Interferon-Free Regimens for Chronic Hepatitis C—A Step Forward

Abstract 1

Poordad F, Lawitz E, Kowdley KV, Cohen DE, Podsadecki T, Siggelkow S, Heckaman M, Larsen L, Menon R, Koev G, Tripathi R, Pilot-Matias T, Bernstein B. Exploratory study of oral combination antiviral therapy for hepatitis C. *N Engl J Med*. 2013 Jan 3; 368(1):45–53.

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Background: There is a need for interferon-free treatment regimens for hepatitis C virus (HCV) infection. The goal of this study was to evaluate ABT-450, a potent HCV NS3 protease inhibitor, combined with low-dose ritonavir (ABT-450/r), in addition to ABT-333, a non-nucleoside NS5B polymerase inhibitor, and ribavirin, for the treatment of HCV infection. **Methods:** We conducted a 12-week, phase 2a, open-label study involving patients who had HCV genotype 1 infection without cirrhosis. All patients received ABT-333 (400 mg twice daily) and ribavirin (1000–1200 mg per day) and one of two daily doses of ABT-450/r. Groups 1 and 2 included previously untreated patients; group 1 received 250 mg of ABT-450 and 100 mg of ritonavir, and group 2 received 150 mg and 100 mg, respectively. Group 3, which included patients who had had a null or partial response to previous therapy with peginterferon and ribavirin, received daily doses of 150 mg of ABT-450 and 100 mg of ritonavir. The primary end point was an undetectable level of HCV RNA from week 4 through week 12 (extended rapid virologic response).

Results: A total of 17 of the 19 patients in group 1 (89%) and 11 of the 14 in group 2 (79%) had an extended rapid virologic response; a sustained virologic response 12 weeks after the end of treatment was achieved in 95% and 93% of the patients, respectively. In group 3, 10 of 17 patients (59%) had an extended rapid virologic response, and 8 (47%) had a sustained virologic response 12 weeks after therapy; 6 patients had virologic breakthrough, and 3 had a relapse. Adverse events included

abnormalities in liver-function tests, fatigue, nausea, headache, dizziness, insomnia, pruritus, rash, and vomiting.

Conclusions: This preliminary study suggests that 12 weeks of therapy with a combination of a protease inhibitor, a non-nucleoside polymerase inhibitor, and ribavirin may be effective for treatment of HCV genotype 1 infection.

Abstract 2

Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, Hindes RG, Berrey MM. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med*. 2013 Jan 3;368(1):34–44.

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Background: The standard treatment for hepatitis C virus (HCV) infection is interferon, which is administered subcutaneously and can have troublesome side effects. We evaluated sofosbuvir, an oral nucleotide inhibitor of HCV polymerase, in interferon-sparing and interferon-free regimens for the treatment of HCV infection.

Methods: We provided open-label treatment to eight groups of patients. A total of 40 previously untreated patients with HCV genotype 2 or 3 infection were randomly assigned to four groups; all four groups received sofosbuvir (at a dose of 400 mg once daily) plus ribavirin for 12 weeks. Three of these groups also received peginterferon alfa-2a for 4, 8, or 12 weeks. Two additional groups of previously untreated patients with HCV genotype 2 or 3 infection received sofosbuvir monotherapy for 12 weeks or sofosbuvir plus peginterferon alfa-2a and ribavirin for 8 weeks. Two groups of patients with HCV genotype 1 infection received sofosbuvir and ribavirin for 12 weeks: 10 patients with no response to prior treatment and 25 with no previous treatment. We report the rate of sustained virologic response 24 weeks after therapy.

Results: Of the 40 patients who underwent randomization, all 10 (100%) who received sofosbuvir plus ribavirin without interferon and all 30 (100%) who received sofosbuvir plus ribavirin for 12 weeks and interferon for 4, 8, or 12 weeks had a sustained virologic response at 24 weeks. For the other patients with HCV genotype 2 or 3 infection, all 10 (100%) who received sofosbuvir plus peginterferon alfa-2a and ribavirin for 8 weeks had a sustained virologic response at 24 weeks, as did 6 of 10 (60%) who received sofosbuvir monotherapy. Among patients with HCV genotype 1 infection, 21 of 25 previously untreated patients (84%) and 1 of 10 with no response to previous therapy (10%) had a sustained virologic response at 24 weeks. The most common adverse events were headache, fatigue, insomnia, nausea, rash, and anemia.

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Conclusions: Sofosbuvir plus ribavirin for 12 weeks may be effective in previously untreated patients with HCV genotype 1, 2, or 3 infection.

COMMENTS

Presently the standard of care (SOC) for the patients with chronic hepatitis C (CHC) is either a dual regimen [Pegylated interferon (Peg IFN) + Ribavirin (Riba)] for genotype 2 and 3 infections or a triple therapy (Peg IFN + Riba + Protease inhibitor-telaprevir or boceprevir) for genotype 1 infections.^{1,2} Sustained virological response (SVR) at 6 months after the end of treatment with these regimens are close to 75% and are almost similar for genotypes 1, 2 and 3 of hepatitis C virus (HCV). Even though there is no change in the SVR rates of genotype 2 and 3 HCV, there has been a major change in patients with genotype 1 HCV infections where the SVR has improved from 40% to 75% with triple therapy in comparison to the dual regimen used earlier.^{1,2}

In spite of a reasonable good response with the present SOC, there is still a scope of improvement in the treatment of both genotype 1 and non-genotype1 infections of HCV. All patients with CHC are not eligible for interferon treatment as interferon based regimens can only be given to patients who qualify certain minimum criteria. Because of the injection based regimens many patients even refuse the treatment especially because of the side effects and adverse reactions related to the effects of interferon. Some patients are even withdrawn from the treatment because of these adverse events. Because of the issues related to the interferon use in patients with CHC and the ever increasing pool of non-responders and relapsers, there is need for the alternative strategies in the treatment of patients with CHC. Direct anti viral drugs (DAA) and host targeting agents (HTA) which can be used without interferon and act at different phases of viral replication cycle and host targets are one of the recent class of drugs which have shown promising results not only in improving the SVR rates but in also avoiding the other problems associated with interferon use.³

Various groups of DAA are now undergoing clinical trials.³ Earliest of the two NS3/4 A protease inhibitors which have been approved by the Food and Drug Administration (FDA), USA for the use as triple therapy (with Peg IFN and Riba) in genotype 1 patients are the telaprevir and boceprevir (first generation PIs).² Other drugs in the same group include Danoprevir, Vaniprevir, BMS-650032, ABT-450 and few more. The group of nucleoside/nucleotide polymerase inhibitors include drugs like Sofosbuvir, PSI-938, Mericitabine and IDX-184. In the non-nucleoside polymerase inhibitors are the drugs like Filibuvir, Tegobuvir, VX-222, ABT-072 and ABT-333 and among the NS5A inhibitors are drugs like Daclatasvir and GS-5885. HTA includes cyclophilin inhibitors like Alisporivir and SCY-635 and the

blockers of micro RNA 122.³ An ideal non-interferon drug for CHC should have high cure rates in all categories of patients (independent of host's and viral characteristics—pan genotype effect), good side-effect profile and it should be an all oral, once-daily regimen with short treatment duration with limited drug–drug interactions (especially with immunosuppressant medications) and should be affordable in all countries. Even though we are far away from such an ideal drug or a combination of such drugs several steps have been made in that direction. Two recent trials (Abstract 1 and 2) published in the recent issue of New England Journal of Medicine are such steps in that direction.^{4,5}

In one of the trials (Abstract 1), ABT-450, a potent inhibitor of the HCV NS3 protease, has been combined with ritonavir (ABT-450/r) to increase the ABT-450 plasma concentration and half-life, permitting once-daily dosing.⁴ The study assessed the safety and efficacy of the combination of ABT-450/r and ABT-333 with ribavirin in previously untreated patients with HCV genotype 1 infection and in patients with a null or partial response to previous treatment with peginterferon and ribavirin. The primary end point in this study was the percentage of patients with virologic suppression by week 4 of treatment and sustained suppression through week 12 (eRVR). That end point was met in 28 of the 33 previously untreated patients and in 10 of the 17 patients who had undergone previous treatment. Among the previously untreated patients, there were no virologic failures during treatment or during 48 weeks of follow-up for those who completed treatment. In contrast, 9 of the 17 patients with a null or partial response to previous therapy either had virologic breakthrough or had a relapse by the date of their first follow-up visit after treatment. In most cases, virologic failure was associated with the emergence of variants with substitutions in both NS3 and NS5B, at positions known to confer resistance in vitro to ABT-450 and ABT-333, respectively.⁴

Even though the results of this study are very encouraging, studies with larger sample size using similar regimens will be needed to confirm these findings in subgroups based on HCV genotype, viral load, race, sex, age, severity of liver disease (cirrhotic Vs non-cirrhotics) and the associated HIV infection. Overall this study suggests the limitation of using all oral regimen in patients with HCV genotype 1 infection with a null or partial response to previous therapy, emergence of variants being the most common reason for virological failure. Whether extending treatment beyond 12 weeks could be of help in these patients need to be studied in separate studies.

Sofosbuvir (formerly known as GS-7977) is a direct-acting nucleotide polymerase inhibitor used as an oral drug for the treatment of CHC. The active triphosphate of nucleotide analogs such as sofosbuvir targets the highly conserved active site of the HCV-specific NS5B polymerase, acting as a non-obligate chain terminator, an effect that

is independent of the viral genotype. Hence sofosbuvir is effective against all genotypes and till date no virologic breakthrough has been observed during sofosbuvir therapy. In another article in the recent issue of NEJM (Abstract 2), authors report results from the Electron trial, a multipart, phase 2a study designed to test the safety and efficacy of sofosbuvir and ribavirin in various interferon-sparing and interferon-free regimens for the treatment of patients with HCV genotype 1, 2, or 3 infections.⁵ Patients with CHC without cirrhosis (serum HCV RNA level, >50,000 IU per milliliter) were enrolled at two centers in New Zealand. Both in the previously untreated and treated patients with HCV genotype 1, 2, or 3 infection, HCV RNA levels declined rapidly after the initiation of treatment. By week 4 of treatment, all 95 patients had an undetectable level of HCV RNA, which was maintained until the end of treatment. All 50 previously untreated patients with HCV genotype 2 or 3 infection who received 8 or 12 weeks of treatment with sofosbuvir and ribavirin, with or without peginterferon alfa-2a, had a sustained virologic response at 24 weeks after treatment. Of 10 patients who received sofosbuvir alone without ribavirin, sustained virologic response was seen in 6 patients. The adverse events that occurred in different groups of patients were generally those associated with peginterferon and ribavirin. No patients discontinued sofosbuvir or ribavirin in any group.⁵

The uniform response obtained in all groups of patients is remarkable because the eight treatment groups included different patient populations, i.e. patients who had an infection with HCV genotype 1, 2, or 3; treatment naive patients; and previous non-responders to interferon and ribavirin. All 10 patients who received sofosbuvir alone also had an undetectable level of HCV RNA by week 4 of treatment, which was maintained for the duration of treatment but 4 of these patients, had a relapse after the end of treatment. These results suggest that in patients with HCV genotype 2 or 3 infection, ribavirin is required with sofosbuvir for the maintenance of an antiviral response. In patients with HCV genotype 1 infection, there were higher rates of sustained virologic response among treatment naive patients, as compared with non-responders to previous treatment with pegylated interferon plus ribavirin. The

absence of viral breakthrough in any patient during treatment in the study confirms that sofosbuvir has a high genetic barrier to resistance.

What we require in India are the interferon free, short duration all oral drugs which are effective against genotype 3, which is the predominant genotype in this country. Though polymerase inhibitors like sofosbuvir have pan genotype effect, other drugs are effective only against genotype 1. The second important issue for us would be cost and thus the affordability and availability of these drugs for the major section of patients with CHC. Other issues which need to be addressed are the drug resistance, efficacy in non-responders and relapsers, drug interactions and their efficacy in patients with cirrhosis and advanced fibrosis. More data is required about efficacy of interferon-free regimens in patients with CHC with respect to the IL-28 genotype and the differences in efficacy between genotype 1a and 1b patients with CHC.

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