Erythropoietic Growth Factors for Treatment-Induced Anemia in Hepatitis C: A Cost-Effectiveness Analysis

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Background & Aims: **Treatment-induced anemia undermines the efficacy of antiviral therapy in hepatitis C by mandating ribavirin dose reduction and diminishing adherence to therapy. Erythropoietic growth factors (EGFs) may correct treatment-induced anemia, facilitate maintenance of full-dose therapy, and improve rates of sustained virologic response (SVR). We sought to determine the cost effectiveness of adjunctive treatment with an EGF vs standard care in the treatment of hepatitis C.** ***Methods:*** **We used a decision analysis to calculate the cost effectiveness of 2 treatment strategies for a patient cohort with chronic hepatitis C, increased transaminase levels, and no cirrhosis who were receiving pegylated-interferon and ribavirin (RBV): (1) RBV dose-reduction for anemia, followed by discontinuation of therapy if anemia persisted (standard care strategy), (2) adjunctive treatment with EGF therapy for anemia, with RBV dose reduction reserved for persistent anemia despite EGF therapy (EGF strategy). We conducted cost-effectiveness and cost-utility analyses to compare short- and long-term outcomes between the strategies.** ***Results:*** **The percentage achieving SVR was 52.3% in the standard care strategy and 59.5% in the EGF strategy. Compared with standard care, the EGF strategy cost an incremental $36,568 per unadjusted life-year gained and $16,443 per quality-adjusted life-year gained. In a sensitivity analysis, if a third-party payer was willing to pay $50,000 per quality-adjusted life-year gained for the use of an EGF, then 86.1% of patients would be within the budget.** ***Conclusions:*** **Compared with standard care, adjunctive therapy with an EGF for the management of treatment-induced anemia may increase the probability of achieving SVR, increase unadjusted lifespan, and increase quality-adjusted lifespan at an acceptable cost.**

Chronic hepatitis C virus (HCV) infection is a prevalent and expensive condition affecting 4 million people in the United States at a cost of over $700 million annually.[1] Combination therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV) is adopted widely as the standard of care for HCV on the basis of its effectiveness[2,3] and cost effectiveness.[4–6] Although this regimen achieves a high rate of sustained virologic response (SVR) when therapeutic adherence is optimal, the SVR rate decreases dramatically when adherence is low.[7] In 1 study of PEG-IFN and RBV, the impact of nonadherence was most pronounced in patients with genotype 1 HCV, in which SVR decreased from 52% in adherent patients (defined as those receiving at least 80% of both drugs for at least 80% of the treatment duration) to only 33% in nonadherent patients.[7] Because the primary goal of treatment in HCV is to achieve SVR and ultimately minimize long-term complications of chronic liver disease, it is imperative to maximize therapeutic compliance to preserve the well-established efficacy of PEG-IFN and RBV.

However, compliance with combination therapy is undermined significantly by the development of anemia resulting from RBV-induced hemolysis[8] and, to a lesser extent, by IFN-related bone marrow suppression.[9] Data indicate that up to one third of patients receiving combination therapy develop anemia (hemoglobin [Hgb] level <12 g/dL or a 3 g/dL decrease from baseline Hgb level)[2] and 13% progress to a Hgb level less than 10 g/dL.[10] Moreover, the fatigue and health-related quality of life (HRQOL) decrement associated with treatment-induced anemia[11] leads to dose reduction or discontinuation in nearly one fourth of all patients receiving combination therapy.[12,13] These data present a marked disconnect between the goal of achieving SVR through optimal adherence and the clinical reality of prevalent noncompliance.

Abbreviations used in this paper: EGF, erythropoietic growth factor; EVR, early virologic response; HCV, hepatitis C virus; Hgb, hemoglobin; HRQOL, health-related quality of life; ICER, incremental cost-effectiveness ratio; PEG-IFN, pegylated interferon; QALY, quality-adjusted life-year; RBV, ribavirin; SVR, sustained virologic response.

1542-3565/05/$30.00
PII: 10.1053/S1542-3565(05)00695-6

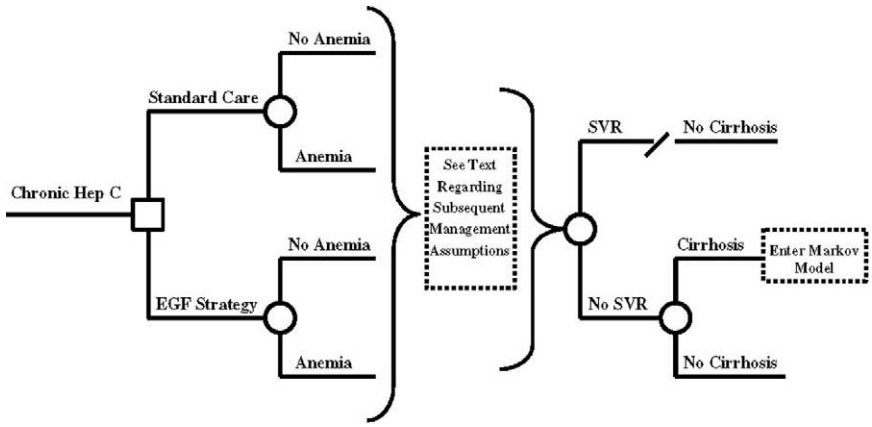

Figure 1. Truncated decision model. The base-case patient has chronic hepatitis C infection, increased transaminase levels, and no clinical or histologic evidence of cirrhosis. The clinician either may treat with IFN and RBV alone without EGF therapy in case of anemia (standard care), or use EGF therapy in case of anemia (EGF strategy). Within each strategy patients either develop treatment-induced anemia or do not. Similarly, in each strategy patients may achieve SVR 6 months after cessation of therapy. Finally, patients failing to achieve SVR are eligible to develop cirrhosis and resulting complications over the course of their lifetime. See text for details regarding specific assumptions governing patient management and probability estimates for individual branch points.

Evolving data indicate that the use of adjuvant erythropoietic growth factors (EGFs) in the treatment of HCV may increase and maintain hemoglobin levels in many patients without requiring RBV dose reduction or outright discontinuation.[14–19] In particular, treating RBV-induced anemia with either epoetin alfa[14–18] or darbepoetin alfa[19] allows maintenance of full-dose therapy in greater than 80% of anemic patients while improving HRQOL.[19,20] In contrast, a recent study showed that only 60% of anemic patients receiving standard care (ie, PEG-IFN and RBV without EGF therapy) were able to maintain full-dose therapy.[16] Taken together, these data suggest that the efficacy of EGF therapy may optimize adherence to full-dose combination therapy by treating anemia, increasing SVR, and, ultimately, minimizing long-term complications of HCV vs the standard approach of relying on RBV dose-reduction alone for treatment-induced anemia. We performed a lifetime cost-effectiveness analysis to determine the degree to which up-front costs of EGF therapy are offset by downstream savings engendered by its improved effectiveness compared with standard care.

Methods

Decision Model Framework

Decision analysis is a quantitative method for estimating the financial costs and clinical outcomes of alternative strategies under conditions of uncertainty.[21] By using decision analysis software (DATA 4.0; TreeAge Software, Inc., Williamstown, MA), we evaluated a hypothetical cohort of 45-year-old patients with chronic HCV infection, increased transaminase levels, and no clinical or histologic evidence of cirrhosis. Patients entered the hypothetical model without previous treatment for HCV and were treated with PEG-IFN and RBV. Patients subsequently received 1 of 2 competing strategies for the management of treatment-induced anemia: (1) RBV dose-reduction if the hemoglobin level decreased to less than 10 g/dL, followed by discontinuation of treatment if the hemoglobin level decreased to less than 8.5 g/dL (standard care strategy), or (2) adjunctive treatment with an EGF for anemia (defined as a Hgb level <12 g/dL or a $\geq$ 3-g/dL decrease) with RBV dose reduction reserved for continued Hgb level decrease despite EGF therapy (EGF strategy).

Figure 1 shows a truncated version of the decision tree. Patients entering the model either developed treatment-induced anemia or maintained an acceptable hemoglobin level. Patients without anemia continued RBV and PEG-IFN treatment at full dose, whereas those with anemia required additional evaluation, as described in the Model Assumptions section later. Patients were followed-up for a lifetime horizon after the initial treatment course. Patients achieving SVR after treatment did not develop cirrhosis and were subjected to a normal life expectancy, as supported by evolving natural history data.[22] In contrast, patients failing to develop SVR were eligible to develop cirrhosis. The subset developing cirrhosis then entered a Markov model governing patient transitions between relevant health states (Figure 2).

Model Assumptions

Base-case patients. To reflect the cohorts described in primary treatment trials, we assumed the base-case patients were 45 years of age and had chronic HCV seropositivity, persistently increased transaminase levels, no symptoms or signs of chronic liver disease, no evidence of anemia, and no other contraindications to treatment. Liver biopsy examination showed no evidence of cirrhosis, although early fibrosis (ie, grades 1–2) was not an exclusion criterion. In accordance with