

Medical Writers' Circle

May • 2006

a series of articles written by medical professionals about the management and treatment of hepatitis C

Robert Gish, MD

California Pacific Medical Center, San Francisco, CA

Hepatitis C: Current Standards of Care and Future Perspectives

Introduction

Hepatitis C affects approximately 4-5 million people in the United States with nearly 75% having long-term hepatitis C virus (HCV).¹ Even with advances in treatment, about one half of patients will not achieve an SVR.^{2,3} Pegylated interferon and ribavirin combination therapy is currently the standard of care for the treatment of chronic hepatitis C.⁴ Overall, sustained virologic responses (SVR) – defined as undetectable HCV RNA in the serum – greater than 50% have been reported from pivotal registration trials. However, pegylated interferon and ribavirin therapy is associated with a high incidence of side effects, including hematologic complications. *Hematologic side effects are particularly common; bone marrow suppression caused by interferon may result in neutropenia and thrombocytopenia, and ribavirin is directly toxic to red blood cells and is associated with hemolysis, which is usually dose-related and generally self-limiting.*⁴ The standard recommendation for management of hematologic side effects of interferon and ribavirin therapy has been dose reduction.⁴ More recently, there has been increasing emphasis on

the use of growth factors such as filgrastim and erythropoietin to stimulate bone marrow production of leukocytes and erythrocytes to allow patients to receive the optimal doses of interferon and ribavirin rather than have the patient undergo dose reduction and risk a decrease in SVR.⁵ This practice is consistent with the available data suggesting that maintenance of optimal doses and adherence during therapy is associated with the best SVR rates.^{6,7} A study published in abstract form by Schiffman et al.⁸ examined the use of erythropoietin at the onset of therapy to maintain hemoglobin between 12-15 g during treatment; three groups were treated with weight based ribavirin (800 to 1600 g/day). A significant increase in SVR rates was observed in the group that received the high weight based ribavirin dose (1000-1600 mg/day).

Today's Standard of Care

Recently the importance of adherence throughout therapy was studied with regards to its affect on SVR.⁸ Maintaining the optimal dose of both interferon and ribavirin is particularly critical in the first 12 to 20 weeks of

therapy.⁹ One factor that determines adherence is the quality of life of patients during therapy. Another important determinant of adherence is the ability to manage the side effects of therapy including hematologic management.¹⁰

There is clear evidence that the response to interferon and ribavirin is greatest among patients who receive the optimal dose of interferon and ribavirin albeit this conclusion comes from retrospective studies. Much of the data has been compiled from post-hoc analyses of the pivotal trials with pegylated interferon alfa-2a and pegylated interferon alfa-2b.

The overall SVR among patients in the pegylated interferon (PEG-IFN) alfa-2b pivotal trial was approximately 54%. However, subgroup analysis among patients who were able to maintain at least 80% of each of the 2 medications for at least 80% of the time demonstrated an SVR of 63%. Among those who did not maintain at least 80% of the doses at least 80% of the time, the sustained response rate was 52%.

Among patients with HCV genotype 1, the patients that are the hardest to clear the virus in, only 34% of patients who did

not maintain adherence to the “80-80-80” rule had an SVR. These data, albeit retrospectively derived, strongly suggest that adherence to optimal dosage regimens does in fact improve SVR.

Recent studies have shown that an early virologic response (EVR) is another important predictor of SVR; furthermore, adherence during the first 12 weeks appears to be a predictor of EVR. Davis et al.¹⁰ showed that patients who were able to maintain at least 80% of each of the drugs during those first 12 weeks had an 80% likelihood of achieving EVR. Shiffman et al. also showed that SVR was lower among patients who were unable to maintain optimal dosing for 20 weeks.¹⁰ Therefore, it is essential that treatment of hepatitis C should focus on the use of optimal dosage of therapy and attempts to minimize side effects to allow adherence.

Dosage and Duration of Therapy

Identifying the correct PEG-IFN/ribavirin dosage and the correct duration for each of the HCV genotypes was the aim of a study led by Hadziyannis et al. There were 4 arms in this study: 2 groups received weight-based ribavirin for 24 and 48 weeks, while the other 2 groups received “flat-dose” ribavirin for 24 and 48 weeks, respectively.¹¹ The study addressed 2 problems, namely the optimal duration of therapy and the optimal ribavirin dose.

Results showed that the responses among patients with HCV genotypes 2 and 3 were similar among groups regardless of ribavirin dose or duration of therapy (24 or 48 weeks).

For patients with HCV genotypes 2 and 3, the National Institutes of Health recommended 24 weeks of therapy with PEG-IFN and ribavirin at a dose of 800 mg a day, regardless of a patient’s weight.

A recent trial by Zeuzum et al. compared response rates between patients with genotypes 2 and 3.^{12,13} All patients were treated for 24 weeks of PEG-IFN and weight-based ribavirin. The SVR was higher among genotype 2 patients compared to those with genotype 3 (93% vs 79%, respectively). This difference was largely due to lower SVR among genotype 3 patients with high viral load. Treatment of genotype 3 with 48 weeks of medication has been proposed for high viral load patients but still needs to be confirmed in prospective studies. Among patients with genotype 1, there was a clear, almost linear response, with the best response rate among patients who received PEG-IFN and weight-based ribavirin for 48 weeks. There was an 11% lower rate of SVR among those who received flat-dose rather than a weight-based ribavirin dose.⁷ This study, among others, supports the use of PEG-IFN and weight-based ribavirin dosing for 48 weeks for patients with genotype 1 HCV. Short term therapy of 12, 14 or 16 weeks is now being considered by a variety of specialists.^{12,13}

A preliminary study presented at the 2004 American Association for the Study of Liver Diseases meeting suggested that prolonged therapy may increase SVR among patients with a “slow” or “delayed” virologic response. Sanchez-Tapias et al. randomized patients with detectable virus after 4 weeks

of therapy to 48 or 72 weeks of therapy. The SVR was superior among patients who had received the longer duration of therapy (46% vs 32%) due to a reduced relapse rate.³¹

A preliminary study presented at 2005 Digestive Disease Weekly meeting suggested that high dose retreatment with PEG-IFN may increase SVR. Gross et al. randomized 650 patients to receive PEG-IFN at 0.5 ug/kg, 1.5 ug/kg or 3.0 ug/kg. Incremental SVR increases were reported in the three groups (4%, 7% and 11% respectively).¹⁴

Hematologic Complications of Today’s Treatments

Cytopenias are among the most common complications of interferon and ribavirin combination therapy. These include neutropenia, thrombocytopenia and anemia.

Neutropenia

Neutropenia is generally defined in many trials as an absolute neutrophil count of less than 750. The cause is usually IFN-induced bone marrow suppression. PEG-IFN causes more neutropenia than standard IFN. The clinical significance of neutropenia associated with IFN therapy is unclear. A study from the NIH suggested that low neutrophil counts in patients being treated with interferon were not associated with an increased incidence of infections.¹⁵ A second study published in abstract form by Jacobsen et al. examined the data on more than 4,000 patients treated with PEG-IFN alfa-2b and ribavirin. This study, entitled the “WIN-R” trial, found that infections were

reported in only 30 patients (0.7%). Serious infections were not associated with low absolute neutrophil counts. Based on these data, the investigators suggested relaxing the criteria for dose reduction of PEG-IFN.¹⁶ Instead consideration should be given to using the growth factor for white blood cells (G-CSF) to treat the neutropenia, rather than lowering the dose. Although G-CSF is not specifically indicated for treatment of neutropenia associated with PEG-IFN therapy, G-CSF at a dose of 300 mcg subcutaneously 3 times weekly may be considered for maintenance of neutrophil counts during therapy. *The use of this agent could occur when dose reductions with the package insert suggest changes, or at an ANC of 250 in patients without cirrhosis or 500 in patients with cirrhosis, to be more conservative with G-CSF use.*

Thrombocytopenia

Thrombocytopenia, defined as platelet count of less than 75,000 is another problem seen with PEG-IFN therapy and is also related to IFN-induced bone marrow suppression. Rustgi et al. authored a brief report addressing the role of oprelvekin (recombinant IL-11), the growth factor for platelets, to support thrombocytopenia associated with PEG-IFN therapy.¹³ The main side effect of oprelvekin is edema, which frequently requires diuretic therapy. However, it is the opinion of many experts that thrombocytopenia due to PEG-IFN therapy is rarely associated with any clinical manifestations. Even patients who have very low platelet counts appear to do well with PEG-IFN. An alarm level of platelets at 20,000 should prompt immedi-

ate therapy discontinuation in any patient, and dose reduction or very close laboratory monitoring at a platelet count of 30,000.

Anemia

Hemolytic anemia related to ribavirin is the major hematologic complication associated with the treatment of HCV. The onset of anemia is observed very soon after initiating therapy; the greatest decrease in hemoglobin is noted approximately 4 to 6 weeks into the course of therapy. The decrease in hemoglobin level is generally in the range of 2.5g/dL to 3.0 g/dL; however, hemolytic anemia may be much more severe. The etiology of hemolysis related to ribavirin is caused by direct cytotoxicity to erythrocytes; hemolysis may therefore reverse with discontinuation of therapy.

Sulkowski and colleagues conducted a retrospective analysis of anemia associated with ribavirin therapy from 2 large studies of standard IFN and ribavirin combination therapy.¹⁷ A total of 595 patients were evaluated. The dose of ribavirin was 1,000 mg per day or greater; interferon dosage consisted of 4-weeks of therapy with 3 million units daily followed by three times per week with 3 million units three times per week. Anemia was found to be very common in this population; over 30% of patients had a decrease in hemoglobin of $\geq 25\%$ or greater. Older age, renal function and hemoglobin level at baseline were factors associated with a significant decrease in hemoglobin. Men had a greater reduction in serum hemoglobin compared to women. A decrease in hemoglobin level of ≥ 3 g/dL was observed in 40% of men. Additionally, he-

moglobin levels in the "critical" range (<10 gm/dL) were more often observed in women. Dose reduction of ribavirin occurred in women 4 times more often than in men.¹⁷

A number of possible mechanisms have been proposed to explain the hemolytic anemia caused by ribavirin. These include oxidative damage to erythrocyte membranes as well as damage to mitochondria, which may be mediated by depletion of adenosine triphosphate (ATP). Ribavirin is concentrated in red blood cells, where it is phosphorylated via adenosine kinase to its monophosphate, diphosphate and triphosphate forms, which are the pharmacologically active compounds. These ribavirin-phosphate conjugates are trapped within erythrocytes as a mixture and are gradually cleared slowly from red cells (half-life of 40 days). Ribavirin is much more rapidly cleared from plasma (half-life 24 hours). Steady-state concentrations of ribavirin are achieved after 2 to 4 weeks of treatment, at which time concentrations within red cells exceed plasma concentrations by a ratio of 60 to 1. De Franceschi and colleagues found that erythrocyte ATP levels were significantly decreased in the presence of RBV and basal hexosemonophosphate shunt (HMS) activity was increased, suggesting increased susceptibility of erythrocytes to oxidative stress.¹⁸ Ribavirin therapy in patients with chronic HCV demonstrated decreased activity of red cell $\text{Na}^+ - \text{K}^+$ and increase in markers of oxidative stress such as malondialdehyde, reticulocytosis and evidence of increased sequestration of red cells by the reticuloendothelial system.

Another recent study examined markers of oxidative stress among patients with HCV before and after treatment with ribavirin and in normal controls. Some of the patients also had concomitant G6PD deficiency.¹⁷ Incubation of erythrocytes with dipyrindamole (DPD), diethylmaleate (DEM) and glutathione ester (GSHE) showed that DEM augmented ribavirin-induced decrease in cellular glutathione, protein sulfhydryls, and osmotic resistance. Coadministration of GSHE and DPD prevented the ribavirin-induced decrease in osmotic resistance, ATP, and 2,3-diphosphoglycerate and reduced oxidative stress, as demonstrated by improved protein stability, increased glutathione levels and formation of thiobarbituric acid reactive substances (TBARs), commonly used markers of oxidative stress. The implications of this study are that erythrocyte antioxidant levels may influence ribavirin-induced cytotoxicity.

The Importance of QOL

The importance of adherence to treatment throughout therapy is probably the single-most important factor that may positively influence response. In particular, adherence during the first 12 weeks is critical, as well as the ability to deliver the optimal dose of ribavirin as demonstrated by Shiffman and colleagues.¹⁸ It is well recognized that an important factor influencing adherence is the quality of life during therapy. Management of side effects, in particular the neuropsychiatric sequelae is important; management of hematological complications is also critical because symptomatic anemia may result in significantly decreased quality

of life during therapy and may lead to dose reduction or even discontinuation of therapy.

While it has generally been assumed that there is a direct relationship between the severity of side effects, quality of life, and, consequently, adherence, resulting in a lower SVR, detailed studies examining these associations have been carried out only recently.¹⁹

The incidence of dose modification due to anemia alone in the large multi-center trials was 22% in a study led by Fried et al., and 9% in Manns et al. However, it is important to remember that patients in the latter trial were given a lower dose of ribavirin than is currently used for genotype 1 disease. In a comparable large trial with PEG-IFN alfa-2b that compared viramidine to weight-based ribavirin, a comparable 25% of patients had a decrease in hemoglobin level to <10 g and would therefore have met criteria for dose reduction according to the package insert.¹⁹

In clinical practice, dose reduction is often performed even if the hemoglobin has not reached a nadir level of 10 g, since many patients become symptomatic with anemia with a 3 g to 4 g decrease from a baseline value of 16 g to 17 g. Addition of a growth factor to avoid dose reduction is becoming increasingly common, as the addition of epoetin alfa can reverse the anemia associated with ribavirin.^{19,20} Ribavirin induces hemolysis by direct cytotoxicity to erythrocytes in a dose-dependent manner that is reversible with discontinuation. The cause of anemia is the loss of a compensatory reticulocytosis due to ribavirin and bone marrow suppression by IFN or PEG-IFN. By promot-

ing erythropoiesis, epoetin alfa therapy can overcome the effect of bone marrow suppression.

A recent controlled trial randomized patients with a decrease in hemoglobin to <12 g while on PEG-IFN/ribavirin therapy to receive epoetin alfa or placebo.²¹ After 8 weeks of double blind treatment, all patients previously given placebo were crossed over to receive open-label epoetin alfa. The initial dose of epoetin alfa used was 40,000 international units (IU) administered subcutaneously once a week. The dose was titrated up to 60,000 IU if the hemoglobin did not respond within 4 weeks. The objective of the study was to determine whether the use of epoetin alfa in comparison to placebo was superior in allowing maintenance of the desired ribavirin dose, alleviated anemia and its symptoms and, in turn, improved quality of life. The researchers reported that ribavirin dose was maintained in a higher proportion of patients who received epoetin alfa (88% vs 60%) during the first 8-week period of treatment with PEG-IFN and ribavirin.

The subsequent data from this study were recently published. The latter study found that even with a relatively short duration of epoetin alfa therapy, ribavirin dose was maintained throughout the entire duration of therapy. There was a significant change in the hemoglobin level only during the period of epoetin alfa treatment. Hemoglobin levels in the placebo group increased to levels comparable to the group receiving epoetin alfa after crossover to active treatment – the ribavirin dose was maintained despite this. Although the SVR was 8% higher in the treated group, the study was not powered to show

a difference in SVR between treatment and placebo groups.

Another important endpoint in this study by Pockros and colleagues was the effect of epoetin alfa on quality of life. Health-related quality of life scores were significantly higher in the epoetin alfa patients, in particular the vitality scores. Nausea was reported more commonly by patients treated with epoetin alfa at a slightly greater rate in the treatment group than the placebo group. Otherwise, there was no difference in the incidence of side effects between the 2 groups. Pockros and colleagues emphasize caution to avoid high hemoglobin values with epoetin alfa because of the risk of cerebral or other thrombosis.²²

The other concern regarding the use of epoetin alfa is the development of pure red cell aplasia (PRCA). Two such cases have been reported in the United States associated with erythropoietin treatment in hepatitis C patients. The clinical signs included lack of response to epoetin alfa and progressive anemia. There was resolution of PRCA in both cases with discontinuation of epoetin alfa therapy.³² Pockros et al. recommended that ribavirin and erythropoietin therapy, as well as IFN should be discontinued in the setting of PRCA, in addition to follow up of reticulocyte count and testing for antibodies against red blood cells along with transfusions if necessary and consultation with a hematologist. The package inserts for epoetin alfa include a safety note to this effect.³³ Pockros et al. found that, compared to placebo, epoetin alfa therapy resulted in a significantly greater proportion of patients maintain-

ing their desired ribavirin dose. Treatment was associated with a higher hemoglobin and better quality of life. Although epoetin alfa was well-tolerated in this study, the authors recommend that patients be monitored for the development of pure red cell aplasia and possible CNS effects during therapy and urge caution to avoid “overshooting” hemoglobin levels to higher than normal.

Current Treatment Challenges

The SVR with PEG-IFN/ribavirin therapy has increased greatly from the initial reports of 10% in 1990 to approximately 50% in the current era. However, this leaves nearly one-half of the HCV population in the category of relapsers and non-responders.

A major challenge in the management of HCV is overcoming treatment barriers among individual patients. One major factor influencing response is the frequent presence of insulin resistance and hepatic steatosis among patients with HCV. Studies have suggested that it occurs in nearly one half of CHC patients.²³ A large proportion of patients with hepatic steatosis are obese or have a body mass index >30. It is thought that non-alcoholic fatty liver disease (NAFLD) associated with obesity may be the major cause of liver disease in the United States and may become an important cause of morbidity and mortality from liver disease in the coming decades. NAFLD may interact negatively with HCV, results in faster progression of fibrosis and lowers response rates to treatment, although the exact mechanisms have not been fully elucidated.²⁴

There is also evidence that HCV, particularly in patients with genotype 3, may independently lead to hepatic steatosis even in the absence of other risk factors for steatosis, such as obesity or type 2 diabetes mellitus.^{25,26} Successful treatment in this setting may lead to resolution of steatosis. However, the presence of visceral obesity, as observed in patients with metabolic syndrome and with a BMI >30 is associated with more advanced liver disease and lower response rates to therapy. Therefore, possible intervention for obesity and hepatic steatosis should be considered prior to initiating therapy.

Special Populations

In addition, certain groups have substantially lower response rates to the current treatment regimens including African-American patients and HIV/HCV-coinfected patients.²⁷⁻²⁹ HIV coinfection with HCV presents treatment challenges and is characterized by more aggressive liver disease. Furthermore, SVR is generally lower among coinfecting patients than among HCV mono-infected patients. The best current results are from the AIDS Pegasys Ribavirin International Coinfection (APRICOT) trial, which reported a 40% SVR with PEG-IFN, compared to 20% in the control group, (usually a standard IFN and ribavirin treatment).³⁰

African-American populations represent another challenging group with regard to PEG-IFN/ribavirin therapy. Two prospective trials so far have demonstrated that using the same regimens, African-Americans respond only half as well to therapy as Caucasian patients treated with the same drug

therapy. Factors associated with SVR include genotype, RNA levels, histology, race, co-infection, and adherence. The response rates to re-treatment with PEG-IFN/ribavirin are highly variable ranging from 4% to 13% of patients previously treated to 0% to 3% among African-American patients who previously did not respond to a course of therapy.

In summary, current therapies have provided unprecedented success in our ability to cure chronic hepatitis C viral disease, but therapy is not always a success. Therefore, there remains an unmet need for other therapies for such patients.

Tomorrow's Standard of Care?

Currently, there are new therapeutic approaches being investigated in an effort to augment SVR rates in all patient groups, especially those who currently have a poor response to therapy. Several novel IFNs, interferon delivery systems, IRES inhibitors, ribavirin-like molecules, protease and polymerase inhibitors, newer immunomodulators, and other hepatitis C replication enzyme inhibitors are currently being studied in clinical trials. In addition, antifibrotic agents, caspase inhibitors and antibody therapies and vaccines are also under development.

Conclusion

The treatment of chronic HCV has advanced greatly over the last 15 years. SVR rates have increased almost 5-fold over the past decade such that overall, 50% to 60% of patients with chronic HCV can expect an SVR with therapy. The current

standard of care is PEG-IFN and ribavirin therapy, administered weekly for 48 weeks to patients with genotype 1 infection and for 6 months to patients with genotypes 2 and 3 infection. The importance of maintaining optimal doses of interferon and ribavirin for the defined duration of therapy has placed greater emphasis on adherence. Therefore, management of neuropsychiatric and hematologic complications during therapy with antidepressants and growth factors has taken precedence to dose reduction. Epoetin alfa is effective in helping to maintain ribavirin dosage among patients with chronic HCV and has been shown to improve quality of life. There are now data to support that this strategy may be associated with improved SVR rates, although very large licensing trials that would provide more definitive data are awaited to clearly demonstrate that the use of epoetin alfa improves SVR among patients being treated with PEG-IFN and ribavirin, and lead to more expanded use and easier reimbursement.

Please visit the HCV Advocate Web site's The Medical Writers' Circle article "Future Therapies for Hepatitis C" by Robert Gish, MD for more information on new therapeutic approaches.

Reference List

¹ Gish RG, Afdhal NH, Dieterich DT, Reddy KR. Management of hepatitis C virus in special populations: patient and treatment considerations. *Clin Gastroenterol Hepatol* 2005; 3(4):311-318.

² Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R et al. Pegin-

terferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; 358(9286):958-965.

³ Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncalves FL, Jr. et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347(13):975-982.

⁴ National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C 2002 (June 10-12, 2002). *Gastroenterology* 2002; 123(6):2082-2099.

⁵ Tien PC. Management and treatment of hepatitis C virus infection in HIV-infected adults: recommendations from the veterans affairs hepatitis c resource center program and national hepatitis C program office. *Am J Gastroenterol* 2005; 100(10):2338-2354.

⁶ Sterling RK, Hofmann CM, Luketic VA, Sanyal AJ, Contos MJ, Mills AS et al. Treatment of chronic hepatitis C virus in the virginia department of corrections: can compliance overcome racial differences to response? *Am J Gastroenterol* 2004; 99(5):866-872.

⁷ Kraus MR, Schafer A, Csef H, Faller H, Mork H, Scheurlen M. Compliance with therapy in patients with chronic hepatitis C: associations with psychiatric symptoms, interpersonal problems, and mode of acquisition. *Dig Dis Sci* 2001; 46(10):2060-2065.

⁸ McHutchison JG, Manns M, Patel K, Poynard T, Lindsay KL, Trepo C et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with

chronic hepatitis C. *Gastroenterology* 2002; 123(4):1061-1069.

⁹ Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology* 2003; 38(3):645-652.

¹⁰ Shiffman ML, Di Bisceglie AM, Lindsay KL, Morishima C, Wright EC, Everson GT et al. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Gastroenterology* 2004; 126(4):1015-1023.

¹¹ Hadziyannis SJ, Sette H, Jr., Morgan TR, Balan V, Diago M, Marcellin P et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; 140(5):346-355.

¹² von Wagner M, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges T et al. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterology* 2005; 129(2):522-527.

¹³ Zeuzem S, Hultcrantz R, Bourliere M, Goeser T, Marcellin P, Sanchez-Tapias J et al. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *J Hepatol* 2004; 40(6):993-999.

¹⁴ Shiffman ML, Hubbard S, Wilson M, Salvatori JJ, Sterling RK, Stravitz RT et al. Treatment of chronic Hepatitis C virus (HCV) genotype 1 with peginterferon alfa-2b(PEGIFN), high weight based dose ribavirin

(RVN) and Epoetin alfa (EPO) enhances sustained virologic response (SVR). *Hepatology* [Nov], abstract. 2005.

¹⁵ Soza A, Everhart JE, Ghany MG, Doo E, Heller T, Promrat K et al. Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. *Hepatology* 2002; 36(5):1273-1279.

¹⁶ Ong JP, Younossi ZM. Managing the hematologic side effects of antiviral therapy for chronic hepatitis C: anemia, neutropenia, and thrombocytopenia. *Cleve Clin J Med* 2004; 71 Suppl 3:S17-S21.

¹⁷ Sulkowski MS. Anemia in the treatment of hepatitis C virus infection. *Clin Infect Dis* 2003; 37 Suppl 4:S315-S322.

¹⁸ De Franceschi L, Fattovich G, Turrini F, Ayi K, Brugnara C, Manzato F et al. Hemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: role of membrane oxidative damage. *Hepatology* 2000; 31(4):997-1004.

¹⁹ Gish RG. Treating HCV with ribavirin analogues and ribavirin-like molecules. *J Antimicrob Chemother* 2006; 57(1):8-13.

²⁰ Gish RG. Maximizing the benefits of antiviral therapy for HCV: the advantages of treating side effects. *Gastroenterol Clin North Am* 2004; 33(1 Suppl): xxiii-xxxiv.

²¹ Afdhal NH, Dieterich DT, Pockros PJ, Schiff ER, Shiffman ML, Sulkowski MS et al. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. *Gastroenterology* 2004; 126(5):1302-1311.

²² Pockros PJ, Shiffman ML, Schiff ER, Sulkowski MS, Younossi Z, Dieterich DT et al. Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. *Hepatology* 2004; 40(6):1450-1458.

²³ Choudhury J, Sanyal AJ. Clinical aspects of fatty liver disease. *Semin Liver Dis* 2004; 24(4):349-362.

²⁴ Lonardo A, Adinolfi LE, Loria P, Carulli N, Ruggiero G, Day CP. Steatosis and hepatitis C virus: mechanisms and significance for hepatic and extrahepatic disease. *Gastroenterology* 2004; 126(2):586-597.

²⁵ Cholet F, Noursbaum JB, Richecoeur M, Oger E, Cauvin JM, Lagarde N et al. Factors associated with liver steatosis and fibrosis in chronic hepatitis C patients. *Gastroenterol Clin Biol* 2004; 28(3):272-278.

²⁶ Gordon FD, Pomfret EA, Pomposelli JJ, Lewis WD, Jenkins RL, Khettry U. Severe steatosis as the initial histologic manifestation of recurrent hepatitis C genotype 3. *Hum Pathol* 2004; 35(5):636-638.

²⁷ Alvarez DF, Latorre JS. Hepatitis C virus and HIV coinfection: clinical management and new strategies. *AIDS Read* 2004; 14(10 Suppl):S16-S21.

²⁸ Daniel S. Chronic hepatitis C treatment patterns in African American patients: an update. *Am J Gastroenterol* 2005; 100(3):716-722.

²⁹ Fleckenstein J. Chronic hepatitis C in African Americans and other minority groups. *Curr Gastroenterol Rep* 2004; 6(1):66-70.

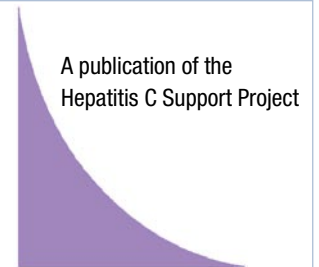
³⁰ Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A

et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004; 351(5):438-450.

³¹ M Diago, Manuel Romero-Gomez, J Crespo, A Oliveira, R Perez, R Barcena, Jose M. Sanchez-Tapias, M Munoz-Sanchez. Peginterferon Alfa-2a (40kd) (Pegasys®) and Ribavirin (Copegus®) in Patients Infected with HCV Genotype 1 Who Failed to Respond to Interferon and Ribavirin: Final Results of the Spanish High-Dose Induction Pilot Trial. *American Association for the Study of Liver Diseases*, 2004, Poster #522.

³² Stravitz RT, Chung H, Sterling RK, Luketic VA, Sanyal AJ, Price AS et al. Antibody-mediated pure red cell aplasia due to epoetin alfa during antiviral therapy of chronic hepatitis C. *Am J Gastroenterol*. 2005;100:1415-19.

³³ The Package Insert for PROCIT® (Epoetin alfa) can be found at http://www.procrit.com/common/prescribing_information/PROCIT/PDF/Procrit-Booklet.pdf



A publication of the
Hepatitis C Support Project

Medical Writers' Circle

The Mission of the Hepatitis C Support Project is to offer support to those who are affected by the hepatitis C Virus (HCV), hepatitis B Virus (HBV) and HCV coinfections.

Support is provided broadly, through information and education, as well as access to support groups. The Project seeks to serve the HCV community as well as the general public.

**Executive Director
Editor-in-Chief,
HCSP Publications**
Alan Franciscus

**Managing Editor /
Webmaster**
C.D. Mazoff, PhD

This information is provided by the Hepatitis C Support Project • a nonprofit organization for HCV education, support and advocacy • © 2006 Hepatitis C Support Project • Reprint permission is granted and encouraged with credit to the Hepatitis C Support Project.

Visit our web site at
www.hcvadvocate.org