Erythropoietin and hepatitis C therapy: Useful adjuvant therapy but remember to treat the patient and not just a number

Eric M Yoshida MD FRCPC¹, Anne Dar Santos BSc Pharm², Nilufar Partovi PharmD², Jo-Ann E Ford MSN³

For most of the decade, the commercial availability of peginterferon (pegIFN) and ribavirin (RBV) combination therapy for the treatment of chronic hepatitis C virus (HCV) has allowed both patients and health care professionals alike to expect a reasonable likelihood of long-term viral clearance. Both pegIFN and RBV combination products (ie, pegIFN α -2a and RBV, [Pegasys RBV, Hoffman-La Roche Ltd, Canada], and pegIFN α -2b and RBV, [Pegatron, Schering Canada Inc]) are associated with sustained virological response (SVR) probabilities of approximately 40% to 50% for genotype 1 and approaching 80% for genotypes 2 and 3 (1-3). Moreover, the impressive results reported in randomized clinical trials have also been reported in a retrospective analysis of clinical practice (4), going against the common wisdom that results obtained in a 'real world' clinical setting cannot match those obtained in the 'ideal world' of controlled trials. Despite this great optimism regarding HCV treatment, the cold hard reality is that pegIFN and RBV combination therapy is lengthy, taking approximately 24 to 48 weeks depending on the genotype; has many adverse effects, such that it is an unpleasant experience for many and punishing for some; and is very expensive, with an associated drug acquisition cost of \$10,000 to \$20,000 for 24 and 48 weeks of therapy, respectively. Although it would appear intuitive for any treatment regimen, that to maximize the likelihood of success one must take as much of the drug as possible, for pegIFN and RBV therapy, given the mentioned problems associated with therapy, the stakes are even higher.

In the July issue of *The Canadian Journal of Gastroenterology*, Sherman et al (5) reviewed the use of recombinant human erythropoietin (EPO) as adjuvant therapy during pegIFN and RBV therapy and suggested clinical guidelines. Recombinant EPO (epoetin alfa, Eprex, Janssen-Ortho Inc, Canada) is a biosynthetic formulation of a physiological endogenous erythroid growth factor, and most clinicians are familiar with its use in the treatment of anemia in chronic renal failure and end-stage renal disease (6). The rationale for its crossover use in HCV treatment is based on the fact that RBV frequently causes anemia. RBV is concentrated in erythrocytes and has a long half-life of 40 days (7), resulting in oxidative damage to the red cell membrane (8). Hemolysis ensues, and when erythrocytes are destroyed faster than erythropoiesis can compensate, anemia results. The severity of anemia increases at RBV doses greater than 800 mg/day, as seen in the pegIFN α -2b and RBV registration trial (2), where the RBV dose for one of the

two pegIFN arms was 800 mg/day, which resulted in 9% to 13% of patients undergoing dose reduction because of anemia. By comparison, in the pegIFN α -2a and RBV registration trial (1), where the RBV dose was 1000 mg/day to 1200 mg/day, 22% underwent dose reduction because of anemia, whereas only 4% in the no RBV placebo arm required anemia-related dose reduction. Likewise, in a large study comparing 800 mg/day of RBV versus 1000 mg/day to 1200 mg/day, Hadziyannis et al (3) reported 15.4% of patients in the 1000 mg/day to 1200 mg/day 48-week arm had a hemoglobin level of less than 100 g/L compared with 6.4% in the 800 mg/day 48-week arm. In the 800 mg/day 24-week arm, the current recommended dosing protocol for genotypes 2 and 3, only 3.4% were reported to have a hemoglobin level of less than 100 g/L. Overall, Hadziyannis et al (3) reported that less than 1% of patients suffered a hemoglobin less than 85 g/L. Generally, in clinical practice, recommendations have been to reduce the dosage in the event of anemia (9). Dose reduction, however, comes at the expense of a decreased likelihood of SVR. As reported by McHutchison et al (10), an optimal probability of treatment success can only be achieved by taking at least 80% of the antiviral drugs with marked attenuation of the likelihood of SVR compared with those who take less.

The questions that arise in the minds of clinicians when presented with potential new drugs include efficacy, effectiveness and the cost-benefit ratio. In terms of efficacy, under the ideal conditions of a clinical trial, and this is not necessarily the same as effectiveness in clinical practice, it cannot be disputed that EPO improves hemoglobin levels in the setting of HCV treatment (11,12). In terms of maintaining RBV dosing, one study (11) did not report a significant difference in RBV dosing, whereas the other study did report a significant difference (12). Although it may be argued that it is a soft end point, quality of life scores have also been reported to be better in those receiving EPO compared with those who did not (12). For clinicians, however, the hard end point is the SVR with and without EPO. To be fair, neither of the mentioned studies (11,12) were designed to study SVR. However, differences in HCV detectability at the end of EPO study follow-up, while on antiviral therapy, were not statistically significant between those receiving EPO and those who did not. Moreover, at the recently concluded Canadian Association for the Study of Liver winter meeting, Fung et al (13), from the University of Toronto (Toronto, Ontario) and the University of Manitoba (Winnipeg, Manitoba), reported

¹Departments of Medicine; ²Faculty of Pharmaceutical Sciences, The University of British Columbia; ³The BC Hepatitis Program, Vancouver, British Columbia

Correspondence: Dr Eric Yoshida, Vancouver General Hospital, Division of Gastroenterology, #100-2647 Willow Street, Vancouver, British Columbia V5Z 3P1. Telephone 604-875-5371, fax 604-875-5373, e-mail eyoshida@interchange.ubc.ca

Received for publication April 5, 2006. Accepted April 6, 2006

that in their 38-patient study, SVRs were significantly improved in those who received EPO compared with those who did not. This is suggestive that there may be a virological benefit with EPO, but further clinical trials will be needed to confirm this. As well, it is important to note that the decrease in RBV throughout the study was protocol-driven – something that may not be the case in the ‘real world’ of the hepatitis clinic.

Finally, where does this leave the clinician and the patient? The recommendations of Sherman et al (5) are reasonable and appropriate. Clearly, some patients would benefit from EPO both in terms of quality of life and maximizing the likelihood of a SVR. Although EPO has been reported to cause an increased incidence of nausea compared with placebo, it is generally well-tolerated. The material risk of pure red cell aplasia (14), although real and something that should be discussed with patients a priori, is an infrequent occurrence. The recommendations of Sherman et al (5), therefore, are a welcome addition to the Canadian hepatitis literature. EPO, however, is costly.

Eprex (Janssen-Ortho Inc, Canada), at the recommended dose of 40,000 IU weekly, costs \$500 per treatment dose. Many patients, with no private insurance coverage, cannot afford to use this adjuvant medication without suffering some economic hardship, and many provincial drug benefit programs will not cover it. In our experience, coming from a province that will not provide reimbursement for EPO in the setting of HCV treatment, we know that for many patients, a low hemoglobin level is just a number and aside from causing anxiety in both patient and health care provider alike, it is tolerable. Sometimes patients are able to tolerate significantly low hemoglobin levels without the need for dose modification. Adjuvant treatment with EPO, therefore, must be an individualized decision and its use should not be dogmatically applied to everyone with anemia. Fortunately, hepatitis research is a dynamic process and HCV antiviral therapies without significant anemia are in development. Hopefully, in a few years, both the recommendations of Sherman et al (5), and the present editorial, will be of historical interest only.

REFERENCES

1. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975-82.
2. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: A randomised trial. *Lancet* 2001;358:958-65.
3. Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-alpha 2a and ribavirin combination therapy in chronic hepatitis C: A randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;140:346-55.
4. Lee SS, Bain VG, Peltekian K, et al. Treating chronic hepatitis C with pegylated interferon alfa-2a (40 KD) and ribavirin in clinical practice. *Aliment Pharmacol Ther* 2006;23:397-408.
5. Sherman M, Cohen L, Cooper MA, et al. Clinical recommendations for the use of recombinant human erythropoietin in patients with hepatitis C virus being treated with ribavirin. *Can J Gastroenterol* 2006;20:479-485.
6. IV. NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: Update 2000. *Am J Kidney Dis* 2001;37(1 Suppl 1):S182-238. (Erratum in 2001;38:442)
7. Glue P. The clinical pharmacology of ribavirin. *Semin Liver Dis* 1999;19 Suppl 1:17-24.
8. De Franceschi L, Fattovich G, Turrini F, et al. Hemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: Role of membrane oxidative damage. *Hepatology* 2000;31:997-1004.
9. Sulkowski MS. Anemia in the treatment of hepatitis C virus infection. *Clin Inf Dis* 2003;37 Suppl 4:S315-22.
10. McHutchison JG, Manns M, Patel K, et al; International Hepatitis Interventional Therapy Group. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology* 2002;123:1061-9.
11. 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;98:2491-9.
12. Afdhal NH, Dieterich DT, Pockros PJ, et al; Proactive Study Group. Epoetin alfa maintains ribavirin dose in HCV-infected patients: A prospective double-blind, randomized controlled study. *Gastroenterology* 2004;126:1302-11.
13. Fung S, Kaita K, Wong F. Effect of erythropoietin-alpha on sustained virologic response in patients with chronic hepatitis C treated with pegylated interferon and ribavirin. *Can J Gastroenterol* 2006;20:199 (Abst).
14. Stravitz RT, Chung H, Sterling RK, 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.