The role of hematopoietic growth factors in special populations with chronic hepatitis C:

Patients with HIV coinfection, end-stage renal disease, or liver transplantation

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ABSTRACT

Certain populations with chronic hepatitis C face special challenges in attaining optimal adherence to antiviral therapy, including patients coinfected with human immunodeficiency virus, patients undergoing dialysis for end-stage renal disease, and liver transplant recipients. These patient groups may stand to gain particular benefit from the expanding use of hematopoietic growth factors to manage the cytopenic effects of antiviral therapy for hepatitis C. This article reviews the rationale, current evidence, and future prospects for the adjunctive use of growth factors in these special populations with hepatitis C.

The challenge of optimizing adherence to therapy for chronic hepatitis C is particularly pronounced in certain patient populations, including patients coinfected with both human immunodeficiency virus (HIV) and hepatitis C virus (HCV), patients undergoing dialysis for end-stage renal disease (ESRD), and liver transplant recipients. The challenge stems from these populations' heightened risk of adverse effects from therapy, including enhanced susceptibility to hematologic toxicities, since these adverse effects often lead to dose reductions or premature discontinuation of pegylated interferon alfa (peginterferon) and ribavirin, the current standard of treatment for chronic hepatitis C.

Managing chronic hepatitis C in these groups is made even more difficult by these patients' apparent risk of more rapidly progressive HCV-associated liver disease, which, in the case of patients with ESRD, pertains especially to the period following renal transplantation. Moreover, for at least two of these populations, patients with HIV/HCV coinfection and liver transplant recipients, ample evidence demonstrates impaired response to combination therapy with peginterferon and ribavirin. For patients with ESRD, ribavirin is considered contraindicated because of the risk of severe anemia.

As clinicians attempt to optimize adherence and avoid dose reductions or premature discontinuation of therapy, the use of hematopoietic growth factors has become increasingly widespread for patients with chronic hepatitis C. Consideration of these growth factors is especially warranted in the patient populations mentioned above, in light of the special challenges they face.

OVERVIEW OF THERAPY-INDUCED CYTOPENIAS

In the preceding article in this supplement, Ong and Younossi review in detail the hematologic side effects of combination therapy for chronic hepatitis C. Briefly, both the conventional and pegylated forms of interferon suppress hematopoiesis, often resulting in neutropenia, thrombocytopenia, and a mild reduction in hemoglobin. Ribavirin results in a dose-dependent, reversible hemolytic anemia in a significant number of patients, and when it is used in combination with interferon, the anemia is far more pronounced than with interferon alone. All of these cytopenias can be managed with dose reductions or discontinuation of peginterferon or ribavirin, but abundant data suggest that dose reductions decrease the likelihood of response to therapy.

Much interest has focused on the clinical signifi-

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cance of cytopenias induced by therapy for hepatitis C. There is no doubt that reductions in hemoglobin may result in impaired functional capacity, reduced quality of life, and even organ manifestations such as cardiac ischemia. In contrast, many clinicians have come to question the degree to which interferon-induced reductions in neutrophil count truly predispose to infection[1,2] or to which interferon-induced thrombocytopenia predisposes to bleeding. Consequently, clinicians generally feel that the risk of clinically significant thrombocytopenia is very low and that reduced platelet counts are the least common hematologic indication for dose reduction or discontinuation. Nevertheless, all clinicians agree on the need to monitor cell counts during therapy and to react to cytopenias of sufficient severity.

HEMATOPOIETIC GROWTH FACTORS: RATIONALE FOR THEIR USE IN SPECIAL POPULATIONS

Recombinant erythropoietin and recombinant granulocyte colony-stimulating factor (G-CSF) have garnered interest as potential tools for limiting hematologic side effects—anemia and neutropenia, respectively—in patients with chronic hepatitis C who are treated with peginterferon and ribavirin. Recombinant erythropoietin has been used successfully in the management of anemia associated with chemotherapy, chronic renal failure, zidovudine therapy for HIV infection, and surgery.[3] G-CSF has been used principally in the management of neutropenia associated with chemotherapy.[4]

Increasing evidence suggests that recombinant erythropoietin[5–9] and G-CSF[9–12] may be used safely in patients treated with peginterferon and ribavirin and may potentially minimize the need for dose reductions or discontinuation of therapy, as well as improve adherence to therapy and quality of life. This may be of greatest importance in patients who face the prospect of rapidly progressive liver fibrosis and in whom hematologic side effects are common, including patients with HIV/HCV coinfection, patients with ESRD undergoing dialysis, and liver transplant recipients. However, the use of hematopoietic growth factors has not been adequately evaluated in these patients and further studies will be needed to determine the appropriate dosing and timing of therapy. Of particular note is the absence of firm data from randomized trials showing that hematopoietic growth factor use results in increased rates of sustained virologic response (SVR).

PATIENTS COINFECTED WITH HIV

Approximately one third of HIV-infected individuals are also infected with HCV.[13,14] Patients coinfected with HIV and HCV are at particular risk of developing anemia and neutropenia during therapy with peginterferon and ribavirin, as they may have underlying HIV-associated hematopoietic dysfunction.[15] Although adherence analyses analogous to those from the large trials in patients infected only with HCV have not yet been presented, the need to provide an optimal course of therapy for HIV/HCV-coinfected patients should be stressed since these patients have higher serum HCV RNA levels, accelerated fibrosis, a higher prevalence of cirrhosis, higher mortality, and lower rates of virologic response to therapy compared with patients infected with HCV alone.[16]

Hematopoietic dysfunction in HIV-infected patients is well described and is likely multifactorial, resulting from direct suppression of progenitor cells by HIV, abnormal cytokine production, medications, opportunistic infection, malignancy, autoantibody production, and the stage of HIV infection.[15,17]

Anemia: A potential role for erythropoietin

Recombinant erythropoietin has been used widely in the management of HIV-infected patients, particularly in association with zidovudine therapy, which may result in bone marrow suppression and anemia, especially at the higher doses that were common before the advent of highly active antiretroviral therapy.[18] In recent reports of HIV/HCV-coinfected patients treated with either nonpegylated or pegylated interferon and ribavirin, mean hemoglobin levels fell by as much as 2.3 g/dL[19–23] and 3.5 g/dL,[24] respectively, during the first 12 to 24 weeks of therapy, similar to the reductions seen in patients infected with HCV alone.

Preliminary studies suggest that, as in patients infected with HCV alone, recombinant erythropoietin may play a significant role in managing anemia during interferon/ribavirin therapy in patients coinfected with HIV and HCV.[24,25] In one study evaluating the use of interferon alfa-2b and ribavirin in 24 coinfected patients,[25] hemoglobin decreased to less than 10 g/dL in 21% of patients. These patients were then treated with recombinant erythropoietin, and their mean hemoglobin level increased to 12.7 g/dL after 4 weeks, although 1 patient was unable to continue therapy because of persistent anemia. Another study,[24] still ongoing, is comparing the use of recombinant erythropoietin with ribavirin dose reduction in coinfected patients who develop anemia during therapy with peginterferon alfa-2b and ribavirin. Patients who received recombinant erythropoietin have demonstrated increases in hemoglobin similar to those achieved by ribavirin dose reduction. These

findings suggest that the use of recombinant erythropoietin in coinfected patients may improve our ability to continue ribavirin therapy at optimal doses in the setting of ribavirin-induced anemia.

Neutropenia: Preliminary evidence for a role for G-CSF

An important concern when treating patients coinfected with HIV and HCV is the risk of interferon-associated neutropenia and lymphopenia, which could result in decreased $CD4^+$ T-cell counts and potentially an increased risk of opportunistic infections. Lymphocytes may be reduced in up to 14% of patients infected with HCV alone who are treated with peginterferon and ribavirin.[26] Preliminary results indicate that $CD4^+$ T-cell counts may decrease in HIV/HCV-coinfected patients treated with either nonpegylated or pegylated interferon combined with ribavirin.[19,21,23,27] However, the relative proportion of $CD4^+$ T cells among total lymphocytes remains unchanged, the significance of which has yet to be established.

As a result of this potential risk, a $CD4^+$ T-cell count of less than 100 cells/mL is a relative contraindication to interferon use, as interferon-induced decreases to this level have resulted in AIDS-defining opportunistic infections.[28] In coinfected patients with $CD4^+$ T-cell counts below 100 cells/mL, antiretroviral treatment should be prioritized in order to improve $CD4^+$ T-cell counts before interferon is prescribed.[29] In coinfected patients with normal $CD4^+$ T-cell counts, the question of which disease to treat initially has not been resolved.

The use of G-CSF in HIV-infected patients has been shown to be effective and well tolerated.[30,31] In patients coinfected with HIV and HCV, preliminary findings suggest that G-CSF may be as effective as peginterferon dose reduction for the management of interferon-induced neutropenia.[24] Although these results appear promising for our ability to avoid potential dose reductions or discontinuation of peginterferon in coinfected patients, further long-term studies will be required to validate them.

PATIENTS RECEIVING DIALYSIS FOR ESRD: ANEMIA IS THE CHIEF CONCERN

Chronic hepatitis C is a frequent problem in patients with ESRD, as 8% to 10% of hemodialysis patients in the United States have been exposed to HCV.[32,33] Studies suggest that chronic hepatitis C is often relatively quiescent in ESRD patients,[33] but disease progression may accelerate after renal transplantation,[34] probably because of the immunosuppressive medications required. Overall, HCV-positive patients undergoing dialysis have higher mortality than HCV-negative ESRD patients,[35] and renal transplantation is beneficial in these patients. Thus, mild chronic hepatitis C is not a contraindication to transplantation.[36] Unfortunately, HCV infection is difficult to treat in patients after renal transplantation because of a substantial risk of graft rejection,[37] which makes clearance of HCV before renal transplantation highly desirable.

Ribavirin not recommended, interferon not well tolerated

Treatment of chronic hepatitis C in patients with ESRD is particularly challenging because ribavirin is considered contraindicated and because these patients have a reduced tolerance for interferon therapy.[33]

Because ribavirin is cleared via renal excretion and only a small fraction is removed by dialysis, patients undergoing dialysis who are treated with ribavirin are at increased risk of severe hemolysis.[38] One recent study suggested that ribavirin may be given safely to these patients in low doses (< 300 mg/d).[39] In this study, patients received careful follow-up, monitoring of plasma ribavirin levels, and high-dose recombinant erythropoietin before and during therapy. Further studies of this nature will be required to enhance clinicians' confidence in the use of ribavirin in dialysis patients.

Because of the concerns about anemia, most studies in this population have used interferon alone, usually at a dose of 3 million units three times a week. Pharmacokinetic studies have shown that dialysis patients have higher peak and more sustained serum interferon levels than patients with normal renal function.[40] A meta-analysis of published trials that used interferon 3 million units three times a week demonstrated a higher rate of SVR in HCV-infected patients undergoing dialysis (33%)[41] than was reported previously in large trials among patients with normal renal function who received interferon monotherapy (13% to 19%).[42,43] At the same time, the incidence of adverse effects appears to be somewhat higher in patients undergoing dialysis. In HCV-infected patients with ESRD, interferon therapy should be strongly considered before renal transplantation, as evidence suggests that renal transplant recipients are at risk of having a severe, accelerated course of HCV-associated liver disease following transplantation while on immunosuppressants.[34]

Anemia associated with renal failure occurs in virtually all patients with ESRD because of deficient renal production of erythropoietin. As a result, recombinant erythropoietin is widely used to treat anemia in patients with ESRD. Ribavirin is currently considered investigational for patients undergoing hemodialysis and cannot be recommended in routine practice. Whether the aggressive use of recombinant erythro-

poietin can allow for the safe use of ribavirin has yet to be demonstrated in controlled clinical trials.

Although anemia predominates as the major challenge facing dialysis patients receiving antiviral therapy for HCV infection, the usual precautions about reductions in the absolute neutrophil count and platelet count also apply.

LIVER TRANSPLANT RECIPIENTS: RECURRENT INFECTION IS COMMON, OFTEN SEVERE

HCV-associated liver disease is the leading indication for liver transplantation in the United States.[44] In liver transplant recipients who had chronic hepatitis C before transplantation, reinfection with HCV following transplantation is almost universal, and these patients are at risk of a severe, accelerated course of HCV-associated graft disease. In addition, recurrent chronic infection with HCV results in decreased patient and graft survival,[45] and the severity of recurrent liver disease is associated with the degree of immunosuppression required after transplantation.[46]

The treatment of patients with recurrent HCV infection following liver transplantation is an area of great interest. Many concerns arise over the tolerability and efficacy of therapy with interferon/peginterferon and ribavirin in this population, as well as over the potential for graft rejection during therapy. Unfortunately, interferon monotherapy has shown minimal efficacy in transplant recipients with recurrent chronic hepatitis C, yielding SVR rates of less than 5%.[47,48] Improved response rates have been observed with the combination of interferon and ribavirin, but efficacy is still poor compared with that in nontransplant patients. One recent study, for example, demonstrated SVR in 21% of liver transplant recipients with recurrent chronic hepatitis C treated with interferon and ribavirin.[49] In this study, 43% of patients discontinued therapy because of ribavirin-associated hemolytic anemia, and only dose reductions or discontinuation of treatment were used to manage adverse events. Others have observed similarly high rates of anemia in this population.[50–52]

The increase in ribavirin-associated hemolytic anemia in these patients may be associated with impaired renal function. Thus, ribavirin dosing in this population may need to be adjusted on the basis of weight and renal clearance to avoid dose reductions or discontinuation.[49]

Preliminary results from a randomized trial in liver transplant recipients with recurrent HCV infection who were treated with peginterferon and ribavirin indicate that larger decreases in hemoglobin were associated with reduced renal clearance, suggesting that preemptive therapy with recombinant erythropoietin may be important in maintaining adequate doses of ribavirin in these patients.[53] Additional studies using hematopoietic growth factors in liver transplant recipients will be required to determine any further benefit in adherence to and tolerance of therapy with interferon/peginterferon and ribavirin.

CONCLUSIONS AND IMPLICATIONS FOR THE FUTURE

Hematopoietic growth factors may offer a number of benefits to patients with chronic hepatitis C who are being treated with the combination of pegylated or nonpegylated interferon and ribavirin. These include improved tolerability of and adherence to combination therapy, a higher likelihood of completing a full course of therapy with minimal dose reductions, improved quality of life, and, potentially, prevention of infections. Growth factors may be of particular benefit in patient populations with impaired tolerability of combination therapy and complex treatment issues. Further studies will be required to validate the potential benefits of recombinant erythropoietin and G-CSF in these special populations and in all patients with chronic hepatitis C. It is likely that recombinant erythopoietin will be commonly used in these special populations and that recombinant G-CSF will have more limited use but still have a role in selected patients with severe neutropenia. A number of questions surrounding the use of growth factors have yet to be fully evaluated, including appropriate dosage, time of initiation, duration of therapy, impact on SVR, and cost-effectiveness.

REFERENCES

1. **Soza A, Everhart JE, Ghany MG, et al.** Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. Hepatology 2002; 36:1273–1279.
2. **Ahmed F, Jacobson IM, Brown RS, et al.** Clinical significance of pegylated interferon induced neutropenia: results from the WIN-R trial. Gastroenterology 2003; 124(suppl 1):A700. Abstract 213.
3. **Fisher JW.** Erythropoietin: physiology and pharmacology update. Exp Biol Med 2003; 228:1–14.
4. **Hubel K, Engert A.** Clinical applications of granulocyte colony-stimulating factor: an update and summary. Ann Hematol 2003; 82:207–213.
5. **Talal AH, Weisz K, Hau T, Krieswirth S, Dieterich DT.** A preliminary study of erythropoietin for anemia associated with ribavirin and interferon-α. Am J Gastroenterol 2001; 96:2802–2804.
6. **Gergely AE, Lafarge P, Fouchard-Hubert I, Lunel-Fabiani F.** Treatment of ribavirin/interferon–induced anemia with erythropoietin in patients with hepatitis C. Hepatology 2002; 35:1281–1282.
7. **Dieterich DT, Wasserman R, Brau N, et al.** Once-weekly epoetin alfa improves anemia and facilitates maintenance of ribavirin dosing in hepatitis C virus–infected patients receiving ribavirin plus interferon alfa. Am J Gastroenterol 2003; 98:2491–2499.
8. **Afdhal NH, Dieterich DT, Pockros PJ, et al.** Epoetin alfa treatment of anemic HCV-infected patients allows for maintenance of ribavirin dose, increased hemoglobin levels, and improves quality of life vs. placebo: a randomized, double-blind, multicenter study. Gastroenterology 2003; 124(suppl 1):A714. Abstract 505.
9. **Senkbeil LE, Moss JG, Gaglio P, et al.** Erythropoietin maintains

ribavirin dose and sustained virologic response during HCV treatment. Hepatology 2003; 38(suppl 1):744A. Abstract 1213.
10. **Van Thiel DH, Faurki H, Friedlander L, et al.** Combination treatment of advanced HCV-associated liver disease with interferon and G-CSF. Hepatogastroenterology 1995; 42:907–912.
11. **Sood A, Reddy N, Russo MW, Brown RS, Jacobson IM.** Use of granulocyte colony stimulating factor (GCSF) for interferon induced neutropenia in patients with chronic hepatitis C infection. Hepatology 2001; 34(4 Pt 2):429A. Abstract 1029.
12. **Carreño V, Parra A, Navas S, Quiroga JA.** Granulocyte-macrophage colony-stimulating factor as adjuvant therapy for interferon α treatment of chronic hepatitis C. Cytokine 1996; 8:318–322.
13. **Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL.** Hepatitis C and progression of HIV disease. JAMA 2002; 288:199–206.
14. **Staples CT, Rimland D, Dudas D.** Hepatitis C in the HIV (human immunodeficiency virus) Atlanta V.A. (Veterans Affairs Medical Center) Cohort Study (HAVACS): the effect of coinfection on survival. Clin Infect Dis 1999; 29:150–154.
15. **Harbol AW, Liesveld JL, Simpson-Haidaris PJ, Abboud CN.** Mechanisms of cytopenia in HIV infection. Blood Rev 1994; 8:241–251.
16. **Gonzalez SA, Talal AH.** Hepatitis C virus in human immunodeficiency virus-infected individuals: an emerging comorbidity with significant implications. Semin Liver Dis 2003; 23:149–166.
17. **Volberding P.** Consensus statement: anemia in HIV infection—current trends, treatment options, and practice strategies. Clin Ther 2000; 22:1004–1020.
18. **Henry DH, Beall GN, Benson CA, et al.** Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy: overview of four clinical trials. Ann Intern Med 1992; 117:739–748.
19. **Zylberberg H, Benhamou Y, Lagneaux JL, et al.** Safety and efficacy of interferon-ribavirin combination therapy in HCV-HIV coinfected subjects: an early report. Gut 2000; 47:694–697.
20. **Nasti G, Di Gennaro G, Tavio M, et al.** Chronic hepatitis C in HIV infection: feasibility and sustained efficacy of therapy with interferon alpha-2b and ribavirin. AIDS 2001; 15:1783–1787.
21. **Landau A, Batisse D, Van Huyen JP, et al.** Efficacy and safety of combination therapy with interferon-alpha2b and ribavirin for chronic hepatitis C in HIV-infected patients. AIDS 2000; 14:839–844.
22. **Sauleda S, Juarez A, Esteban JI, et al.** Interferon and ribavirin combination therapy for chronic hepatitis C in human immunodeficiency virus–infected patients with congenital coagulation disorders. Hepatology 2001; 34:1035–1040.
23. **Rockstroh JK, Mudar M, Lichterfeld M, et al.** Pilot study of interferon α high-dose induction therapy in combination with ribavirin for chronic hepatitis C in HIV-co-infected patients. AIDS 2002; 16:2083–2085.
24. **Golia P, Talal AH, Jacobson IM, Flynn S, Golia P.** A preliminary study of growth factors versus dose reduction for peginterferon alfa-2b and ribavirin associated neutropenia and anemia in HIV/HCV co-infected patients. Gastroenterology 2003; 124(suppl 1):A766. Abstract T1207.
25. **Dieterich D, Weisz K, Goldman D, et al.** Interferon and ribavirin therapy for hepatitis C in HIV-coinfected patients. In: Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, Calif., 1999. Washington, D.C.: American Society for Microbiology; 1999:415. Abstract H-105.
26. Pegasys (peginterferon alfa-2a) package insert. Nutley, N.J.: Roche Pharmaceuticals; December 2003.
27. **Chung R, Anderson J, Alston M, et al.** A randomized, controlled trial of pegylated interferon alpha-2a with ribavirin vs. interferon alpha-2a with ribavirin for the treatment of chronic HCV in HIV co-infection. ACTG A5071. Presented at: Ninth Conference on Retroviruses and Opportunistic Infections; 2002; Seattle, Wash. Abstract LB15.
28. **Pesce A, Taillan B, Rosenthal E, et al.** Opportunistic infections and CD4 lymphocytopenia with interferon treatment in HIV-1 infected patients [letter]. Lancet 1993; 341:1597.
29. **Talal AH.** Opportunistic infections in HIV-infected individuals: hepatitis C virus. Lancet 2002; 360:584–586.
30. **Nielsen SD, Sorensen TU, Aladdin H, et al.** The effect of long-term treatment with granulocyte colony-stimulating factor on hematopoiesis in HIV-infected individuals. Scand J Immunol 2000; 52:298–303.
31. **Aladdin H, Ullum H, Dam NS, et al.** Granulocyte colony-stimulating factor increased CD4+ T cell counts of human immunodeficiency virus–infected patients receiving stable, highly active antiretroviral therapy: results from a randomized, placebo-controlled trial. J Infect Dis 2000; 181:1148–1152.
32. **Tokars JI, Frank M, Alter MJ, et al.** National surveillance of dialysis-associated diseases in the United States, 2000. Semin Dial 2002; 15:162–171.
33. **Meyers CM, Seeff LB, Stehman-Breen CO, Hoofnagle JH.** Hepatitis C and renal disease: an update. Am J Kidney Dis 2003; 42:631–657.
34. **Zylberberg H, Nalpas B, Carnot F, et al.** Severe evolution of chronic hepatitis C in renal transplantation: a case control study. Nephrol Dial Transplant 2002; 17:129–133.
35. **Nakayama E, Akiba T, Marumo F, Sato C.** Prognosis of anti-hepatitis C virus antibody-positive patients on regular hemodialysis therapy. J Am Soc Nephrol 2000; 11:1896–1902.
36. **Pereira BJG, Natov SN, Bouthot BA, et al.** Effect of hepatitis C infection and renal transplantation on survival in end-stage renal disease. Kidney Int 1998; 53:1374–1381.
37. **Rostaing L.** Treatment of hepatitis C virus infection after renal transplantation: new insights. Nephrol Dial Transplant 2000; 15(suppl 8):74–76.
38. **Tan AC, Brouwer JT, Van Leusen R, et al.** Safety of interferon and ribavirin therapy in dialysis patients with chronic hepatitis C: results of a pilot study. Hepatology 1999; 30(4 Pt 2):364A. Abstract 813.
39. **Bruchfeld A, Stahle L, Andersson J, Schvarcz R.** Ribavirin treatment in dialysis patients with chronic hepatitis C virus infection—a pilot study. J Viral Hepat 2001; 8:287–292.
40. **Rostaing L, Chatelut E, Payen JL, et al.** Pharmacokinetics of alphaIFN-2b in chronic hepatitis C virus patients undergoing chronic hemodialysis or with normal renal function: clinical implications. J Am Soc Nephrol 1998; 9:2344–2348.
41. **Russo MW, Goldsweig CD, Jacobson IM, Brown RS.** Interferon monotherapy for dialysis patients with chronic hepatitis C: an analysis of the literature on efficacy and safety. Am J Gastroenterol 2003; 98:1610–1615.
42. **Poynard T, Marcellin P, Lee SS, et al.** Randomised trial of interferon α2b plus ribavirin for 48 weeks or for 24 weeks versus interferon α2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 1998; 352:1426–1432.
43. **McHutchison JG, Gordon SC, Schiff ER, et al.** Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998; 339:1485–1492.
44. **Kim WR, Brown RS Jr, Terrault NA, et al.** Burden of liver disease in the United States: summary of a workshop. Hepatology 2002; 36:227–242.
45. **Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR.** The association between hepatitis C infection and survival after orthotopic liver transplantation. Gastroenterology 2002; 122:889–896.
46. **Saab S, Wang V.** Recurrent hepatitis C following liver transplant: diagnosis, natural history, and therapeutic options. J Clin Gastroenterol 2003; 37:155–163.
47. **Wright TL, Combs C, Kim M, et al.** Interferon-α therapy for hepatitis C virus infection after liver transplantation. Hepatology 1994; 20:773–779.
48. **Feray C, Samuel D, Gigou M, et al.** An open trial of interferon alfa recombinant for hepatitis C after liver transplantation: antiviral effects and risk of rejection. Hepatolgy 1995; 22:1084–1089.
49. **Samuel D, Bizollon T, Feray C, et al.** Interferon-α 2b plus ribavirin in patients with chronic hepatitis C after liver transplantation: a randomized study. Gastroenterology 2003; 124:642–650.
50. **Bizollon T, Palazzo U, Ducerf C, et al.** Pilot study of the combination of interferon alfa and ribavirin as therapy of recurrent hepatitis C after liver transplantation. Hepatology 1997; 26:500–504.
51. **Firpi RJ, Abdelmalek MF, Soldevila-Pico C, et al.** Combination of interferon alfa-2b and ribavirin in liver transplant recipients with histological recurrent hepatitis C. Liver Transplant 2002; 8:1000–1006.
52. **Shakil AO, McGuire B, Crippin J, et al.** A pilot study of interferon alfa and ribavirin combination in liver transplant recipients with recurrent hepatitis C. Hepatology 2002; 36:1253–1258.
53. **Ghalib RH, Levine CD, Hollinger B, et al.** Changes in hemoglobin during therapy with PEG IFN alfa-2b plus ribavirin in patients with recurrent hepatitis C after liver transplantation. Hepatology 2003; 38(suppl 1):535A. Abstract 776.