

Individualizing HCV treatment with peginterferon and ribavirin: what needs to be done?

Donald M. Jensen

Therapeutic Advances in Gastroenterology

(2009) 2(1) 5–10

DOI: 10.1177/
1756283X08099398

© The Author(s), 2009.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

While we continue to wait for small molecule hepatitis C virus (HCV) lifecycle inhibitors to truly increase sustained viral response (SVR) rates and enlarge the pool of potential treatment candidates, we are obliged to investigate other means to improve outcomes with the therapies currently at hand. Improved outcomes may take many forms, as follows:

- improved SVR rates with higher doses of interferon or ribavirin;
- shortened treatment duration with similar SVR rates;
- earlier stopping rules to lessen the burden of therapy in those unlikely to respond;
- lengthening treatment duration to decrease relapse rates in those with a slow response to treatment;
- unique approaches for those who are difficult-to-treat, such as those with cirrhosis and obesity/insulin resistance.

Each of these goals is potentially achievable and impacts the way we approach patients with chronic hepatitis C infection. What is the evidence supporting these modes of treatment?

The key to unlocking the evidence for individualized therapy came not from identifying better pre-treatment predictors, but rather from an improved understanding of how HCV responds during the first few weeks of treatment, and then studying the downstream effects on treatment outcome. Clearly, genotype and viral load affect initial responses, but it is the early viral kinetics that

ultimately drives subsequent response rates. Fried and colleagues recently confirmed this in a retrospective analysis of a large multinational HCV database [Fried *et al.* 2008a]. Shiffman *et al.* [2008] showed that time to HCV RNA undetectability was more important than baseline factors in predicting SVR in genotype-1 patients. Regardless of genotype or viral load, the ability to achieve rapid virologic response (RVR, undetectable HCV RNA at week 4) was the most important predictor of subsequent SVR [Fried *et al.* 2008a]. Across all genotypes, RVR was associated with a high SVR rate [Fried *et al.* 2008a]. It has been the ability to utilize this information to develop improved strategies for HCV treatment that has led to the concept of individualized therapy, or ‘response-directed therapy’.

Increasing the dose of interferon or ribavirin

It would seem, on the surface, to be an obvious strategy: give more interferon at early time points to drive the virus more quickly to undetectability, thus providing more patients with RVR and improving SVR. Unfortunately, ‘induction’ dosing of interferon has proven to be an elusive therapeutic panacea. Numerous, well-controlled investigations have demonstrated that, whereas induction interferon may provide an increase in early on-treatment responses, this has not translated into improved SVR rates. Why? It is unclear, but may relate to the duration of the higher dose given. Most investigations have applied induction

Correspondence to:
Donald M. Jensen
Center for Liver Diseases,
University of Chicago
Medical Center
Chicago, USA
[djensen@medicine.bsd.
uchicago.edu](mailto:djensen@medicine.bsd.uchicago.edu)

dosing for only four to twelve weeks, then reverted to standard dosing. This may be too short. In the REPEAT trial of genotype-1, peginterferon/ribavirin nonresponders, 360 µg of peginterferon alfa-2a with 1200 mg ribavirin was administered for twelve weeks in two arms of the trial and compared to standard dosing [Jensen and Marcellin, 2007]. After 12 weeks, the two induction arms had achieved a greater number of responders, but this initial benefit was lost once the dose was reduced after week 12 for the remaining 36 or 60 weeks [Jensen and Marcellin, 2007]. In this regard, Fried and colleagues recently demonstrated that higher doses of both peginterferon (270 µg vs 180 µg) and ribavirin (1600 mg vs 1200 mg) given for 48 weeks was superior to standard doses in particularly difficult-to-treat individuals (genotype 1, high viral load, weighing more than 85 kg) [Fried *et al.* 2008b].

There is evidence from several investigations that higher doses of ribavirin appear to improve SVR rates by decreasing virologic relapse, albeit at the cost of increased anemia. Jacobson and colleagues demonstrated that the use of weight-based ribavirin was associated with improved SVR rates in individuals with high body weight [Jacobson *et al.* 2007]. In fact, the use of very high ribavirin doses (averaging 2500 mg/day), when supported by growth factors and blood transfusions, has been associated with a 90% SVR rate in a small cohort of difficult-to-treat genotype-1 patients [Lindahl *et al.* 2005].

Evidence for the use of higher-dose peginterferon plus ribavirin is less clear for other genotypes. Although Hadziyannis *et al.* [2004] demonstrated that 24 weeks of therapy, incorporating 800 mg/day of ribavirin, gave equivalent treatment results to 48 weeks and 1000–1200 mg/day of ribavirin in non-1 genotypes, the non-1 genotypes were not evaluated separately for differences in response. Subsequent studies have borne this out – genotype 2 does respond better than genotype 3 to the same treatment regime [von Wagner *et al.* 2005]. It is conceivable that specific subgroups of genotype 2 and 3 might benefit from more intensive therapy; for example, genotype 3 with high viral load. Further studies are needed.

Stopping rules

Perhaps one of the more important observations coming out of the registration trials of the two

commercial peginterferon compounds was the ability to define a point in the therapy at which continued treatment would be associated with such a low SVR rate as to make continued treatment unnecessary. Manns *et al.* [2001] noted that if the HCV RNA was still detectable at week 24, continued treatment of genotype 1 was associated with a <1% SVR rate. Fried *et al.* [2002] showed that if the HCV RNA did not decrease at least 2 log₁₀ from baseline by week 12, continued treatment was associated with only a 3% SVR rate. Therefore, the concept of ‘stopping rules’ grew out of these observations: stop treatment if HCV RNA has not declined by at least 2 logs by week 12, or is still detectable by week 24. Whether earlier time points might prove as accurate in defining treatment futility remains to be tested, but it seems likely. The advantages of defining stopping rules are obvious – it limits the burden of therapy to those most likely to have a long-term response. It is important to remember, however, that these rules only apply to patients treated with approved doses of medication over approved treatment durations, and are generally most relevant to patients infected with genotype 1.

Lengthening treatment duration in slow responders

Extending treatment in patients with genotype 1 from 48 to 72 weeks is associated with improved SVR, but would mean treating all patients for this duration [Berg *et al.* 2006]. As more and more patients have been treated with peginterferon plus ribavirin, more robust datasets have allowed identification of additional patient subsets based upon viral kinetics. A particularly intriguing group are those in whom a slow or partial reduction in viral load during the first twelve weeks leads to an eventual end-of-treatment response but a high relapse rate. Would these individuals benefit from an extended treatment duration? Several groups of investigators have tested this hypothesis using different randomization points. Sánchez-Tapias *et al.* [2006] randomized HCV patients after four weeks: those with detectable HCV RNA were randomized to receive either 48 or 72 weeks of total therapy. This study demonstrated a clear benefit to extending treatment duration in those who were still HCV RNA positive at week 4, but suffered from using a low dose of ribavirin (800 mg instead of 1000–1200 mg). Other investigators have confirmed

the value of extended therapy for slow responders [Mangia *et al.* 2008; Pearlman *et al.* 2007; Ferenci *et al.* 2006]. This is an important observation, which appears to confirm the analysis of Drusano and Preston [2004] that the duration of HCV RNA undetectability is an important determinant of SVR.

Shortening treatment duration in rapid responders

Perhaps one of the more exciting concepts to arise from on-treatment viral kinetics was the possibility that treatment duration could actually be shortened in some individuals who responded most dramatically to therapy. This observation, however, entailed earlier routine assessment of HCV RNA than had previously been standard. Ferenci and colleagues revealed a close relationship between time to HCV RNA undetectability and subsequent SVR rate [Ferenci *et al.* 2005]. Studies by Zeuzem *et al.* [2006], and later by Jensen *et al.* [2006], demonstrated that 24 weeks of treatment provided similar overall SVR rates when compared to 48 weeks in genotype-1 patients who had no detectable virus at week 4 (RVR). These 'super responders' were generally comprised of a subset of patients with a low baseline viral load. In a further assessment of the effect of RVR upon treatment duration, Yu *et al.* [2008] performed a prospective, randomized trial in 200 HCV genotype-1 subjects and demonstrated that SVR rates were lower for those treated for 24 weeks, even in those achieving an RVR. This difference was primarily the result of patients with high baseline viral load, since there was no statistical difference in those with low baseline viral load.

Several studies have evaluated the possibility of shortening treatment duration in genotypes 2 and 3 [Lagging *et al.* 2008; von Wagner *et al.* 2005; Shiffman *et al.* 2007; Mangia *et al.* 2005; Zeuzem *et al.* 2004]. Patients infected with genotypes 2 and 3 might respond comparably to a shortened treatment duration, compared with 24 weeks, based upon initial rapid viral response [Mangia *et al.* 2005; von Wagner *et al.* 2005; Zeuzem *et al.* 2004]. It is interesting to speculate why some studies conclude that if an RVR is achieved, treatment of genotype 2 and 3 may be shortened without significant loss of SVR [Mangia *et al.* 2005; von Wagner *et al.* 2005; Zeuzem *et al.* 2004], while others fail to confirm such noninferiority

[Lagging *et al.* 2008; Shiffman *et al.* 2007]. There are clearly many differences in study design, week 4 HCV RNA cut-off for definition of RVR, and dose of ribavirin. Furthermore, these studies suggest that genotype 2 responds more favorably than genotype 3, but loses this difference when treatment duration is shortened following RVR [Shiffman *et al.* 2007]. The interrelationship of genotype, viral load, liver histology and age, as well as dose of ribavirin, could be explanations, but further investigation is required.

Genotype-4-infected patients may also benefit from shortened treatment duration based upon the clinical trial results of Kamal *et al.* [2007]. Genotype-4 patients who achieved an RVR were randomized to receive either 24 or 48 weeks of treatment. Those achieving an RVR had similar SVR rates with either treatment duration.

How much of an impact will these changes in treatment make? Mangia *et al.* [2008] performed a prospective, controlled trial of RVR-based treatment duration in genotype-1-infected patients. These investigators found that shortening treatment duration from 48 to 24 weeks in those achieving an RVR was associated with a quantitatively lower SVR, which did not reach clinical significance. Likewise, extending the duration of therapy from 48 to 72 weeks in those subjects still HCV RNA detectable at week 12 was associated with a small but notable gain in SVR. Therefore, it appears that altering treatment duration in response to early or rapid viral response may not necessarily be associated with significant overall improvements in SVR rate, but may certainly allow more targeted treatment durations – limiting the burden of therapy in those with an RVR, while improving SVR in those with a slow initial response at the cost of additional treatment duration.

Cirrhosis

HCV cirrhosis represents another subgroup of patients for whom treatment may require individualization [Strader *et al.* 2004]. Not only is there concern for increased side effects, decompensation and infection risk [Crippin *et al.* 2002], but patients with cirrhosis seem to respond less well to conventional doses and durations of peginterferon and ribavirin [Crippin *et al.* 2002; Fried *et al.* 2002; Manns *et al.* 2001]. Perhaps more

than any other subgroup of patients, cirrhotic patients have the most to gain from successful viral eradication. Several studies have reported a lower incidence of hepatocellular carcinoma [Shiratori *et al.* 2005], and possibly a decreased requirement for liver transplantation in successfully treated HCV cirrhosis [Everson *et al.* 2005]. How then should we treat patients who have cirrhosis? Well-compensated cirrhotic patients with preserved hematologic parameters probably require no revision of current treatment guidelines. On the other hand, we are in need of good prospective studies of treatment approaches for patients with decompensated liver disease and those with significant cytopenias.

Insulin resistance and fatty liver

Obesity and hepatic steatosis have been associated with a decreased response to interferon plus ribavirin therapy [Westin *et al.* 2007; Charlton *et al.* 2006; Negro 2006; Patton *et al.* 2004; Bressler *et al.* 2003]. Several mechanisms may be responsible for this interference, including a decrease in hepatocyte interferon signaling. It remains less clear, however, whether weight loss and/or treatment of the metabolic syndrome will improve subsequent interferon plus ribavirin therapy. Although it seems intuitive that it should, few studies have examined the effect of weight loss on steatosis in HCV-infected subjects. Hickman and colleagues demonstrated that a 10% reduction in body weight was associated with significant reductions in hepatic steatosis [Hickman *et al.* 2004, 2002]. Should we advise patients who are overweight and have evidence of steatosis to lose weight prior to treatment? Assuming the treatment is not urgent, such a recommendation seems to make sense on a number of levels.

Future studies

Although we have made significant improvements in HCV therapy, we still have many unanswered questions:

- We seem locked in to a 12-, 24-, 48-, 72-week treatment duration paradigm. Should we examine alternative treatment durations (36 weeks, 60 weeks)?
- Is there a role for induction therapy with either peginterferon or ribavirin (or both)? If so, at what dose and for what treatment duration?

- What is the appropriate way to treat decompensated cirrhotics, if at all? Should they be treated prior to transplant? If so, how? What is the risk? What is the upside gain if we are successful?
- Does pretreatment, or concomitant treatment, with an insulin sensitizer improve response to peginterferon plus ribavirin in those subjects with steatosis and the metabolic syndrome?
- Which, if any, obese patients should be recommended to lose weight prior to initiation of therapy?

Clearly there is still much work left to do, the results of which should enhance our ability to more effectively treat our HCV patients.

Conflict of interest statement

Research support: Roche, Schering-Plough, Boehringer-Ingelheim, Vertex, Globeimmune
Consultant: Abbott, Roche, Boehringer-Ingelheim, Vertex, Globeimmune

References

- Berg, T., von Wagner, M., Nasser, S., Sarrazin, C., Heintges, T., Gerlach, T. *et al.* (2006) Extended treatment duration for hepatitis C virus type 1: comparing 48 vs 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology* 130: 1086–1097.
- Bressler, B., Guindi, M., Tomlinson, G. and Heathcote, J. (2003) High body mass index is an independent risk factor for nonresponse to antiviral treatment in chronic hepatitis C. *Hepatology* 38: 639–644.
- Charlton, M., Pockros, P. and Harrison, S. (2006) Impact of obesity on treatment of chronic hepatitis C. *Hepatology* 43: 1177–1186.
- Crippin, J.S., McCashland, T., Terrault, N., Sheiner, P. and Charlton, M.R. (2002) A pilot study of the tolerability and efficacy of antiviral therapy in hepatitis C virus-infected patients awaiting liver transplantation. *Liver Transpl* 8: 350–355.
- Drusano, G.L. and Preston, S.L. (2004) A 48-week duration of therapy with pegylated interferon alpha 2b plus ribavirin may be too short to maximize long-term response among patients infected with genotype-1 hepatitis C virus. *J Infect Dis* 189: 964–970.
- Everson, G.T., Trotter, J., Forman, L., Kugelmas, M., Halprin, A., Fey, B. *et al.* (2005) Treatment of advanced hepatitis C with a low accelerating dosage regimen (LADR) of antiviral therapy. *Hepatology* 42: 255–262.

- Ferenci, P., Laferl, H., Scherzer, T.M., Maieron, A., Gshwanter, M., Brunner, H. *et al.* (2006) Customizing treatment with peginterferon alfa-2a (40 KD)(Pegasys) plus ribavirin (Copegus) in patients with HCV genotype 1 or 4 infection. Interim results of a prospective, randomized trial. *Hepatology* 48: 336A.
- Ferenci, P., Fried, M., Shiffman, M., Smith, C., Marinos, G., Goncales, F. *et al.* (2005) Predicting sustained virological response in chronic hepatitis C patients treated with peginterferon alfa-2a (40 KD)/ribavirin. *J Hepatol* 43: 425–433.
- Fried, M., Hadziyannis, S., Shiffman, M., Messinger, D. and Zeuzem, S. (2008a) Rapid virological response is a more important predictor of sustained virological response (SVR) than genotype in patients with chronic hepatitis C infection. *J Hepatol* 48: S5.
- Fried, M.W., Jensen, D.M., Rodriguez-Torres, M., Nyberg, L.M., Di Bisceglie, A.M., Morgan, T.R. *et al.* (2008b) Improved outcomes in patients with hepatitis C with difficult-to-treat characteristics: Randomized study of higher doses of peginterferon α -2a and ribavirin. *Hepatology* 48: p1033–1043.
- Fried, M.W., Shiffman, M.L., Reddy, K.R., Smith, C., Marinos, G., Goncales, Jr. F.L. *et al.* (2002) Combination of peginterferon alfa-2a plus ribavirin in patients with chronic hepatitis C virus infection. *N Engl J Med* 347: 975–982.
- Hadziyannis, S.J., Sette, Jr. H., Morgan, T.R., Balan, V., Diago, M., Marcellin, P. *et al.* (2004) Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 140: 346–355.
- Hickman, I.J., Jonsson, J.R., Prins, J.B., Ash, S., Purdie, D.M., Clouston, A.D. *et al.* (2004) Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. *Gut* 53: 413–419.
- Hickman, I.J., Clouston, A.D., MacDonald, G.A., Purdie, D.M., Prins, J.B., Ash, S. *et al.* (2002) Effect of weight reduction on liver histology and biochemistry in patients with chronic hepatitis C. *Gut* 5: 89–94.
- Jacobson, I., Brown, R., Freichlich, B., Afdal, N., Kwo, P., Santoro, J. *et al.* (2007) Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. *Hepatology* 46: 982–990.
- Jensen, D.M. and Marcellin, P. (2007) Pegylated interferon alfa-2a (40KD) plus ribavirin (RBV) in prior non-responders to pegylated interferon alfa-2b (12KD)/RBV: final efficacy and safety outcomes of the REPEAT study. *Hepatology* 46: 291A.
- Jensen, D.M., Morgan, T.R., Marcellin, P., Pockros, P.J., Reddy, K.R., Hadziyannis, S. *et al.* (2006) Early Identification of HCV genotype 1 patients responding to 24 weeks peginterferon α -2a (40kd)/ribavirin therapy, *Hepatology* 43: 954–960. [Erratum, *Hepatology* 43: 1410].
- Kamal, S.M., El Kamary, S., Shardell, M., Hashem, M., Ahmed, I., Muhammadi, M. *et al.* (2007) Peginterferon alpha-2b plus ribavirin in patients with genotype 4 chronic hepatitis C: the role of rapid and early virologic response. *Hepatology* 46: 1732–1740.
- Lagging, M., Langeland, N., Pedersen, C., Förkkilä, M., Buhl, M.R., Mørch, K. *et al.* (2008) Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. *Hepatology* 47: 1837–1845.
- Lindahl, K., Stahle, L., Bruchfeld, A. and Schvarcz, R.. (2005) High-dose ribavirin in combination with standard dose peginterferon for treatment of patients with chronic hepatitis C. *Hepatology* 41: 275–279.
- Mangia, A., Minerva, N., Bacca, D., Cozzolongo, R., Ricci, G., Carretta, V. *et al.* (2008) Individualized treatment duration for hepatitis C genotype 1 patients: A randomized controlled trial. *Hepatology* 47: 43–50.
- Mangia, A., Santoro, R., Minerva, N., Ricci, G., Carretta, V., Persico, M. *et al.* (2005) Peginterferon alfa-2b and ribavirin for 12 vs 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 352: 2609–2617.
- Manns, M.P., McHutchison, J.G., Gordon, S.C., Rustgi, V.K., Shiffman, M., Reindollar, R. *et al.* (2001) Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 358: 958–965.
- Negro, F. (2006) Insulin resistance and HCV: Will new knowledge modify clinical management? *J Hepatol* 45: 514–519.
- Patton, H.M., Patel, K., Behling, C., Bylund, D., Blatt, L.M., Vallee, M. *et al.* (2004) The impact of steatosis on disease progression and early and sustained treatment response in chronic hepatitis C patients. *J Hepatol* 40: 484–490.
- Pearlman, B.L., Ehleben, C. and Saifee, S. (2007) Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis C genotype 1-infected slow responders. *Hepatology* 46: 1688–1694.
- Sánchez-Tapias, J.M., Diago, M., Escartin, P., Enriquez, J., Romero-Gómez, M., Bárcena, R. *et al.* (2006) Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology* 131: 451–460.
- Shiffman, M., Chung, R. and Hamzeh, F. (2008) Time to HCV RNA undetectability supersedes baseline factors in predicting SVR in patients with HCV genotype 1. *J Hepatol* 48: S313.
- Shiffman, M.L., Suter, F., Bacon, B.R., Nelson, D., Harley, H., Sola, R. *et al.* (2007) Peginterferon

alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 357: 124–134.

Shiratori, Y., Ito, Y., Yokosuka, O., Imazeki, F., Nakata, R., Tanaka, N. *et al.* (2005) Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. *Ann Intern Med* 142: 105–114.

Strader, D., Wright, T., Thomas, D. and Seeff, L. (2004) Diagnosis, management and treatment of hepatitis C. *Hepatology* 39: 1147–1171.

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

Westin, J., Lagging, M., Dhillon, A.P., Norkans, G., Romero, A., Pawletsky, J.M. *et al.* (2007) Impact of hepatic steatosis on viral kinetics

and treatment outcome during antiviral treatment of chronic HCV infection. *J Viral Hepatitis* 14: 29–35.

Yu, M.L., Dai, C.Y., Huang, J.F., Chiu, C.F., Yang, Y.H., Hou, N.J. *et al.* (2008) Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial. *Hepatology* 47: 1884–1893.

Zeuzem, S., Buti, M., Ferenci, P., Sperl, J., Horsmans, Y., Cianciara, J. *et al.* (2006) Efficacy of 24 weeks treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia. *J Hepatol* 44: 97–103.

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

Visit SAGE journals online
<http://tag.sagepub.com>

 SAGE JOURNALS
Online