition, the natural history of transfusion-associated HCV infection may differ according to the underlying disease for which transfusion is required. Some children who were transfused at the time of surgery for congenital heart disease developed chronic hepatitis, but others cleared the infection. Secondary hemochromatosis may contribute to the hepatic injury in children with thalassemia, and may mitigate the response to therapy in this group. Children treated for leukemia prior to 1990 have a very high rate of HCV infection, but in one cohort prolonged followup (13–27 years) did not commonly reveal serious liver disease. In contrast, an American study of individuals treated for childhood cancer revealed one death from liver disease and two deaths due to hepatocellular carcinoma in the decades following HCV acquisition. The same report described 3 (9 percent) cases of cirrhosis 9–27 years after diagnosis of the primary malignancy. Clearly, some cases of HCV infection acquired in childhood by transfusion are associated with serious liver disease in the decades following infection.

Whether the natural history of infection acquired perinatally is different from HCV acquired by transfusion is not yet clear. Vertically infected infants typically have elevated alanine aminotransferase (ALT) levels for a few years, and those levels often become normal. Virtually all children who undergo liver biopsy have histologic chronic hepatitis. Thus it appears that HCV infection acquired vertically is frequently associated with biochemical evidence of hepatic injury early in life, persists in the majority, but not all, instances, and causes only mild liver disease in the first decades. However, in some children the infection takes an aggressive course leading to cirrhosis and even end-stage liver disease during childhood; the factors responsible for this are as yet unidentified.

There are no reports of treatment of acute HCV infection in children; acute infection is rarely recognized. In addition, no large, multicenter, randomized, controlled therapeutic trials have been performed in children with chronic HCV infection. Studies of treatment in children are most often uncontrolled, include small numbers of patients, and sometimes include only select patient groups, such as hemophiliacs or individuals

with thalassemia. Details of the interferon monotherapy trials in children with chronic HCV infection were recently reviewed: even though the studies included several types of patients and used different dosages, schedules, and types of interferon, in general the sustained virologic response (SVR) rate was remarkably similar in most studies, ranging from 33–45 percent. This is significantly higher than the SVR rates reported in large trials of interferon monotherapy in adult patients. An analysis of these heterogeneous studies that included 11 manuscripts and 3 abstracts (in total included 270 treated children and 37 control subjects) describes a SVR rate of 35 percent, 26 percent for genotype 1 and 70 percent for others. This higher response rate in children could be related to factors such as earlier stage of disease, higher relative interferon dosage, or lack of co-morbid conditions or aggravating cofactors. Alternatively, this finding could simply be a statistical artifact of the small, uncontrolled trials. In any case, given the superiority of combination therapy with interferon and ribavirin in adults, it is unlikely that a large, randomized, controlled trial of interferon monotherapy will be undertaken in children with chronic HCV infection.

There are few data regarding the use of combination therapy in children. A recent abstract described a cohort of 61 children treated with 3 MU/m² of interferon thrice weekly, and 8, 12, or 15 mg/kg of ribavirin daily. The pharmacokinetic properties of the drugs were similar to those in adults, and the therapy was well tolerated, with dose-dependent anemia from the ribavirin that was somewhat less severe than that observed in adults. The 15 mg/kg ribavirin dose was chosen for a larger efficacy study which has recently been completed; results are expected in the coming months. There are no data regarding the use of the pegylated interferons in children.

Prevention of new HCV infections in older children requires education about high-risk behaviors. Although commercial body piercing and tattooing are not clearly associated with risk, self-tattooing and self-piercing with shared needles are fairly common practices and might be associated with HCV acquisition. Transmission of infection in intravenous drug users is well understood, but the risk from sharing straws or other implements for intranasal cocaine administration may not be appreciated by teenagers.

The primary target for prevention strategies should be perinatal transmission. Currently, universal testing of pregnant women for HCV infection is not recommended. Post-exposure immune globulin is not effective. Maternal HIV co-infection has been addressed with aggressive antiretroviral therapy. There are no safe measures to decrease maternal HCV viremia at delivery, since interferon and ribavirin are contraindicated during pregnancy. If the importance of obstetrical factors is confirmed, changes may become necessary in the care of infected women.

In summary, HCV infection in children is not rare and is under-recognized. The natural history is either more benign or more prolonged when compared to adult-onset infection. Children may have a better response rate to current therapies, but well-designed studies have not yet been done. Prevention efforts should focus on perinatal transmission.

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Patients with Normal ALT Levels

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At the 1997 NIH Consensus Development Conference on Management of Hepatitis C, it was concluded that "...treatment of patients with persistently normal ALT is not beneficial and may actually induce liver enzyme abnormalities." (1) Since that time, this issue has been controversial with some investigators supportive of treatment and others suggesting that no work-up or therapy is necessary for these patients. Approximately 30 percent of patients with chronic hepatitis C have normal ALT levels, and another 40 percent have ALT levels that are less than two times the upper limit of normal. (2) Most patients with normal ALT levels have mild degrees of inflammation with mild or no fibrosis and their rate of disease progression is reduced compared to those with elevated ALT levels. (3,4) However, some patients with persistently normal ALT levels can progress to advanced fibrosis and cirrhosis. (3-6)

The issue regarding treatment of these patients has often focused on how to proceed in patients with mild disease, recognizing that ALT levels may actually be just a proxy for mild histology. The best treatment trials that have been performed are the registration trials for FDA approval, and those have all required that patients have elevated ALT levels to be included in the study. Therefore, there are no large treatment trials of normal ALT patients. When interferon monotherapy was used for HCV patients with normal ALT levels, sustained response (SR) rates generally ranged from 15 percent to 20 percent. These SR rates are similar to the results of studies obtained when interferon monotherapy was used to treat patients with elevated ALT levels.

Since the NIH Consensus Conference recommendations were issued in 1997, treatment of chronic hepatitis C has progressed from interferon monotherapy to combination therapy using interferon and ribavirin, and more recently to pegylated interferon and ribavirin. A few studies of interferon plus ribavirin in chronic hepatitis C patients with normal or near normal ALT levels have been reported. Gordon and colleagues studied patients from one of the large registration trials in which a total of 1,744 patients with hepatitis C received either interferon and placebo or interferon and ribavirin for 24 or 48 weeks. (7) Of these, 105 individuals (6 percent) had minimally elevated ALT levels, defined as = 1.3 times the upper limit of normal (ULN), at their entry visit. Histologic activity index and fibrosis scores were lower amongst these patients with baseline ALT levels = 1.3 times the ULN. There was no difference in SR between patients with ALT levels = 1.3 times the ULN (24.8 percent) compared to those with ALT levels > 1.3 times the ULN (26.8 percent) for all treatment groups. Lee and Sherman studied 19 patients with ALT levels that were either normal or < 1.5 times the ULN. (8) Nine of the 19 patients (47 percent) had an SR. In studies from our group at Saint Louis University, Di Bisceglie, et al. reported on a group of interferon monotherapy nonresponders who were re-treated with the combination of interferon and ribavirin. (9) In total, of 124 patients were studied; 24 had normal ALT levels and 100 had elevated ALT levels. There was no difference in SR between the two groups (26 percent vs. 34 percent). Further, we have coordinated an investigator-initiated multicenter study evaluating the use of interferon and ribavirin in treatment of naïve patients with chronic hepatitis C who have persistently normal ALT levels. One hundred seventeen patients have been enrolled in this study and are currently in treatment or followup phases of the study. Thus, all reported studies have shown that SR rates for normal or near normal ALT patients are equivalent to those of elevated ALT patients when the combination of interferon and ribavirin is used.

Currently, the standard of care for most patients with chronic hepatitis C is to use the combination of pegylated interferon and ribavirin. Overall SR rates of about 55 percent can be achieved. There are no studies of normal ALT patients being treated with pegylated interferon and ribavirin, although a large investigator-initiated multicenter study is currently under way. When evaluating the effect of pegylated interferon and ribavirin, Manns and colleagues compared patients with minimal or no fibrosis to those with bridging fibrosis or cirrhosis. (10) When pegylated interferon and ribavirin were used as therapy, the SR rates for those with mild histologic changes were better (57 percent) than those with more advanced histology (44 percent).

In summary, approximately 30 percent of patients with chronic hepatitis C have normal ALT levels and another 40 percent have ALT levels < 2 times the ULN. The majority of these patients have disease that is histologically mild, but these patients can have progressive liver disease with the development of advanced fibrosis and cirrhosis. It no longer seems reasonable to conclude that SR rates for patients with normal ALT

levels are any different than those for patients with elevated ALT levels. The issue at hand is whether or not patients with mild liver disease should be treated. There are numerous other factors which impact on this decision, including genotype, histology, patient motivation, symptoms, co-morbid illness, and the age of the patient. ALT levels may have less importance in deciding who should be treated.

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Patients with Advanced Disease

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The majority of patients with HCV infection have mild liver disease, and concern about this virus would be vastly reduced if it were not for the minority that progress to cirrhosis. All of the potentially life-threatening complications of HCV infection such as hepatocellular carcinoma, bleeding esophageal varices, life-threatening infections, hepatic synthetic failure, and intractable ascites occur in patients with advanced liver disease. Unfortunately, it is not possible to reliably identify those patients who are risk for developing cirrhosis. The management of HCV disease is further complicated because, in general, therapeutic interventions are more successful in patients with early disease than in those with advanced liver disease.

With that background, how successful are existing interventions in patients with advanced liver disease? First and foremost, available therapies are currently limited. Many patients with advanced HCV disease are not candidates for interferon plus ribavirin. Contraindications in this population include cytopenias (platelet counts less than 75 k/mm^3 and white cell counts less than $1,500/\text{mm}^3$) and/or co-morbid conditions such as uncontrolled psychiatric disease that preclude therapy.

Data on safety and efficacy of interferon (standard or pegylated) with or without ribavirin in patients with compensated cirrhosis or transition to cirrhosis have often been derived from subgroup analysis of larger trials, ^(1–3) although in some studies, this population has been the sole focus of the trial. ⁽⁴⁾ In patients with sufficient platelets and white blood cells to tolerate therapy, pegylated interferon alfa 2b in combination with ribavirin has been studied at two different dosing regimens and compared to standard interferon plus ribavirin (Table 1). Viral clearance in patients with advanced liver disease was the similar with all three regimens (41–44 percent), but was lower in patients with advanced liver disease than in patients with

minimal or no fibrosis (Table 1). Similar analyses have been performed in patients receiving combination therapy, which includes pegylated interferon alfa 2a (Table 2). In patients with advanced liver disease, viral clearance ranged from 43 percent in patients receiving pegylated interferon alfa 2a in combination with ribavirin to 21 percent in patients receiving pegylated interferon alfa 2a as monotherapy. Response was 33 percent in patients receiving standard interferon alfa 2b plus ribavirin (Table 2). As for the results from other studies, (2) sustained virological response with all three regimens was lower in patients with advanced liver disease than in patients without cirrhosis (Table 2). Comparisons between trials should not be performed without information about distribution of other variables, such as infecting genotype, that could influence response in the different treatment arms.

In patients with advanced liver disease receiving pegylated interferon alfa 2a in combination with ribavirin, the optimal dose of ribavirin appears to be 1,000 mg/1,200 mg, rather than 800 mg, and the optimal duration of treatment appears to be 48 rather than 24 weeks. (5) Efficacy of different doses of ribavirin in combination with pegylated interferon alfa 2b is under study. Median reductions in white blood cell count and platelet count are greater in patients receiving pegylated interferon than in those receiving standard interferon. (2-4) Thus patients with significant cytopenias in the setting of advanced liver disease who receive antiviral therapy should be monitored closely.

Table 1. Comparison of Treatment With Standard Interferon Alfa 2b Plus Ribavirin vs. Pegylated Interferon Alfa 2b in Combination With Ribavirin for 48 Weeks (Manns et al., Reference 2)

	<i>IFN Alfa 2b (3mU tiw, 48 weeks) Plus Ribavirin 1,000 mg/1,200 mg</i>	<i>PEG IFN Alfa 2b (1.5 mcg/kg) SQ q week Plus Ribavirin 800 mg/d</i>	<i>PEG IFN Alfa 2b (1.5mcg/kg/0.5mcg/kg) Plus Ribavirin 1,000 mg/1,200 mg</i>
SVR in patients with cirrhosis or transition to cirrhosis	41 percent (54/132)	44 percent (60/136)	43 percent (63/146)
SVR in patients no or minimal fibrosis	49 percent (164/336)	57 percent (189/333)	51 percent (175/345)

Table 2. Comparison of Treatment With Standard Interferon Alfa 2b vs. Pegylated Interferon Alfa 2a in Combination With Placebo or With Ribavirin (1,000–1,200mg/D) for 48 Weeks (Roche Data on File)

	<i>IFN Alfa 2b (3mU tiw, 48 weeks) Plus Ribavirin 1,000 mg/1,200 mg</i>	<i>PEG IFN Alfa 2a (180 mcg) SQ q week Plus Placebo</i>	<i>PEG IFN Alfa 2a (180 mcg) SQ q week Plus Ribavirin 1,000mg/1,200mg</i>
SVR in patients with cirrhosis or transition to cirrhosis	33 percent (N=54)	21 percent (N=34)	43 percent (N=56)
SVR in patients without cirrhosis	47 percent (N=390)	31 percent (N=190)	58 percent (N=397)

Another end point of therapy that is pertinent to patients with advanced liver disease is delay in histological disease progression. The premise is that therapy, while not clearing virus, achieves a “clinically meaningful end point” usually defined as a reduction by two or more points in the histological activity index. The clinical relevance of achieving such an end point is currently under evaluation in an NIH-sponsored study (the HALT-C trial) of suppressive therapy with pegylated interferon alfa 2a in preventing the development of complications of advanced liver disease in patients who have previously failed pegylated interferon plus ribavirin. Prior to the availability of results from this trial, it will be necessary to rely on analysis of subsets of patients with advanced liver disease included in multicenter trials of ribavirin plus pegylated interferon alfa 2a or alfa 2b combination therapy. Improvement in liver histology (defined as a reduction of two or more points in the histological activity index) is observed in 68 percent of patients receiving pegylated interferon alfa 2b (1.5mcg/kg SQ q week) plus ribavirin 800mg/day for 48 weeks, compared with 69 percent of patients receiving standard interferon alfa 2b plus ribavirin. (2) Improvement in fibrosis score was seen less frequently

(21 and 20 percent, respectively). (2)

During the lead-in phase of the HALT-C trial, on-treatment virological response has been observed in 30 percent of patients receiving pegylated interferon alfa 2a plus ribavirin who had previously failed standard interferon plus ribavirin. (6) Thirty-nine percent of patients required dose reduction of either interferon or ribavirin, but only 6 percent could not tolerate treatment. (6) Thus, pegylated interferon plus ribavirin, appears to be tolerated in the majority of patients with advanced HCV cirrhosis who have not yet developed clinical complications of their liver disease. Thus, it is likely that hepatitis C therapy can slow histological disease progression in patients with histologically advanced liver disease, and that sustained viral clearance can be achieved in a proportion of patients. Whether this “histological slowing” translates into reduction in development of life threatening complications remains to be determined.

A more problematic group of patients are those with decompensated cirrhosis. Patients with HCV-related cirrhosis who meet criteria for listing for liver transplantation have a five year survival rate of only 50 percent. (7) There are small case series of treating patients awaiting liver transplantation (8,9) that suggest that viral clearance is achievable in a proportion of patients with advanced liver disease although adverse events, including potentially life-threatening adverse events, have been observed. If viral clearance is achieved, these patients may be virus-free after liver transplantation. (8)

Until complete data are available on the safety and efficacy of pegylated interferon plus ribavirin in patients with advanced decompensated HCV-disease, such patients should, when possible, be enrolled in clinical trials. Pegylated interferon plus ribavirin is clearly indicated in patients with compensated HCV disease who have pre-treatment platelet and white blood cell counts that are sufficient to accommodate the cytopenias associated with therapy, but treatment is relatively contraindicated in patients with decompensated cirrhosis, particularly in patients with Childs-Pugh-Turcotte scores of greater than 10. (6)

What of interventions in patients with HCV disease following liver transplantation? Hepatitis C infection of the graft is the rule following liver transplantation, and disease progression is accelerated compared to immune competent patients with HCV disease. (10) Moreover, once histological cirrhosis of the allograft occurs, the risk of complications of liver disease is even higher than in the immune competent patients with cirrhosis. (11) Variables associated with post-transplantation disease progression include pre-transplantation antiviral therapy, HCV RNA level at the time of transplantation, and advanced age of the organ donor, as well as treatment of rejection in the post transplantation period. (10)

There has been interest in “pre-emptive” antiviral therapy early in the post transplantation period as well as treatment of established liver disease of the allograft. Responses to standard interferon plus ribavirin are generally lower following liver transplantation than in immune competent patients. Moreover, since many patients have renal insufficiency secondary to immunosuppressive agents, ribavirin is poorly tolerated, and if used, ribavirin dose should be reduced. Studies of pegylated interferon with or without ribavirin are under way.

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Therapy of Acute Hepatitis C

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Acute hepatitis C is uncommon and difficult to recognize and to diagnose. The main reasons are the following: a) the incidence of new infections with HCV has greatly decreased during the past decade in all civilized countries; b) acute hepatitis C is often mild and asymptomatic; c) there is no specific diagnostic test to identify acute infection with HCV and to distinguish it from reactivation phases that may occur in chronic infection. As a consequence, acute hepatitis C has been difficult to study and there is still limited information about its natural history and optimal management strategies. Early studies, which were conducted mainly in cases with acute post-transfusion NANB (Type C) hepatitis, indicated that this condition has an extremely high propensity to become chronic. On the basis of these observations, and of the data on the treatment of chronic hepatitis C with interferon, a number of studies have been conducted since the early 1990s to assess whether interferon therapy could prevent chronic outcome of acute hepatitis C.

Seventeen studies on the treatment of acute HCV infection with interferon have been published either as full papers (13) or as letters/abstracts (4), including 7 randomised controlled trials, 5 controlled but not randomised trials, and 5 studies without an untreated control group. Of these latter, 2 were randomised trials in which different treatment schedules were compared. In all these studies interferon (alfa or beta) monotherapy was used; there are no available reports on the treatment of acute hepatitis C with interferon plus ribavirin combination therapy or with the pegylated interferons. Overall, 295 treated patients and 162 untreated cases with acute hepatitis C have been included, with a sample size of 6–97 patients in each individual study. Analysis of the 17 published reports reveals great heterogeneity with respect to: (1) inclusion criteria and patients characteristics (for example, some studies included asymptomatic cases seen during prospective surveillance of transfused or otherwise exposed patients while others included only symptomatic cases identified clinically; 7 studies were conducted in PTH cases, 6 in patients with non-transfusion related hepatitis C, and 4 included a mixture of the two subgroups); (2) timing of treatment initiation (early or delayed treatment after infection or after clinical onset); (3) type of interferon used (interferon alfa: 12 studies, interferon beta: 5 studies); (4) dose and schedule of administration (total cumulative dose ranging from 8.4 MU to 780 MU, with daily administration in 4 studies, tiw administration in 10 studies, and daily induction followed by tiw administration in 3 studies); (5) duration of post-treatment followup (ranging from 6 to 36 months); (6) end points of biochemical (ALT) response only: 5 studies; biochemical (ALT) and virological (HCV-RNA) response: 12 studies.

Pooling all data from the 17 studies, an end-of-therapy biochemical (ETR-ALT) and virological (ETR-HCV-RNA) response was seen in 76 percent (range 15–100 percent) and in 82 percent (37–100 percent) of treated patients and in 24 percent (10–44 percent) and in 10 percent (0–20 percent) of untreated patients, respectively. A sustained biochemical (SR-ALT) and virological (SR-HCV-RNA) response was seen in 61 percent (25–100 percent) and 62 percent (37–100 percent) of treated patients and in 26 percent (16–50 percent) and 12 percent (0–20 percent) of untreated cases, respectively.

Results of RCTs

Among the 7 RCTs published, 4 were conducted in PTH cases with an identical schedule of 3 MU tiw of interferon alpha given for 12 weeks. These 4 studies were homogeneous and could be pooled together in a recent meta-analysis (Cochrane review). According to the results of this analysis, the ETR-HCV-RNA was 42 percent (95 percent CI 30–56 percent) with interferon vs. 4 percent (0–13 percent) with no treatment ($p < 0.00001$), while SR-HCV-RNA was 32 percent (21–46 percent) with IFN vs. 4 percent (0–13 percent) without therapy ($p = 0.00007$). IFN therapy was associated with 45 percent (31–59 percent, $p = 0.00001$) and 29 percent (14–44 percent, $p = 0.0002$) increase in ETR-HCV-RNA and SR-HCV-RNA, respectively, compared with no treatment. These results prove that interferon therapy is associated with a significant reduction of chronicity when given to patients with post-transfusion acute hepatitis C, even using a relatively low dose for a relatively short period. However, around 2/3 of the patients treated with this regimen still developed chronic infection.

Other Studies

Other studies have used more aggressive treatment schedules with higher IFN dosages and longer periods of administration, and these approaches have usually resulted in higher rates of sustained virological response. Unfortunately, most of these studies were conducted without a randomised untreated control group. Furthermore, many of them included patients with acutesymptomatic hepatitis C often acquired through a non transfusion source. In these cases, rates of spontaneous resolution of acute hepatitis C might be significantly higher than in asymptomatic cases with PTH. In studies where 5–10 MU of interferon were given daily for 4–12 weeks or up to ALT normalization, followed by the same or a lower IFN dose given tiw for 20–40 additional weeks, rates of sustained virological response reached 83 to nearly 100 percent. In other studies, conducted in similar patient cohorts treated with lower doses of IFN (3–6 MU tiw for 3–6 months), rates of sustained virological response were between 37 and 64 percent. In one study comparing different regimes of daily beta IFN, there was a clear dose dependent effect on sustained response rates. In those studies where an untreated control (although not randomised) group was included for comparison, rates of spontaneous resolution were usually lower (8–21 percent) although a statistically significant difference was rarely obtained due to the small number of patients included. These results indicate that high rates of sustained virological response (24 week SR) can be achieved in acute hepatitis C with IFN monotherapy, in a setting where the expected rate of spontaneous resolution can be estimated around 10–40 percent.

Predictors of Response

Pre-treatment HCV-RNA levels were reported in 5 studies. In 3 of them there was a statistically significant correlation with sustained virological response that was higher with lower viraemia. Interestingly, this association was lost when high dose IFN (5–10 MU daily) schedules were used. The HCV genotype was reported in 7 studies, but in only 2 of them was there a significant association between the HCV type and response (better with HCV2/3 and worse with HCV1).

Tolerability Profile

Detailed description of side/adverse effects seen during therapy has been reported only in 7 studies, with a total of 145 treated patients. The tolerability profile of IFN therapy was very similar to that usually observed when treating patients with chronic hepatitis C. Therapy was well tolerated also in patients with jaundice or very high ALT levels. No ALT flares or deterioration of liver function were observed during therapy, apart from one single patient treated with 10MU daily who developed “acute lobular hepatitis” after HCV-RNA clearance and required a short period of steroid treatment. Overall, the available data do not indicate higher rates of IFN associated side/adverse effects or unexpected adverse effects in patients with acute hepatitis C when compared with what is reported in patients treated for chronic hepatitis C.

Unsolved Issues and Conclusions

Whom to treat: Acute HCV infection may be seen in individuals with minimally elevated or completely normal

ALT and serum HCV-RNA positivity following known exposure or needle-stick injury or in sick patients with symptomatic acute hepatitis C, exemplified by very high ALT levels and jaundice. Available data would indicate that the effect of IFN therapy is independent of the clinical phenotype, although more data is needed to better define outcomes with and without therapy in different patient subgroups and to determine safety of therapy in severely ill cases.

When to start therapy: Immediate treatment of all cases with acute HCV infection means giving unnecessary therapy to those who would have recovered spontaneously. A strategy of delaying therapy by 2–3 months after diagnosis should allow giving treatment only to patients with a high risk of chronic outcome. This approach might be particularly rational in those subgroups of patients in which a high rate of spontaneous recovery is expected, such as children, young adults (particularly women), and patients with jaundice. It remains to be defined whether delaying therapy could reduce its efficacy due to HCV quasispecies expansion towards a more heterogeneous and resistant virus population, as the infection evolves into chronicity. Available data, albeit limited, tends to suggest that delaying therapy by 2–3 months does not compromise the probability of a favorable response to interferon.

How to treat: The optimal schedule in terms of risk/benefit and cost/effectiveness ratio is far from having been defined. Available data would indicate that the minimum requirement for obtaining a significant benefit compared to untreated patients is to use 3 MU tiw for at least 12 weeks. With such a regimen, however, only between 30 and 40 percent of treated patients develop a sustained virological response. More aggressive regimens, based on induction with daily IFN (5 to 10 MU) followed by tiw therapy for 4–6 months, may allow the achievement of a sustained virological response (24 week SVR) in almost 100 percent of the cases. On the basis of these findings, studies with the PEG-IFNs are urgently needed. Combination therapy with addition of ribavirin might not be essential to treat most cases of acute hepatitis C, but this also needs to be explored in clinical trials.

Long-term benefit of treatment: More prolonged followup of patients with acute hepatitis C treated with interferon is needed. Most published studies refer to sustained virological response at 24 weeks after therapy. Studies on the natural history of acute hepatitis C have indicated the need for an accurate and prolonged virological followup to predict long-term outcomes as transient phases of HCV-RNA negativity occur after acute phase in patients with chronic evolution of hepatitis C. Furthermore, long-term clinical outcomes should be accurately modeled in treated and untreated patients considering the low rate of clinically relevant chronic sequelae seen during the first two decades of infection with HCV. Nevertheless, if a near 100 percent eradication of HCV can be achieved with IFN therapy in acute infection, it seems quite difficult not to believe that this result should transfer into significant clinical benefit in many of the patients.

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