

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Telaprevir in the Treatment of Patients With Genotype 1 Hepatitis C

Andrew J. Muir, MD, MHS  
Associate Professor of Medicine  
Director, Gastroenterology/Hepatology Research  
Duke University School of Medicine  
Durham, North Carolina

### **A discussion of:**

*JG McHutchison, MP Manns, A Muir, N Terrault, IM Jacobson, NH Afdhal, E Heathcote, S Zeuzem, HW Reesink, M Bsharat, S George, N Adda, AM Di Bisceglie. PROVE3 Final Results and 1-Year Durability of SVR with Telaprevir-Based Regimen in Hepatitis C Genotype 1-Infected Patients with Prior Non-response, Viral Breakthrough or Relapse to Peginterferon-Alfa-2a/b and Ribavirin Therapy. Presented at the 60<sup>th</sup> Annual Meeting of the American Association for the Study of Liver Diseases; October 30–November 3, 2009; Boston, MA.*

### **G&H** Why did this study focus on the genotype-1 subgroup of hepatitis C virus–infected patients?

**AM** Genotype 1 is the most common subgroup of patients infected with the hepatitis C virus (HCV), the most common in the United States, comprising approximately 75% of the patient population. Genotype-1 patients also require the longest treatment duration and have the lowest response rates. In other words, there is a strong need for improvements in therapy for this particular patient population.

### **G&H** Why is it important to find new treatment options for nonresponding or relapsed patients?

**AM** This study focused on patients who had previously failed standard-of-care treatment. Typically, these patients

have not had many treatment options. For nonresponding patients—those who did not experience a complete clearance of the virus during a previous course of treatment for HCV—the odds of experiencing a response to the same therapy are extremely low. Currently, treatment options for these patients are very limited.

The other group of patients included in this study were those who did clear their virus during prior treatment but then relapsed after treatment was discontinued. These patients may respond to additional therapy with the same regimen, perhaps with slight alterations. It may be that a previous dose reduction was inappropriate and that re-administering the same drugs will have some beneficial effect. However, in general, relapsed patients do not respond well to a repetition of the same treatment.

This study evaluated whether a protease inhibitor added to the standard treatment regimen would improve responses for these patients.

### **G&H** What was the rationale for the inclusion of telaprevir?

**AM** Telaprevir targets the NS3 protease enzyme and is one of an emerging group of therapies referred to direct antiviral medication. Peginterferon alfa, which is essentially the backbone of therapy, attacks hepatitis C through modulation of the immune system. By contrast, telaprevir targets the virus directly.

### **G&H** Why does it need to be given in combination with peginterferon alfa and ribavirin?

**AM** On their own, protease inhibitors are not strong enough to cure patients of HCV. Patients develop resistance to these agents very quickly when given alone. We found early on that we need to combine the direct antiviral agent with peginterferon alfa and ribavirin in order for patients to experience a therapeutic benefit.

**G&H** What was the aim of the PROVE3 study?

**AM** After seeing the benefit of telaprevir in combination with peginterferon alfa and ribavirin for treatment-naïve HCV patients, the next logical question was: Will this drug also benefit patients who have failed the standard combination regimen? As described above, these patients are more difficult to treat. The aim of the PROVE3 trial was to evaluate whether adding telaprevir to peginterferon alfa and ribavirin was beneficial for previously treated patients.

**G&H** Was there a phase I study of this regimen?

**AM** A phase I study was conducted in treatment-naïve patients, which was followed by PROVE1, a phase II study also with treatment-naïve patients.

**G&H** Could you describe the methods of the PROVE3 study?

**AM** A total of 453 genotype-1 HCV patients who had either not responded or failed standard-of-care treatment were recruited for this trial. All patients were randomized to 1 of 4 groups: 12 weeks of triple combination therapy followed by 12 weeks of peginterferon alfa-2a plus ribavirin; 24 weeks of the triple combination followed by 24 weeks of peginterferon alfa-2a plus ribavirin; telaprevir plus peginterferon alfa-2a for 24 weeks, with no ribavirin administered; or with the control arm of peginterferon alfa-2a and ribavirin alone.

**G&H** Were relapsed and nonresponding patients randomized together, or were they separated prior to randomization?

**AM** Patients were categorized according to achievement or nonachievement of undetectable HCV RNA during their previous course of treatment, and randomization was stratified according to this response with the prior course of treatment. The patients who had not achieved undetectable HCV RNA were nonresponders. Most of the patients who had been undetectable were relapsers with a smaller group of patients who had viral breakthrough in that previous course of treatment.

**G&H** What comparisons did having 4 separate groups enable the investigators to make?

**AM** Randomizing patients to 4 treatment groups enabled us to compare different durations of treatment (24 weeks vs 48 weeks), ribavirin versus no ribavirin

when telaprevir was included in the regimen, and telaprevir versus no telaprevir.

**G&H** What were the response rates among the different groups?

**AM** The primary endpoint was sustained virologic response (SVR), defined as undetectable hepatitis C RNA at 24 weeks after stopping therapy. Fifty-one percent of patients in the first treatment group and 53% in the second group experienced this response. The third treatment group, which included no ribavirin, had a response rate of only 24%. The control group, which included no telaprevir, had a response rate of 14%.

The number of patients who achieved undetectable HCV at 24 weeks was higher among the treatment groups that included telaprevir compared with those that did not, and the triple combination was associated with better responses than regimens that excluded either ribavirin or telaprevir.

**G&H** Was there a difference in response between patients who had not responded to prior therapy versus patients who had relapsed?

**AM** Yes. Patients who relapsed with their prior therapy had a higher overall response rate compared to previously nonresponding patients. That being said, the latter group did respond quite favorably to the triple combination compared to the control group.

**G&H** Could you explain why the overall response rate was higher among relapsed patients versus previously nonresponding patients?

**AM** Relapsed patients are those who experienced a reduction in viral load after previous therapy, even achieving a negative virus status. This outcome indicates that the standard of care was effective, but not strong enough to completely cure these patients. For this group, adding telaprevir gives the therapeutic boost that is necessary for these patients to be cured of HCV. Patients who did not respond to prior therapy are clearly more difficult to treat; their disease is more resistant.

**G&H** What did the investigators conclude about the benefit of telaprevir for the patient populations included in this study?

**AM** The results of this phase II study need to be confirmed in a phase III study, which is ongoing. Based on these findings, we concluded that, when added to the

standard treatment regimen, telaprevir is a good option for HCV genotype-1 patients who had either failed or not responded to prior therapy.

**G&H** Did the findings conclusively indicate that a longer duration (48 weeks) of the triple combination does not confer a statistically significant benefit compared with a shorter duration (24 weeks)?

**AM** The results for the 24- and 48-week treatment arms were similar in this study, and this question is being assessed in other ongoing studies with telaprevir.

**G&H** Were there any significant side effects?

**AM** Side effects observed among patients who received the triple combination included those seen with peginterferon alfa and ribavirin alone: flu-like symptoms, fatigue, and bone marrow suppression. Ribavirin causes anemia as its main side effect.

Telaprevir is associated with a rash, which was severe in 5% of patients in this study. Patients who experience this adverse event should be watched closely. Depending on the severity of the rash, telaprevir may need to be stopped either temporarily or completely.

**G&H** According to the findings of this study, is ribavirin a necessary component of a telaprevir-containing regimen for HCV?

**AM** Yes, we anticipate that the ultimate treatment regimen that includes telaprevir will also include ribavirin. In

this and in other studies with telaprevir, regimens without ribavirin are less effective.

**G&H** Is there a clear sense why telaprevir is beneficial for these patients?

**AM** Telaprevir acts directly against the virus. Prior to this study, there was concern about giving protease inhibitors to patients who had not responded to prior therapy. As mentioned above, patients who received just telaprevir alone developed resistance very quickly. If a patient experienced very little or no antiviral benefit from peginterferon alfa and ribavirin, there was concern that adding telaprevir to this combination could be akin to administering monotherapy with just the protease inhibitor. There was a concern that nonresponders would be more likely to experience resistance to the triple combination. The results from this study would suggest that this concern was not realized. It was encouraging that we did see good response rates among patients who were previous nonresponders.

### Suggested Reading

McHutchison JG, Manns MP, Muir AJ, et al. Telaprevir for previously treated chronic HCV infection. *N Engl J Med.* 2010;362:1293-1303. Erratum in: *N Engl J Med.* 2010;362:1647.

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