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■ Hepatitis C Support Groups
  Inova Fairfax Hospital
  3300 Gallows Road, Falls Church, VA
  Conference Rooms D, E, & F (located above the cafeteria)
  Third Tuesday of every month at 7:30 p.m.
Management of Anemia Related to Antiviral Therapy for Chronic Hepatitis C

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In 2004, the most effective therapy for chronic hepatitis C (HCV) is a combination of pegylated interferon alfa and ribavirin (combination therapy) with a sustained virologic response (SVR) rate of up to 56 percent. This rate is lower in patients with HCV genotype 1 (45 percent) and higher for patients with genotype 2 and 3 (80 percent).

Once SVR is achieved, most patients will experience long-term remission and are “cured” from HCV. However, this efficacy is lower if the optimal dose of this antiviral regimen is not delivered. Delivery of the optimal dose of combination therapy is limited by the development of side effects that can result in either dose reduction or drug discontinuation. Among the side effects, anemia is a frequent indication for dose reduction. Anemia is important as it can negatively impact patients’ health-related quality of life and may be the main determinant of fatigue. It is also an important predictor of discontinuation of treatment.

The average decrease in hemoglobin is around 3 g/dL during antiviral therapy with pegylated interferon and ribavirin. The hemoglobin level generally reaches its lowest level within the first four to eight weeks, reaching a plateau thereafter and returning to baseline values after discontinuation of treatment.

In a number of studies, higher doses of ribavirin have been associated with higher rates of viral eradication.

There are several mechanisms for anemia related to the combination therapy for HCV. The predominant cause is a dose dependent and reversible hemolytic anemia that is due to ribavirin. After entering red blood cells, ribavirin is phosphorylated into its active form, leading to depletion of adenosine triphosphate, which in turn leads to impaired antioxidant mechanisms resulting in membrane oxidative damage and subsequent extravascular red blood cell removal by the reticuloendothelial system. Interferon contributes to this anemia via bone marrow suppression.

Approaches to the management of anemia during antiviral therapy can vary widely. Information contained in the product insert for ribavirin recommends ribavirin dose reduction at hemoglobin levels < 10 g/dL and permanent discontinuation for levels < 8.5 g/dL. It has recently been recognized that ribavirin dose reduction may have an adverse effect on SVR. In a number of studies, higher doses of ribavirin have been associated with higher rates of viral eradication. Patients receiving more than 80 percent of their interferon and ribavirin dose for 80 percent of the intended duration of therapy have higher SVR. Furthermore, patients receiving > 10.6 mg/kg/day of ribavirin have higher SVR.

Additionally, delivering this optimal dose of antiviral therapy may be
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critical during the first 12 weeks of therapy, the period of most significant decline in hemoglobin. An alternative strategy for the management of anemia is the use of growth factors such as epoetin alfa, or darbepoetin alfa.

Epoetin alfa is recombinant human erythropoietin that is approved for use in anemia associated with cancer chemotherapy and hemodialysis. The use of epoetin alfa for treating anemia (defined as hemoglobin < 12 g/dL) of combination therapy has been evaluated in two studies. In a randomized open-label trial, epoetin alfa was compared against standard of care in regards to hemoglobin levels and ribavirin dose. The investigators found that patients receiving epoetin alfa had significantly higher hemoglobin levels (14.2 g/dL vs. 11.2 g/dL) and higher ribavirin dose (895 mg/day vs. 707 mg/day) at 16 weeks after randomization.

In another multicenter study, 186 patients were randomized to receive either epoetin alfa or placebo. After eight weeks, patients receiving epoetin alfa had improvement in their anemia with a higher proportion able to maintain their ribavirin dose and have higher mean hemoglobin levels. Additionally, improvement in hemoglobin was an independent predictor of health related quality of life (HRQL) scores as measured by the Linear Analog Scale Assessment and Medical Outcomes Survey Short Form – 36. They suggest that since epoetin alfa increases hemoglobin levels in anemic patients it can increase their HRQL, which in turn can improve their adherence to therapy. Neither study was designed to evaluate the effect of epoetin alfa on virologic response. Epoetin alfa was generally well tolerated in both studies.

Darbepoetin alfa is a novel erythropoietic protein that has recently been approved for treatment of anemia associated with cancer chemotherapy and chronic renal failure. Darbepoetin alfa is a hyperglycosylated protein that renders it to be longer acting, thereby allowing for less frequent dosing. Darbepoetin alfa stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. In a number of studies, darbepoetin alfa had similar efficacy and safety profile but needed less frequent dosing when compared with epoetin alfa. Preliminary data from a recent study conducted at Center for Liver Diseases at Inova Fairfax Hospital shows that darbepoetin alfa in patients with chronic hepatitis C increases hemoglobin levels, allows ribavirin dose maintenance and may be beneficial as adjunct to the combination therapy. Improvements in health-related quality of life were also noted after initiation of darbepoetin alfa therapy. To date no significant toxicity has been noted with the use of darbepoetin alfa in this study.

In summary, abnormalities in hematologic parameters such as anemia are common during combination therapy with interferon and ribavirin for chronic hepatitis C. Ribavirin contributes to anemia as a result of hemolysis of red blood cells and interferon compounds this problem by suppressing the bone marrow. Hematopoietic growth factors such as epoetin alfa and darbepoetin alfa may be useful adjuncts to the treatment of anemia related to the combination therapy.

The Center for Liver Diseases at Inova Fairfax Hospital is involved in a number of protocols assessing the potential efficacy and safety of hematopoietic growth factors to deliver the optimal dose of antiviral therapy to patients with chronic hepatitis C. For more information, call the Center for Liver Diseases at 703-698-3182.
The Center for Liver Diseases at Inova Fairfax Hospital began its collaboration with the Center for the Study of Genomics in Liver Diseases at George Mason University in 2001. This Center was established to develop cutting-edge translational research projects for patients with liver disease. The Center uses the advances in microarray technology and proteomics to determine the pathogenic basis for a number of important liver diseases. Through better understanding of phenotype-genotype association, the Center is contributing to the knowledge about liver disease and to the development of improved treatment interventions.

Zobair M. Younossi, MD, MPH, director of Inova’s Center for Liver Diseases, and Vikas Chandhoke, PhD, associate dean of research for the College of Arts and Sciences, George Mason University, are co-directors of this Center. The Center includes research teams working collaboratively on over 10 genomics and proteomics projects in fatty liver, obesity, metabolic syndrome, hepatitis C and hepatic fibrosis. Over the past two years, members of both Centers have presented in numerous international meetings and are considered leaders in this area of research.

The Center is located on George Mason University’s Prince William campus in the Innovations at Prince William technology corridor near Manassas, VA. The Center is part of the College of Arts and Sciences’ Life Sciences initiative. For more information, call the Center for Liver Diseases at 703-698-3182, http://www.inova.org/inovapublic.srt/liver, or visit http://gunston.gmu.edu/liverdisease.

CURRENT GENOMIC PROJECTS:

- Genomic Study of Nonalcoholic Fatty Liver Disease (NAFLD)
- Proteomic Study of Nonalcoholic Fatty Liver Disease (NAFLD)
- Genomic Study of Obesity
- Proteomic Study of Obesity
- Genomics and Proteomics of Hepatic Fibrosis
- Genomics of Chronic Hepatitis C: Relationship to Stage of Liver Disease and Efficacy of Treatment
- Genetic Epidemiology of Nonalcoholic Fatty Liver Disease (NAFLD)