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Hepatitis C and HIV

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An estimated 150–300 thousand person are infected with both hepatitis C virus (HCV) and HIV in the United States. Although the management of hepatitis C in HIV infected persons in 2002 is largely predicated on data from persons without HIV, it is important to appreciate the extent to which HIV infection may modify the transmission, natural history, diagnosis, and treatment of hepatitis C. ⁽¹⁾

Transmission

In more than 60 percent of published studies, the rate of HCV transmission from an HIV/HCV co-infected mother to her infant is greater than from HIV uninfected mothers. Increased heterosexual HCV transmission from HIV/HCV co-infected persons also has been reported, but in fewer than half of studies. Nonetheless, these data do not substantially modify existing United States Public Health Service recommendations for recognition and prevention of HIV and HCV transmission. ^(2,3)

Natural History

In the majority of published studies, progression of hepatitis C to cirrhosis and end-stage liver disease occurs more rapidly and in a greater proportion of HIV/HCV co-infected persons, and in several hemophilia cohorts and HIV treatment clinics, end-stage liver disease is *a* or *the* leading cause of death among HIV infected persons. Although the risk of cirrhosis associated with HIV infection varies substantially in different settings, in a meta-analysis, Graham and coworkers estimated that the average risk of progressive liver disease is 2.9-fold (95 percent CI, 1.7–5.0) higher in HIV/HCV co-infected persons. ⁽⁴⁾ Large prospective studies are needed in unbiased HIV/HCV co-infected populations to characterize the risk of cirrhosis more precisely. In the meantime, decisions regarding the timing of medical treatment and the frequency of monitoring HIV/HCV co-infected persons (e.g., by liver biopsy or with fibrosis markers, if available) should be commensurate with the observed increased risk and rate of progression to end-stage liver disease.

Diagnosis and Screening

Because the prevalence of hepatitis C is increased in HIV infected persons and HIV/HCV co-infected persons have an increased risk of cirrhosis and HAART-related liver toxicity, the United States Public Health Service and Infectious Diseases Society of America recommend that all HIV infected persons be screened for hepatitis C by using an enzyme immunoassay for detection of antibodies to HCV.⁽³⁾ HCV antibodies can be detected in the majority of HIV/HCV co-infected persons. However, in some studies HCV antibodies were not be detected in up to 10 percent of HIV/HCV co-infected persons, especially in those with advanced HIV-

related immune suppression (CD4+ lymphocytes < 100/mm³). Thus, it is reasonable to test for HCV RNA in HCV antibody negative, HIV infected persons with unexplained liver enzyme elevations.

Treatment

No medications are approved by the United States Food and Drug Administration for the treatment of HCV infection in HIV infected persons, reflecting the absence of completed, randomized controlled trials investigating the treatment of more than 100 HIV/HCV co-infected persons. Therefore, the timing and choice of medical treatment for HIV/HCV co-infected persons are largely driven by their increased rate of progression of liver disease and the results of treatment of HIV uninfected persons. Nonetheless, a number of important issues in the treatment of hepatitis C in HIV infected persons can be addressed by accumulating published and formally presented data.

1. Sustained virologic responses can be achieved in HIV infected persons. Soriano et al. have demonstrated loss of HCV RNA from serum for >3 years after a course of interferon alpha in HIV infected persons. ⁽⁵⁾
2. The addition of ribavirin to interferon alpha improves the likelihood of on-treatment (and presumably sustained) virologic responses in HIV/HCV co-infected persons. In an interim analysis of data from 110 HIV/HCV co-infected persons randomized to interferon alfa-2b with ribavirin or placebo, HCV RNA was undetectable after 12 weeks of therapy among 23 percent of persons receiving combination therapy compared to 5 percent of those receiving interferon alone. ⁽⁶⁾
3. On-treatment virologic responses to pegylated interferon and ribavirin are better than responses to unpegylated interferon alpha and ribavirin. In ACTG a5071, in which 134 persons were randomized to pegylated interferon alpha plus ribavirin or unpegylated interferon alpha plus ribavirin, week 24 virologic responses were noted in 15 percent of those in the unpegylated arm vs. 44 percent of those randomized to pegylated interferon alpha, an effect that was also observed among persons with genotype 1 infection (7 percent vs. 33 percent, respectively). ⁽⁷⁾
4. Although in vitro studies suggest ribavirin may diminish the efficacy of AZT, d4T, and 3TC, and increase levels of ddI, in several small published and presented case series, HIV RNA levels do not increase more in HIV/HCV co-infected persons taking ribavirin than in controls. Given apparent benefits and the burden of disease, many experts currently recommend its use in the treatment of hepatitis C in HIV/HCV co-infected persons, with careful monitoring.
5. As with HIV uninfected persons, the likelihood of a sustained virologic response in HIV/HCV co-infected persons varies by HCV genotype, pretreatment immune status, and other factors like HCV RNA level, stage of liver disease, gender, possibly race, and duration of treatment, which may need to be longer when virologic responses are delayed and in immunosuppressed persons.
6. Some HIV/HCV co-infected persons will not be able to take existing medical therapies, and liver transplant is rarely available for HIV/HCV co-infected persons.

Conclusion

Given the mounting morbidity and mortality associated with hepatitis C in HIV infected persons, the management tools (e.g., HCV RNA testing and liver biopsy) and therapies (e.g., pegylated interferon alpha and ribavirin) recommended for management of hepatitis C in persons without HIV should be made available for HIV/HCV co-infected persons while research is vigorously conducted to demonstrate their optimal use.

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Injection Drug Use and Hepatitis C

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Injection drug users (IDUs) constitute the largest group of persons infected with the hepatitis C virus (HCV) in the United States, and most new infections occur in IDUs. Controlling the HCV epidemic, therefore, will require developing, testing, and implementing prevention and treatment strategies that will be effective in persons who inject drugs. Preventing morbidity and mortality from HCV will require reducing exposure to HCV, reducing infection among those exposed, and reducing disease among those infected. Injection drug use could be greatly reduced if all those who needed substance abuse treatment could get it (prevention of exposure). HCV spread among drug users can be prevented if drug users have access to sterile syringes, HCV counseling and testing, and outreach programs that teach them how they can avoid acquiring and transmitting the virus (prevention of infection). Finally, barriers to medical treatment must be overcome so that drug users can benefit from advances in HCV treatment (prevention of disease). ⁽¹⁾ HCV treatment may also reduce transmission (prevention of infection), because HCV-infected IDUs are the source for most HCV transmission in the United States. Efforts are particularly important to identify persons with new HCV infections, in whom treatment may be more effective during the acute phase than later, and those with advanced hepatic fibrosis, in whom treatment may improve survival.

Caring for drug user's presents special challenges to the health care team that require patience, experience, and tolerance. Fortunately, substantial research and clinical experience in the prevention and management of chronic viral infections among IDUs, especially HIV infection, has led to the development of effective principles for engaging drug users in health care relationships (Table). ^(2–5) Learning from this experience will be critical for efforts to control HCV. Successful programs invariably adopt a respectful approach to substance users, understand the medical and behavioral sequelae of addiction, and refrain from moralistic judgments. These strategies reflect a harm reduction approach. ^(6,7) Harm reduction strategies help patients reduce high-risk behaviors without imposing unrealistic demands for global change. When ceasing all drug use is not likely in the immediate future, other measures must be taken to help patients reduce the harmful consequences of injection drug use. ^(8,9)

Decisions about the treatment of HCV infection in patients who use illicit drugs, as in other patients, should be made by the patients together with their physicians based on individualized risk-benefit assessments. ⁽¹⁾ Adherence, psychological side effects, and the possibility of reinfection present challenges to effective treatment for some drug users. Fortunately, an array of effective strategies exists to overcome each of these challenges. Attention to ensuring optimal adherence is important for all patients, not just those who use drugs. ⁽¹⁰⁾ This is so because although certain risk factors for noncompliance have been identified, including depression, psychological stress, homelessness, lack of social support, and drug use, physicians are not able to predict accurately which patients will adhere to a treatment regimen. ⁽¹¹⁾ Effective strategies for improving adherence range from basic clinical practices—such as establishing a consistent, trusting physician-patient relationship, providing clear information about intended effects and side effects of medication, and paying careful attention to perceived side effects—to specialized tools such as electronic reminder systems, directly observed therapy, and cash incentives. ^(12–17) Simplifying complex treatment regimens, treating depression, or helping a homeless patient find housing can help improve adherence.

Patients may also benefit from counseling addressing individual barriers to and facilitators of adherence in the patient's life.

Table. Principles for managing health care relationships with substance-using patients .

1. Establish a climate of mutual respect.
2. Maintain a professional approach that reflects the aim of enhancing patients' well-being; avoid creating an atmosphere of blame or judgment.
3. Educate patients about their medical status, proposed treatments, and their side effects.
4. Include patients in decision-making.
5. If possible, establish a multidisciplinary team consisting of primary care physicians, HIV specialists, psychiatrists, social workers, and nurses.
6. Have a single primary care provider coordinate the care delivered by such a team to maximize consistency and continuity.
7. Define and agree on the roles and responsibilities of both the health care team and the patient.
8. Set appropriate limits and respond consistently to behavior that violates those limits.
9. Minimize barriers to participation (penalties for missed visits, etc.).
10. Recognizing that patients must set their own goals for behavior change, work with patients to achieve commitment to realistic goals for healthier behaviors.
11. Acknowledge that abstinence is not always a realistic goal; emphasize risk reduction measures for patients who continue to use drugs.
12. Acknowledge that sustaining abstinence is difficult and that success may require several attempts
13. Be familiar with local resources for the treatment of drug users

The psychological side effects of interferon-based regimens for the treatment of HCV infection is of concern in all patients. Interferon may have severe psychological side effects in patients with or without pre-existing psychiatric disorders. (18,19) To minimize psychological toxicity, all patients should be screened for depression and other mental health conditions before undergoing HCV treatment, treated for these conditions if necessary, and monitored for them during HCV treatment.

Because those successfully completing HCV therapy may be at risk for reinfection, drug users need detailed counseling and support to avoid risky injection practices in case they continue or return to injecting drugs. Those who inject drugs after receiving effective treatment for HCV infection can avoid reinfection by using a new sterile syringe for each injection and by not sharing their injection equipment with other users. (20,21) There are 174 syringe exchange programs in 120 cities in 34 states in the United States, and the number is increasing yearly. For drug users without access to such programs, physicians in at least 46 states are allowed by law to prescribe syringes so that their patients can avoid acquiring and transmitting blood borne infections. (22–24) IDUs can master safe injection practices, and many do inject safely. When given access to sterile syringes, IDUs readily make use of them, reducing their high-risk behavior (25–27) and rates of disease transmission. (28,29) Physicians should refer patients who inject drugs to syringe exchange programs or, if necessary, prescribe syringes for them. HCV may be more readily transmitted than the human immunodeficiency virus (HIV) through the sharing of injection equipment other than syringes, such as “cookers” (bottle caps, spoons, and other containers used to dissolve drugs) and “cottons” (filters used to draw up the drug solution into a syringe). (30) Thus, it is particularly important for physicians to instruct their patients not to share these items. (20,21)

All injection drug users should be offered treatment for substance abuse and such treatment should be provided to those wishing it. Medical services should be integrated with substance abuse treatment. (3) Alcohol treatment is particularly important because of the strong effect of heavy alcohol intake on the progression of hepatitis C. Finally, all patients with HCV infection should be instructed in how to avoid transmitting the infection to others. Patients should be warned that their blood may be infectious even in minute quantities. Those who inject drugs should be instructed not to share syringes or any other injection equipment with other persons and to avoid blood contact with others. They should be given biohazard sharps containers or instructed to safely dispose of injection equipment in puncture-resistant containers. (31)

Clinical Data

There is abundant evidence that when treatment strategies for drug users take into account the circumstances of their lives, very high rates of adherence can be achieved. (11,15–17,32–38) Several recent studies have demonstrated the safety and effectiveness of hepatitis C treatment in drug users, even when they are not completely abstinent from drug use. (39–41) Backmund et al. reported a 36 percent sustained virologic response rate in 50 injection drug users who were treated simultaneously for HCV infection and substance abuse, even though 80 percent of the patients relapsed to drug use. (39) Sustained response rates were not significantly different for patients who relapsed and those who did not. All patients were treated and supervised by physicians who specialized in both hepatology and addiction medicine. Patients who relapsed to drug use were offered opiate replacement therapy and were allowed to continue their HCV treatment even if they injected heroin again. The strongest predictor of virologic response was whether patients continued to keep their appointments; 45 percent of those who kept > 67 percent of their appointments but only 6 percent of those who did not had sustained virologic responses. This study demonstrates the importance of combining expertise in both hepatology and substance abuse and maintaining strong relationships with patients that can be sustained even through relapse to drug use.

Sylvestre et al. have treated 67 methadone maintenance patients with combination interferon/ribavirin, with an interim sustained virologic response rate in the first 59 patients of 29 percent, a rate identical to that in a comparison group of nonopioid-dependent patients. (40) No serious side effects occurred, although 61 percent of the patients had a prior psychiatric diagnosis. Response rates were not significantly different in patients who did or did not have 6 months of sobriety, or in patients who did or did not consume alcohol. They were not significantly worse in patients who continued using drugs unless they used every day. This study demonstrates that HCV can be effectively treated in patients receiving maintenance opiate replacement therapy despite substantial pre-existing psychiatric disease and despite ongoing, intermittent drug use.

Finally, Backmund et al. reported no reinfection during 24 weeks in 10 patients who continued to inject heroin. (39) They carefully instructed their patients how to avoid acquiring HCV when injecting drugs. Dalgard et al. reported one reinfection during 5 years in 9 patients who relapsed to injection drug use after sustained virologic responses to HCV treatment. (41)

Success in treating HCV infection in IDUs will require collaboration between experts in hepatitis and substance use to create programs specifically designed for drug users. Efforts to control HCV, including both prevention and treatment, can benefit from the expertise of those with experience working with drug users. Substance abuse treatment professionals have expertise working with drug users in treatment. Harm reduction workers and many substance abuse researchers have expertise working with out-of-treatment drug users. And many AIDS medical providers have expertise providing medical care to drug users both in and out of substance abuse treatment. Involvement of these professionals in HCV prevention and treatment efforts will greatly improve their effectiveness.

A sound policy for the control of the hepatitis C epidemic will require implementing prevention and treatment programs designed for IDUs, the group most severely affected by the epidemic. (42) Controlling the HCV epidemic, therefore, will require further research to develop and test prevention and treatment strategies that will be effective in persons who inject drugs. In the meantime, however, substantial progress can be made to control hepatitis C if existing knowledge and resources are brought to bear.

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Alcohol and Hepatitis C

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Excess alcohol consumption can worsen the course and outcome of chronic hepatitis C. ⁽¹⁻³⁾ However; adverse effects of moderate amounts of alcohol intake have not been clearly shown. ⁽⁴⁾ Alcohol use has been reported in some studies to be associated with higher HCV RNA levels and lower responses to therapy. ⁽⁵⁾ Despite a large number of publications on the topic of alcohol and hepatitis C, current evidence from the literature is not adequate to provide clear and definitive recommendations regarding alcohol use in patients with hepatitis C. In the absence of conclusive data, a conservative approach is taken and abstinence is usually recommended.

What Level of Alcohol Intake Is Harmful in Chronic Hepatitis C?

Poynard and coworkers compared liver histology of patients with hepatitis C drinking >50 g per day to that of non-drinkers and found a 34 percent increased rate of progression of fibrosis in heavy drinkers. ⁽¹⁾ Associations between fibrosis progression and lesser amounts of alcohol intake were not significant, but the measurement of alcohol intake was assessed in a uniform, standardized manner. The HCV National Register Steering Group in the UK traced 924 patients who had received an anti-HCV-positive unit of blood for an average of >10 years after transfusion and assessed alcohol intake using validated questionnaires. ⁽⁶⁾ Liver-related deaths were increased among those who drank >20 units per week (approximately 30 g per day) in both patients with hepatitis C and controls. The Dionysos study analyzed hepatitis virus markers, alcohol intake (assessed by questionnaires of daily and lifetime intake), and clinical and biochemical evidence for liver disease among 6,917 unselected residents of two Northern Italian cities. ^(3,7) In all, 2.3 percent had HCV RNA and 62 percent drank alcohol, including 21 percent who drank more than 30 g per day. Both control subjects and persons with HCV who drank more than 30 g per day for >10 years had a threefold higher risk of cirrhosis (95 percent CI = 1.2 to 7.4, p<0.01). Intake below 30 g per day did not increase the risk of clinically apparent cirrhosis, but histology was not assessed in most patients. Harris and coworkers analyzed factors associated with cirrhosis among 206 patients who developed hepatitis C after

transfusion and were followed for an average of 15 years in addition to a cohort of controls who were transfused but did not develop hepatitis C. (8) Among those with hepatitis C, 17 percent developed cirrhosis. The risk of cirrhosis increased fourfold among those who were also heavy drinkers (>80 g per day). Corrao and Arico analyzed results from two hospital-based, case-control studies of 285 patients with cirrhosis and 417 controls. (4) A lifetime daily alcohol intake of >50 g per day was associated with an increased risk of cirrhosis in both HCV-positive and negative subjects. The combination had an additive effect on the risk, and these risks were multiplied (synergism) at very high levels of alcohol intake (>125 g per day). Wiley and coworkers analyzed factors associated with more advanced liver disease in a cohort of 176 patients who underwent liver biopsy for chronic hepatitis C. (2) Alcohol intake of > 80 g daily was associated with a higher rate of cirrhosis (56 percent vs. 22 percent) and an increase in the estimated rate of progression of fibrosis. In a study from Japan, Khan and Yatsunami found higher degrees of fibrosis on liver biopsies from patients with chronic hepatitis C who drank alcohol compared to those who did not, and this increase was seen with both heavy (>80 g per day) and “moderate” (<80 g per day) alcohol intake. (9) Further delineation of effects of lower levels of alcohol intake was not given. Excess alcohol intake can also predispose to the development of liver cancer. (10) Thus, multiple studies have shown that heavy alcohol intake increases the risk of cirrhosis and liver cancer in hepatitis C, but the effects of moderate alcohol intake have not been adequately evaluated.

Are There Gender Differences in Effect of Alcohol on Progression of HCV Infection?

Chronic hepatitis C is often milder in women, but women may be more sensitive to the adverse effects of alcohol. The Dionysos cohort study found the risk of cirrhosis was twice as high in women as in men with the same alcohol intake. (3,7) Wiley et al. found a lower alcohol threshold for development of cirrhosis in women. (2) Thus, women may be at increased risk of alcohol effects on chronic hepatitis C.

What Are the Effects of Alcohol Consumption on Treatment of Hepatitis C?

Alcohol can affect the outcome of therapy in decreasing adherence or interfering with the antiviral actions of interferon or combination therapy. Virtually all large trials of therapy of hepatitis C have excluded persons who have a recent history of alcohol abuse, requiring a one- to two-year period of abstinence before therapy is initiated. However, the need for a period of abstinence has never been shown. Among patients treated for hepatitis C, a proportion continued drinking, and the ultimate response rate correlated inversely with the level of alcohol intake during therapy. The mechanism of the decreased response rate in patients drinking alcohol has not been defined. Some studies have shown that alcohol intake is associated with higher levels of HCV RNA (1,5) but other studies have not, (2,3,10) and the increase in HCV RNA levels with drinking alcohol has been modest. Thus, continued alcohol intake during therapy is likely to adversely affect the response to treatment, and both counseling and monitoring before and during therapy is recommended.

Does Alpha Interferon Therapy Cause Increase in Rate of Relapse Among Persons with a History of Alcohol Abuse or Dependence?

Relapse in alcohol intake during alpha interferon therapy has been reported, but the rate of relapse has not been compared in studies using untreated control patients. Nevertheless, the depression, irritability, and anxiety that occur in 20–30 percent of patients treated with alpha interferon are likely to be difficult for the patient with a recent history of alcohol dependence and predisposition to relapse.

Conclusions

While the effects of heavy daily alcohol intake on the course of chronic hepatitis C appear to be incontrovertible, lesser amounts of alcohol may not be harmful. On the other hand, abstinence appears to be prudent for the patient with chronic hepatitis C, particularly while receiving a course of alpha interferon or combination therapy. Patients with a history of alcohol abuse or dependence should be asked to be abstinent for a period before starting therapy and need to be supported by professional counseling and monitoring during therapy. Better studies using validated instruments to measure alcohol intakes in larger

numbers of patients, followed for longer periods and with careful histological documentation, are needed to better define the effects of moderate alcohol intake on chronic hepatitis C and the need for abstinence before and during therapy. At the present time, there is no reason to withhold antiviral therapy of chronic hepatitis C from the patient with a history of alcoholism as long as adequate support can be provided during the period of therapy.

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Special Populations

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The current recommendations for the *management* of patients with chronic hepatitis C are derived from a number of excellent multicenter trials. However, these trials primarily involve the *treatment* of a *select group* of patients with a single therapy, interferon plus ribavirin in combination. The selection of appropriate candidates for therapy involves an informal assessment of the patient's eligibility for treatment, followed by *screening* of all eligible candidates. It is unclear how many patients are not initially assessed as eligible, yet among those who are considered eligible and subsequently screened for therapy, reports from recent clinical trials indicate that 30–50 percent do not satisfy inclusion criteria. (1–4) The most common reasons for exclusion include severe psychiatric illness; active alcohol and substance abuse, comorbid illnesses such as autoimmune disease, hemophilia, and renal disease; decompensated liver disease; normal ALT; and refusal to participate. In addition, recent data on the response rate of those who receive treatment with combination therapy (standard or pegylated interferon plus ribavirin) suggest that at best, 50 percent achieve a sustained viral response (SVR). (5–7) These data indicate that at least 60 percent of anti-HCV-positive patients are either ineligible for therapy or do not respond to the available therapy. This suggests that the bulk of data obtained regarding hepatitis C and the management recommendations that followed were gathered from a small minority of pristine patients. While extrapolations regarding the management of the larger population of patients with HCV and confounding medical problems were made, the body of emerging data indicates that this may not have been appropriate. It is evident from previous discussions during this Conference that some exclusion criteria may have been too rigid, and that the reported response and adverse event rates may not be widely applicable. As a result, it appears that a large proportion of patients with HCV do not benefit from current antiviral therapy. What is missing from the literature is management guidance with respect to this large group of patients.

Before management decisions can be made, it is necessary to ask several important questions. First, “Is current anti-HCV therapy optimal?” Clearly, if therapy is optimal, all available resources should be channeled into treating as many patients as is safely possible. However, if available therapy is not optimal, research into alternative therapies should be pursued. Optimal therapy should be considered both safe and efficacious among the broadest cohort of affected patients. Current accessible data from anti-HCV treatment trials with pegylated interferon plus ribavirin report SVRs of approximately 50 percent among the relatively small group who qualify for treatment. This compares favorably with previously reported overall SVRs of 38 percent among those treated with standard interferon plus ribavirin. While few published data exist regarding the response rates of standard IFN plus ribavirin post-marketing, review of a few studies, as well as unpublished data obtained from several investigators indicates that the actual observed SVR is closer to 15–25 percent. ^(1,2) Although the SVRs with pegylated IFN plus ribavirin are expected to be higher, using the above data it is likely that less than 50 percent of treated patients will achieve an SVR. Therefore, it seems prudent to encourage research into novel forms of therapy.

Preliminary work on a number of potential candidates is already under way. It appears that as with therapy for HIV, therapy for HCV may require a multi-drug approach that exploits the replicative process at various stages, thereby containing, or at best eliminating, infection. Possible therapies include protease inhibitors, helicase inhibitors, NS5B RNA-dependent RNA polymerase blockers, modified ribavirins, and HCV immunotherapy. ⁽⁸⁾ These and other novel therapies will be discussed in detail in a subsequent discussion and may be the best hope for successful treatment of hepatitis C.

Second, “In lieu of other therapies, what can be done to increase the eligibility of HCV-infected patients currently considered ineligible for treatment?” A great deal of effort has recently been expended in attempts to enlarge the pool of eligible candidates, therapy either by liberalizing the inclusion criteria or by prophylaxing against or aggressively treating common side effects. Crude estimations from available data suggest that among those excluded from treatment trials, 20 percent have ongoing alcohol abuse, 19 percent have severe psychiatric illness, 12 percent use illicit intravenous drugs, 10 percent have comorbid disease, 10 percent have decompensated liver disease, 5 percent have normal ALT, and the remainder refuse therapy, are of advanced age, are undergoing evaluation for treatment, or are homeless. Treatment strategies for those with alcohol or drug abuse, normal ALT, co-infection with HIV, and those with organ transplants have been extensively discussed during the course of this Conference. While not discussed herein, there are some helpful data regarding the management of patients with HCV and hemophilia, renal disease, autoimmune hepatitis, severe psychiatric disease, and anemia. For example, recent studies in hemophiliac children with HCV suggest that therapy with IFN plus ribavirin is safe and well-tolerated in carefully monitored patients. ⁽⁹⁾ Conversely, data show that hepatitis C is common among hemodialysis patients and may adversely affect long-term graft survival in renal transplant recipients. Unfortunately, ribavirin is not dialyzed during standard dialysis and is associated with a dose-dependent hemolytic anemia, thereby limiting its use. Likewise, therapy of hepatitis C after renal transplantation has been disappointing. While one study showed an encouraging 16 percent sustained viral response rate and a 3 percent rejection rate, several others have shown a 50 percent incidence of graft rejection in renal transplant recipients. ⁽¹⁰⁾ As a result, an upcoming NIH workshop is planned to define the impact of HCV on the morbidity and mortality of those with end-stage renal disease as well as identify appropriate HCV treatment strategies in such patients. Trials in patients with HCV and autoimmune disease (hepatitis, sarcoidosis, SLE, etc.) advocate primary treatment of the autoimmunity as it appears that the risk of augmenting HCV with steroids is less than the risk of exacerbating autoimmune disease with interferon. ⁽¹¹⁾ However, it is unclear whether this recommendation is absolute or whether there are “degrees” of autoimmunity (low ANA, mild disease) for which treatment with interferon is not contraindicated. Finally, attempts to increase the number of patients completing the full course of HCV antiviral therapy have been relatively successful using prophylactic antidepressants, aggressively treating interferon-induced depression, and advocating the use of erythropoietin or GM-CSF for hematopoietic side effects. ^(12,13)

It is clear that the approach of liberalizing inclusion criteria and aggressively treating side effects may be laudable and reasonable among some patients, particularly those with genotypes 2 or 3 in whom the likelihood of achieving a SVR is approximately 80 percent. However, this approach may be more difficult to

defend when considering those with less favorable genotypes and severe coronary or cerebrovascular disease, severe diabetes, mental retardation, seizures or neurologic disorders, or cytopenias. In addition, there are groups of patients for whom the safety and efficacy of IFN plus ribavirin are less clear, specifically the elderly and African-Americans. It is reasonable to assume that patients with severe CAD or cerebrovascular disease are at increased risk for the potential adverse effects of hemolytic anemia. Similarly, interferon has been suggested to increase insulin resistance and it is possible that severe diabetes may complicate response to HCV antiviral therapy by its effects on hepatic steatosis. However, to my knowledge, no data exist regarding the treatment of HCV-infected patients with mental retardation, seizures or neurologic disorders, and the elderly. By contrast, a great deal of data is beginning to surface with respect to the disparity in response to antiviral therapy among patients of different racial groups. Although the numbers of patients are small, the data suggest that African-American patients with HCV are less likely to respond to IFN plus ribavirin than whites, Hispanics, or Asians. In addition, some trials indicate that African-American patients are more likely to suffer treatment side effects. At present, the NIH is conducting a trial evaluating the efficacy of IFN plus ribavirin therapy among African-American patients infected with HCV.

In this author's view, the potential risk of adverse events does not appear to be balanced by the small potential benefit of a sustained viral response in the patient groups described above. Even if the goal is halting the progression of fibrosis, an appropriately designed prospective trial is necessary to definitely demonstrate the histologic benefit of interferon therapy in the absence of loss of virus before it can be routinely recommended to push interferon in those currently considered ineligible or who suffer severe side effects. Recommendations for the management of HCV among these groups should be individualized until further study, such as with pegylated interferons, provide guidance.

Finally, and importantly, "What is the appropriate management of patients who cannot be treated or fail to respond to treatment?" It is incumbent upon us to remember that "management" does not necessarily mean "treatment." Management involves providing education and counseling, initiating treatment when indicated, and supplying supportive care to those for whom no clear options are available. The latter is particularly important in order to allay fears and ensure that patients are not lost to follow-up. At present, many patients with HCV who are not on treatment have a physical examination, blood tested for aminotransferase and AFP levels, and an abdominal US (if indicated) every 6–12 months. While these practices are conventional, few data can provide an absolute timetable for follow-up. It is well-known that ALT level fluctuates during the course of HCV infection and is not an adequate marker of progression of disease. ⁽¹⁴⁾ Although abnormalities in albumin and prothrombin time may provide more information regarding the degree of liver disease, they are not specific for liver injury, are only prognostic markers, and decline at a rate that varies from patient to patient. In addition, somewhat contradictory information exists in the literature. On the one hand, the Japanese literature recommends AFP plus ultrasound screening every 3–4 months to detect early hepatic tumors, while on the other, several studies suggest that AFP is not a sensitive surveillance test for the presence of HCC and a number of other tests including descarboxyprothrombin time, isoforms of AFP, and an isoenzyme of γ GT have been advocated as alternatives. ^(15–17) Similarly, the pros and cons of the usefulness and timing of liver biopsy have been much debated and intensive research in identifying surrogate serum markers of inflammation and fibrosis is ongoing. These data underscore the controversies and challenges regarding the type and schedule of tests and visits needed to appropriately follow patients with HCV.

In the meantime, it is important that physicians provide HCV-infected patients with up-to-date information about the expected course of their infection, methods of preventing transmission of HCV, and avoidance of practices (such as alcohol abuse) which may contribute to worsening liver function. In addition, we must provide *balanced* advice regarding the risks and benefits of current therapy and any new therapies as they become available. Until further data are known, it is reasonable to perform a physical exam, perform a liver panel (include PT and platelet count), and check an AFP every 6–12 months. Finally, in lieu of a serum marker of hepatic fibrosis, it may also be prudent to consider a liver biopsy every 3–5 years, particularly in those whose liver function appears to be deteriorating. While it is clear that abnormalities in these tests will be apparent before clinical symptoms appear, data to assist in determining the frequency with which they should be obtained are necessary.

Hepatitis C research has come a long way in the past 10 years. We are able to identify and quantify the virus, and in recent years, extensive investigation has identified ways to successfully treat some infected patients. Treatment of the approximately 30 percent of eligible patients with HCV has taken center stage, and a great deal of data has been generated regarding this population. However, it is clear that our obligation is to the universe of patients with HCV, not merely those who are candidates for current therapy. As physicians we must remember to provide “care,” not merely “treatment.” It is quintessential that we not marginalize our patients in our zeal to eradicate their disease. Solutions to the above problems are essential if we are to adequately follow and advise patients for whom therapy is not an option or has failed.

[Note: Beyond the scope of this discussion is the management of institutionalized patients infected with HCV, particularly those in correctional facilities. In many such institutions the mechanisms necessary to provide appropriate management are not available, and the cost of treatment is prohibitive. In fact, the focus on treatment of HCV rather than treatment of substance abuse or other comorbid illnesses may be counterproductive. Further study into the medical and social implications of HCV infection in institutions is needed.]

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Side Effects of Therapy and Management

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Introduction

The side effect profile of combination therapy of standard interferon plus ribavirin is well known. In the registration trials of these agents, significant side effects were noted that resulted in discontinuation of treatment in approximately 20 percent of subjects. ^(1,2) The major types of side effects of combination therapy include influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms. Pegylated interferons (pegylated interferon alfa-2a and pegylated interferon alfa-2b) have significantly improved pharmacokinetics, ^(3–5) resulting in improved antiviral efficacy, that also has the potential to alter the side effect profile. This review will focus on the prevalence and management of side effects reported with the use of pegylated interferon plus ribavirin for the treatment of chronic hepatitis C.

Peginterferon Alfa-2a Plus Ribavirin

The results of a large, phase III clinical trial of peginterferon alfa-2a plus ribavirin have recently been reported in preliminary form. ⁽⁶⁾ Over 1,100 subjects were randomized to therapy with peginterferon alfa-2a plus ribavirin, peginterferon alfa-2a plus placebo, or standard interferon alfa-2b plus ribavirin. Premature withdrawal from therapy due to laboratory abnormalities or adverse events in the combination arms with either pegylated interferon alfa-2a (10 percent) or standard interferon alfa-2b (11 percent) was comparable. The most common reason for withdrawal was depression, although the rate of depression in subjects treated with peginterferon alfa-2a was lower than those treated with standard combination therapy (22 percent vs. 30 percent). Influenza-like symptoms were also lower in the peginterferon treatment groups.

Dose reductions of peginterferon alfa-2a for any adverse event were required in 32 percent in the combination arm. Laboratory abnormalities such as anemia, neutropenia, and thrombocytopenia were the most frequent indications for dose reductions. Thus, approximately 25 percent of participants required at least one dose reduction (temporary or permanent) for laboratory abnormalities during therapy. The frequency of ribavirin dose reduction for anemia was similar in the combination arms of the study. The frequency of dose reduction for neutropenia was greater in the peginterferon combination arm compared to standard interferon (20 percent vs. 5 percent). Thrombocytopenia was also more common in the peginterferon arms. However, only a minority of patients discontinued therapy due to laboratory abnormalities in the two combination arms (peginterferon + ribavirin = 3 percent vs. standard interferon plus ribavirin = 1 percent).

Peginterferon Alfa-2b Plus Ribavirin

In a large, phase III study that compared the antiviral efficacy of two different regimens of peginterferon alfa-2b plus ribavirin to standard interferon alfa-2b plus ribavirin, ⁽⁷⁾ premature withdrawal from therapy due to an adverse event occurred in 14 percent of participants treated with the higher dose of peginterferon. Discontinuation of therapy due to neutropenia (~1 percent) or anemia was very uncommon. Dose reductions for any adverse event occurred in 42 percent of patients treated with the higher dose peginterferon alfa-2b plus ribavirin compared to 34 percent treated with standard interferon and ribavirin. Dose reduction due to neutropenia was also more common in the higher dose combination (18 percent) than in the low dose pegylated (10 percent) or the standard interferon combination arms (8 percent).

Few differences were noted in the side effect profile in the pegylated combination arms compared to those seen with standard interferon plus ribavirin. The incidence of depression was similar in all treatment arms (~30 percent). The increase of several flu-like symptoms over standard therapy was attributed to the higher dose of interferon provided by the pegylated preparation. Injection site reaction, generally mild, was also noted to be more common in those receiving peginterferon alfa-2b (58 percent) compared to the standard interferon alfa-2b (36 percent).

Management of Side Effects

General strategies for management of side effects of combination therapy have been previously reviewed

and are applicable to the newer agents. ⁽⁸⁾ Before starting treatment, patient education about expectations and self-management techniques are most beneficial. Regular follow-up visits during therapy and a supportive environment will permit early detection and intervention for developing adverse events and will also encourage patient adherence to the medication regimen.

Depression is a frequent and often dose-limiting side effect of combination therapy with pegylated interferon and ribavirin. The mechanism of interferon-associated depression remains largely speculative. Directed questioning of the patient and significant others, when available, about the presence and severity of depression is warranted. Treatment should be discontinued immediately in patients with suicidal ideation and, for patients judged to be in potential danger; immediate referral should be made to a mental health professional. Antidepressants, particularly selective serotonin-reuptake inhibitors, are prescribed frequently for less severe depression associated with antiviral therapy. Prophylactic paroxetine, evaluated in patients treated with high-dose interferon alfa-2b for melanoma, was shown to minimize depressive symptoms and decrease the rate of interferon discontinuation compared to placebo. ⁽⁹⁾ However, prophylactic strategies could result in inappropriate use of these agents in the 70–80 percent of patients that do not develop significant depression while on combination therapy for hepatitis C. Thus, additional information is needed concerning the mechanisms of interferon-associated depression and the optimal treatment regimen that will minimize disruptions to antiviral therapy.

Anemia, thrombocytopenia, and especially, neutropenia occur regularly in patients treated with peginterferon and ribavirin. To date, management of hematologic abnormalities in all phase III clinical trials has relied upon dose reductions of study medications according to predetermined criteria. This has proven to be a safe and effective approach to management; hemoglobin, absolute neutrophil and platelet counts improve quickly so that discontinuation of therapy is rarely necessary. Nevertheless, the possibility that adherence to study medications may affect sustained virological response has encouraged evaluation of erythropoietin and granulocyte stimulating factors as adjunctive therapies to minimize dose reductions of interferon and ribavirin. Preliminary data suggest that the dose of ribavirin may be maintained with epoietin alfa. ⁽¹⁰⁾ However, no study thus far has demonstrated that the use of stimulating factors to maintain full doses of interferon and ribavirin will improve sustained virological response. Furthermore, the incidence of serious sequelae associated with hematologic abnormalities appears to be low. Thus, these adjunctive agents cannot be routinely recommended as treatment for the hematologic abnormalities induced by combination therapy for hepatitis C. Additional studies are required to better understand the consequences of neutropenia in the patient with chronic hepatitis C and to determine whether lower levels of neutropenia can be safely tolerated. Detailed investigations of the relationship between dose reduction on outcome and prospective trials of alternative methods for managing hematologic abnormalities with growth factors are necessary.

In summary, no unique or unexpected side effects have been noted with the administration of pegylated interferons plus ribavirin in two large phase III trials of these agents. Hematologic abnormalities requiring dose reductions may be more common with the newer agents. Additional emphasis on improving patient management strategies is warranted.

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Future Therapy of Hepatitis C

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Introduction

Although current therapies are effective in more than half of all treated patients, therapy is costly, associated with significant morbidity, requires substantial commitment from the patient and medical staff, and is not suitable for all patients. Thus, there is an important need for more effective therapies, and this remains a priority in terms of continued research endeavours. The lack of an effective cell culture system and small animal model for HCV infection has hampered the development and discovery of alternative effective small molecules or vaccines. Nevertheless, the ideal therapy for patients with chronic hepatitis C would be cost-effective, be orally bioavailable, have an acceptable side effect profile, and be effective in the majority of patients. Such therapies are probably unlikely to be developed in the near future. Therapies in current development and/or in human clinical trials will be discussed.

Adjuvant Agents That May Be Added to Current Regimens

Alternative Interferons or Interferon Inducing Agents

The development of alternative type 1 interferon compounds or methods of delivering longer acting preparations with theoretically different pharmacokinetic profiles may lead to the availability of alternate interferon preparations. Whether these will improve or enhance sustained response rates or side effect profiles in combination with ribavirin or other agents in larger clinical trials is unknown and is currently under early stage clinical investigation. Oral interferon inducing agents are also in pre-clinical trials, and probably phase I human development will occur in late 2002.

IMPDH Inhibitors. The development of compounds which specifically inhibit inosine 5 monophosphate dehydrogenase (IMPDH) may provide an alternative for patients with chronic hepatitis C when combined with interferon. This enzyme, which is also inhibited by ribavirin and mycophenolate, is essential for modulation of host cellular pathways and has antiviral and immunomodulatory effects. Phase I and II clinical trials in patients with chronic hepatitis C have shown one such agent (VX-497) to be safe, but with no observable antiviral effect when given alone. As in the initial ribavirin monotherapy studies, ALT reductions were also noted in some patients. A subsequent phase II, randomized, double-blind study of VX-497 combined with interferon in treatment naïve patients for 4 weeks indicated safety in combination with interferon, but no enhancement of antiviral activity. Further development of more potent and specific IMPDH inhibitors will require randomized controlled clinical trials to determine their efficacy and future place in the management of patients with chronic hepatitis C.

Alternative Ribavirin-Like Drugs. Other agents similar to ribavirin that bias the immune response toward a

type 1 profile are in development. These drugs will further test the hypothesis that a significant component of the benefit of ribavirin is by its action as a type 1 cytokine enhancer. Levovirin, the I-isomer of ribavirin, is associated with lesser degrees of hemolytic anemia, appears safe in animal studies, and has been well tolerated in phase I dose finding studies in healthy volunteers. Viramidine, a ribavirin prodrug, also produces less hemolysis, is converted rapidly to ribavirin in vivo, has a three- to sixfold longer residence time in the liver, and is less concentrated in peripheral blood red cells compared to ribavirin. The safety, utility and future development of these and other similar agents will need to be established in larger-scale clinical trials in combination with alpha interferons.

Other Immunomodulators

Histamine. Histamine dihydrochloride, through binding of H2 receptors on phagocytic cells, disrupts NADPH-oxidase responsible for the production of reactive oxygen species and is also an immunomodulator acting on NK and T cells. This compound has been tested in combination with interferon in certain malignancies and in initial pilot studies in patients with hepatitis C. In two phase II studies where histamine dihydrochloride was administered to patients along with interferon, or in combination with interferon and ribavirin, the data suggest there may be benefit in terms of end of treatment and sustained response rates. An ongoing European, multinational trial is currently evaluating the safety and efficacy of peginterferon plus ribavirin vs. peginterferon plus ribavirin plus histamine injections in hepatitis C patients.

Molecular Based Therapies

Hepatitis C Specific Viral Enzyme Inhibitors

Based upon current knowledge of the structural biology and actions of HCV specific enzymes during viral replication, many groups are pursuing the development of compounds that specifically inhibit enzymes critical to the HCV life cycle. There are three initial and important virus specific targets for antiviral drug development including the HCV protease, polymerase, and helicase enzymes. The efficacy of these compounds is now being evaluated using the HCV replicon model system, and promising compounds will undergo testing in animals for oral bioavailability and toxicity. The structure of many potential inhibitors has been described, and a number of early phase I trials are being undertaken with HCV specific protease and polymerase inhibitors in chronic hepatitis C patients.

Barriers to the development of these agents are numerous, and include the shallow protease binding cleft, viral drug resistance, and the fact that such agents will be required to have activity profiles against a broad range of HCV genotypes. Also, the importance of combination therapy to multiple enzyme targets has been demonstrated in the HIV clinical setting to avoid the selection of resistant viral strains. As such, multiple targets of this class will be required in order to reduce or eliminate drug resistant HCV quasispecies, and assays to detect viral resistance patterns must be established.

Antisense Oligonucleotides

HCV specific antisense oligonucleotides, short sequences of 15–40 nucleotides stabilized to protect these molecules against cellular nuclease degradation, can hybridize to and prevent translation of viral RNA and thus inhibit disease causing protein expression. A 20 nucleotide phosphorothioate oligonucleotide with a sequence complementary to the HCV translation initiation region (ISIS 14803) is currently undergoing phase I and II clinical trials in patients who have failed to respond to available antiviral therapies. Some patients have had viral load reductions of = 1 log drop in HCV RNA after 28 days of therapy. For unexplained reasons these viral load changes are sometimes, but not always, associated with asymptomatic but significant ALT elevations. The efficacy and safety of this compound is now being evaluated in phase II studies of 12 weeks' duration in previous nonresponders to other antiviral therapies.

HCV Specific Ribozymes

Synthetic nuclease resistant ribozymes designed to cleave the hepatitis C virus IRES are currently in phase II clinical trials. These stabilized ribozymes contain modified nucleotides and phosphorothioate linkages and are efficiently taken up by the liver. In preliminary cell culture studies, these ribozymes inhibited viral replication in a dose dependent fashion, and this effect was potentiated by interferon. Phase II trials administering these HCV specific ribozymes, alone or in combination with interferon for 12 weeks' duration, are currently in progress.

While these newer small molecule approaches provide hope and excitement for the treatment of HCV infected patients, many further studies will be necessary to determine the safety and efficacy of these approaches, their effect on liver histology, and the mechanisms of any antiviral effects, and to evaluate whether such agents will need to be administered in combination with our available antiviral therapies to prevent the development of resistance.

Strategies to Minimize Hepatic Fibrosis

Interferon Gamma. Interferon γ is an antifibrotic cytokine in murine and human hepatic stellate cells, is an immunomodulatory cytokine, and has HCV specific antiviral activity. A phase II randomized, double-blind, multicenter trial to determine the antifibrotic efficacy of interferon gamma 1b is currently underway in patients with hepatic fibrosis due to hepatitis C and compensated cirrhosis, using a histologic primary end point.

Cellular immuno therapy. Cytotoxic T lymphocytes play an important role in viral clearance and immunological memory in chronic hepatitis B, and likewise it is thought that a strong, multispecific directed CTL response contributes to HCV clearance in those individuals who are fortunate enough to spontaneously resolve HCV infection. Various groups have created vaccines containing HCV specific viral epitopes that are recognized by cytotoxic T-cells. Whether these agents can be successfully used as potential vaccines in the primary prophylaxis setting, or in the setting of a therapeutic vaccine to modify the host immune response in patients with chronic hepatitis C infection is currently unknown. One such agent is currently in early phase human trials.

Conclusion

Although many of these future strategies are currently in development, it will require a number of years before the safety, short- and long-term efficacy, clinical value, and appropriate setting for each of these agents alone and in combination regimens is established. For these reasons, it is unlikely that many of these newer therapies, even if proven to be effective, will be available for routine clinical use within the next 3–5 years.

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