VALUE IN HEALTH 15 (2012) 876–886

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Cost-Effectiveness of Truncated Therapy for Hepatitis C Based on Rapid Virologic Response

Ziad F. Gellad, MD, MPH[1,2,3,], Andrew J. Muir, MD, MHS[1,2], John G. McHutchison, MD[4], William Sievert, MD[5], Ala I. Sharara, MD[6], Kimberly A. Brown, MD[7], Robert Flisiak, MD[8], Ira M. Jacobson, MD[9], David Kershenobich, MD[10], Michael P. Manns, MD[11], Kevin A. Schulman, MD[1,2], Shelby D. Reed, PhD[1,2]*

[1]*Duke Clinical Research Institute and* [2]*Department of Medicine, Duke University School of Medicine, Durham, NC, USA;* [3]*Durham Veterans Affairs Medical Center, Durham, NC, USA;* [4]*Gilead Pharmaceuticals, Foster City, CA, USA;* [5]*Monash Medical Centre, Monash University, Melbourne, Australia;* [6]*American University of Beirut Medical Center, Beirut, Lebanon;* [7]*Henry Ford Hospital, Detroit, MI, USA;* [8]*Medical University of Bialystok, Bialystok, Poland;* [9]*Weill Cornell Medical College, New York, NY, USA;* [10]*Universidad Nacional Autónoma de México, Hospital General de México, Mexico City, Mexico;* [11]*Medical School of Hannover, Hannover, Germany*

A B S T R A C T

Background: Shortened courses of treatment with pegylated interferon alfa and ribavirin for patients with hepatitis C virus infection who experience rapid virologic response can be effective in appropriately selected patients. The cost-effectiveness of truncated therapy is not known. **Objective:** To assess the cost-effectiveness of response-guided therapy versus standard-duration therapy on the basis of best available evidence. **Methods:** We developed a decision model for chronic hepatitis C virus infection representing two treatment strategies: 1) standard-duration therapy with pegylated interferon alfa and ribavirin for 48 weeks in patients with genotype 1 or 4 and for 24 weeks in patients with genotype 2 or 3 and 2) truncated therapy (i.e., 50% decrease in treatment duration) in patients with rapid virologic response. Patients for whom truncated therapy failed began standard-duration therapy guided by genotype. We used a Markov model to estimate lifetime costs and quality-adjusted life-years. **Results:** In the base-case analysis, mean lifetime costs were \$46,623 ± \$2,483 with standard-duration therapy and \$42,354 ± \$2,489 with truncated therapy. Mean lifetime quality-adjusted life-years were similar between the groups (17.1 ± 0.7 with standard therapy; 17.2 ± 0.7 with truncated therapy). Across model simulations, the probability of truncated therapy being economically dominant (i.e., both cost saving and more effective) was 78.6%. The results were consistent when we stratified the data by genotype. In one-way sensitivity analyses, the results were sensitive only to changes in treatment efficacy. **Conclusion:** Truncated therapy based on rapid virologic response is likely to be cost saving for treatment-naive patients with chronic hepatitis C virus infection. Cost-effectiveness varied with small changes in relative treatment efficacy.

Keywords: chronic, cost-effectiveness, hepatitis C, interferon alfa-2a, interferon alfa-2b, personalized therapy, response-guided therapy, ribavirin, treatment outcome.

Introduction

It is estimated that 2% of the world's population is infected with hepatitis C virus (HCV), representing more than 170 million people [1]. Antiviral therapy with pegylated interferon alfa and ribavirin has shown moderate success in the treatment of patients with chronic HCV infection, although treatment is associated with significant costs and potential side effects [2,3].

Current guidelines in the United States recommend that patients receive a combination of pegylated interferon alfa and ribavirin for durations that vary on the basis of viral genotype. Patients with genotype 1 or 4 receive treatment for 48 weeks; patients with genotype 2 or 3 receive treatment for 24 weeks [4]. In contrast, the most recent guidelines from the European Association for the Study of the Liver [5] recommend that shorter courses of antiviral therapy guided by rapid virologic response (i.e., undetectable viral RNA at week 4) should be considered in appropriately selected patients.

These recommendations are based on data from both observational analyses and randomized clinical trials in which the strength of association between rapid virologic response and sustained virologic response was mixed [6–25]. Furthermore, it is unclear whether the potential short-term benefits to patients and health care systems in reducing treatment duration are offset by a higher proportion of patients who do not have sustained virologic response and experience long-term complications of hepatitis. Nevertheless, clinical consensus in many countries, as represented by the European guidelines, now recommend basing the duration of treatment on rapid virologic response and genotype, also known as response-guided therapy. Thus, the goal of our analysis was to assess the cost-effectiveness of response-guided therapy versus standard-duration therapy on the basis of best available evidence. Although response-guided therapy has not been adopted in the United States, this analysis may help providers evaluate the balance of short-term and long-term costs and benefits of response-guided therapy and provide guidance for the design of future studies to validate the use of rapid virologic response as an actionable biomarker.

* *Address correspondence to:* Ziad F. Gellad, Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715.
E-mail: ziad.gellad@duke.edu.

1098-3015/\$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2012.06.010

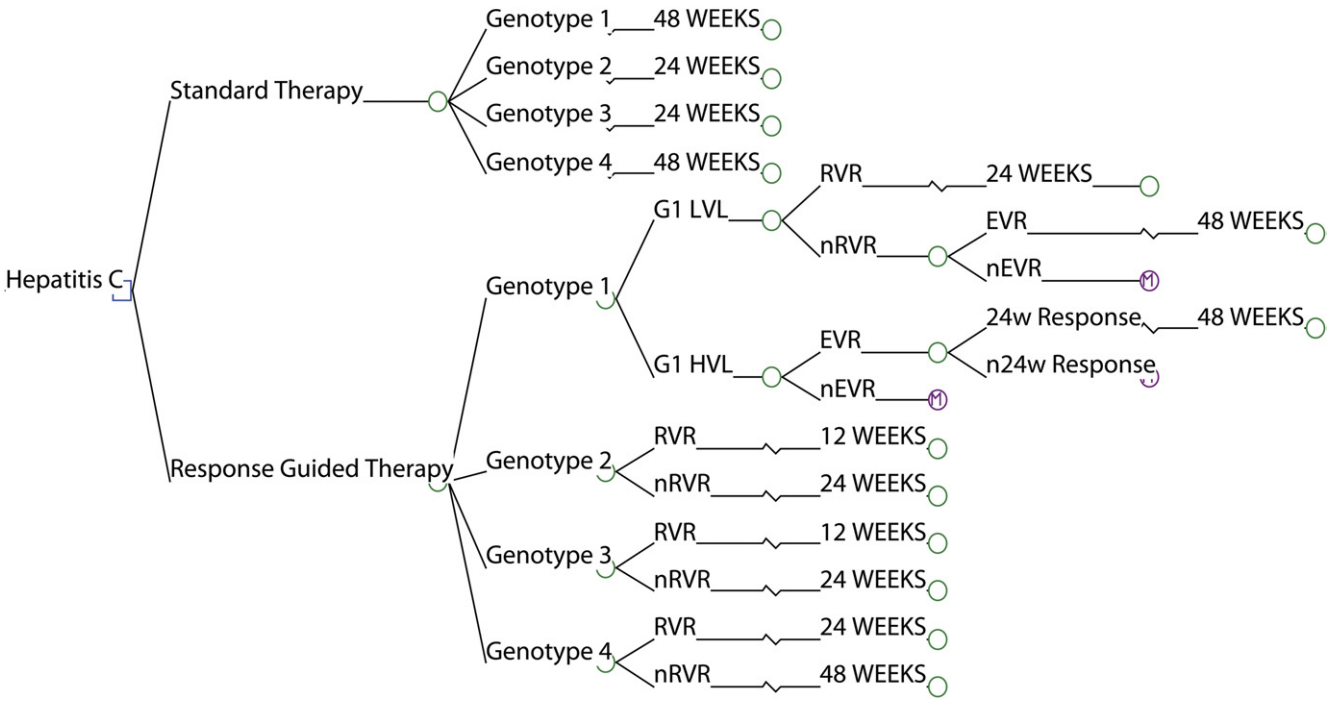

Fig. 1 – Decision tree for standard-duration therapy and response-guided therapy. EVR, early virologic response; HVL, high viral load; LVL, low viral load; nRVR, no rapid virologic response; nSVR, no sustained virologic response; RVR, rapid virologic response; SVR, sustained virologic response.

Methods

In a decision-analytic model (Fig. 1), we compared standard-duration therapy with response-guided therapy in a hypothetical population of treatment-naive patients with chronic HCV infection. In the standard-duration arm, patients with viral genotype 1 or 4 received ribavirin and pegylated interferon alfa for 48 weeks and patients with genotype 2 or 3 received the same therapy for 24 weeks. Treatment of patients with genotype 1 or 4 was halted at week 12 if the patient did not experience early virologic response (i.e., had <2 log reduction in viral RNA at week 12). Patients with genotype 2 or 3 received 24 weeks of therapy regardless of viral kinetics.

In the response-guided arm, the duration of therapy varied on the basis of genotype, baseline viral load for patients with genotype 1, and rapid virologic response at week 4. Treatment duration was truncated by 50% for patients with genotype 1 and low viral load (≤600,000 IU/mL) and for patients with genotypes 2, 3, or 4 who experienced rapid virologic response. Patients with genotype 1 and high viral load stopped treatment at week 12 or 24 if response to therapy was inadequate (i.e., <2 log reduction in viral RNA at week 12 or detectable viral RNA at week 24). The remaining patients in the genotype 1 group without rapid virologic response continued with the full course (i.e., 48 weeks) of treatment. Patients for whom truncated therapy failed were re-treated with standard-duration therapy (i.e., 24 or 48 weeks) guided by viral genotype.

Probabilities of treatment efficacy

Table 1 shows the probabilities used in the decision tree. An international panel of physicians with expertise in viral hepatitis reviewed the published literature for reports comparing the efficacy of standard-duration and response-guided therapy [6–25]. When possible, we selected base-case probabilities and standard errors from a single source in which all relevant probabilities within a genotype were available. For genotype 1, no randomized trial contained both viral kinetic data and rates of sustained virologic response. Thus, we obtained the majority of our estimates from the Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy study [26]. We selected this study because the study sponsor provided robust data on viral kinetics, which are critical to the decision model. Because the Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy trial did not evaluate outcomes with shortened antiviral therapy, we applied the rate of sustained virologic response conditional on having experienced rapid virologic response from a trial designed to test the efficacy of truncated therapy [25]. We selected these rates so that the overall rates of sustained virologic response in the standard-duration and response-guided therapy groups would be similar, consistent with a recent meta-analysis [27].

For genotypes 2 and 3, we obtained estimates of treatment efficacy for standard and truncated therapy from a 2008 meta-analysis by Andriulli et al. [6]. Again, because this source did not report viral kinetics, we used data on rapid virologic response from one of the randomized trials included in the meta-analysis and varied this probability widely in the sensitivity analysis [23]. Treatment efficacy data for genotype 4 were derived from a single published randomized trial [13].

We determined probability ranges on the basis of a review of all available evidence, summarized in Table 1. When relevant alternative estimates were not found (i.e., probability of early virologic response in patients with high viral load, probability of 24-week response in patients with high viral load, and probability of sustained virologic response in patients with high viral load), we estimated ranges as 20% higher or lower than the baseline value. For response-guided therapy, we assumed that the probability of sustained virologic response with re-treatment after failed truncated therapy was 20% in the base-case model and varied this value widely in sensitivity analyses. Finally, we did not assume long-term treatment benefit for patients who experienced relapse and for whom re-treatment failed.