Accepted Manuscript

Oral combination therapy: future hepatitis C virus treatment?

Christophe Hézode

PII: S0168-8278(11)00382-5
DOI: 10.1016/j.jhep.2011.04.018
Reference: JHEPAT 3846

To appear in: *Journal of Hepatology*

Received Date: 2 March 2011
Revised Date: 29 March 2011
Accepted Date: 3 April 2011

Please cite this article as: Hézode, C., Oral combination therapy: future hepatitis C virus treatment?, *Journal of Hepatology* (2011), doi: 10.1016/j.jhep.2011.04.018

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Oral combination therapy: future hepatitis C virus treatment?

Christophe Hézode,[1,2]

[1]*Department of Hepatology and Gastroenterology, Hôpital Henri Mondor, Université Paris-Est, Créteil, France;* [2]*INSERM U955, Créteil, France.*

Address**:** Service d'Hépatologie et de Gastroentérologie, Hôpital Henri Mondor, 51 avenue du Maréchal de Lattre de Tassigny, 94010 Créteil Cedex, France. Tel.: +33 1 49 81 23 25; fax: +33 1 49 81 23 52

E-mail address: christophe.hezode@hmn.aphp.fr (C.Hézode)

COMMENTARY ON:

Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose-escalation trial. Gane EJ, Roberts SK, Stedman CA, Angus PW, Ritchie B, Elston R, Ipe D, Morcos PN, Baher L, Najera I, Chu T, Lopatin U, Berrey MM, Bradford W, Laughlin M, Shulman NS, Smith PF. Lancet. 2010 Oct 30;376(9751):1467-75. Reprinted from The Lancet, Copyright (2010), with permission from Elsevier.

http://www.ncbi.nlm.nih.gov/pubmed/20951424

Abstract. Background*: Present interferon-based standard of care treatment for chronic hepatitis C virus (HCV) infection is limited by both efficacy and tolerability. We assessed the safety, tolerability, and antiviral activity of an all-oral combination treatment with two experimental anti-HCV drugs-RG7128, a nucleoside polymerase inhibitor; and danoprevir, an NS3/4A protease inhibitor-in patients with chronic HCV infection.*

Methods*: Patients from six centres in New Zealand and Australia who were chronically infected with HCV genotype 1 received up to 13 days oral combination treatment with RG7128 (500 mg or 1000 mg twice daily) and danoprevir (100 mg or 200 mg every 8 h or 600 mg or 900 mg twice daily) or placebo. Eligible patients were sequentially enrolled into one of seven treatment cohorts and were randomly assigned by interactive voice or web*

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

response system to either active treatment or placebo. Patients were separately randomly assigned within each cohort with a block size that reflected the number of patients in the cohort and the ratio of treatment to placebo. The random allocation schedule was computer generated. Dose escalation was started in HCV treatment-naive patients; standard of care treatment-experienced patients, including previous null responders, were enrolled in higher-dose danoprevir cohorts. Investigators, personnel at the study centre, and patients were masked to treatment allocation. However, the pharmacist who prepared the doses, personnel involved in pharmacokinetic sample analyses, statisticians who prepared data summaries, and the clinical pharmacologists who reviewed the data before deciding to initiate dosing in the next cohort were not masked to treatment allocation. The primary outcome was change in HCV RNA concentration from baseline to day 14 in patients who received 13 days of combination treatment. All patients who completed treatment with the study drugs were included in the analyses. This study is registered with ClinicalTrials.gov, NCT00801255.

***Findings**: 88 patients were randomly assigned to a study drug treatment regimen (n=74 over seven treatment groups; 73 received at least one dose of study drug) or to placebo (n=14, all of whom received at least one dose). The median change in HCV RNA concentration from baseline to day 14 ranged from -3·7 to -5·2 log(10) IU/ml in the cohorts that received 13 days of combination treatment. At the highest combination doses tested (1000 mg RG7128 and 900 mg danoprevir twice daily), the median change in HCV RNA concentration from baseline to day 14 was -5·1 log(10) IU/ml (IQR -5·6 to -4·7) in treatment-naive patients and -4·9 log(10) IU/ml in previous standard of care null responders (-5·2 to -4·5) compared with an increase of 0·1 log(10) IU/ml in the placebo group. The combination of RG7128 and danoprevir was well tolerated with no treatment-related serious or severe adverse events, no grade 3 or 4 changes in laboratory parameters, and no safety-related treatment discontinuations.*

***Interpretation**: This oral combination of a nucleoside analogue polymerase inhibitor and protease inhibitor holds promise as an interferon-free treatment for chronic HCV.*

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

In the last decade, insights into the virology of HCV have unraveled several targets for potential novel therapeutics that, unlike interferon (IFN)-α and ribavirin, are specifically targeted to HCV. Several new drug therapies such as protease and polymerase inhibitors, designated as direct-acting antivirals (DAAs) have reached clinical development [1,2]. Gane and colleagues have recently published in the Lancet the results of the first study with a combination of two (DAAs) without interferon (IFN) or ribavirin in patients with chronic hepatitis C. The aim of the proof-of-concept INFORM-1 trial was to assess the efficacy and safety of the combination of two drugs in development, danoprevir, an NS3/4A protease inhibitor, and RG7128, a nucleoside analogue inhibitor of HCV RNA-dependent RNA polymerase, over two weeks of administration. In this randomised, double-blind, placebo-controlled trial, 88 patients infected with HCV genotype 1 were enrolled into one of seven treatment arms, randomised to different doses and schedules of study drugs or placebo for up to 13 days. Then, patients were rolled over into the current standard of care (SOC), i.e. pegylated interferon (PEG-IFN) and ribavirin (RBV). The vast majority of patients had never been treated before, whereas 16 of them had failed to eradicate HCV with SOC. The main finding of the study was the demonstration of a substantial, sustained, dose-dependent HCV RNA level reduction, whatever the treatment group. The viral level reduction reached -5 log on average after 14 days of combination with the highest drug doses i.e. 1000 mg b.i.d of RG7128 and 900 mg b.i.d. of danoprevir. Undetectable HCV-RNA (<15 IU/ml) was achieved in 44% of patients overall. The antiviral efficacy was similar in treatment-naïve patients and in patients who failed to eradicate HCV after a first course with PEG-IFN and RBV, including null-responders included in the highest dose group. No evidence of emergence of HCV variants resistant to either compound was reported during the short-term administration of the drugs. Treatment was well tolerated and no serious adverse event, dose modification or premature discontinuation were reported over the two weeks of administration.

Virtually any step of the HCV lifecycle can be a target for HCV inhibitors. The most successful approach so far has been targeting the HCV protease. The triple combination of PEG-IFN, RBV and a first-generation protease inhibitor (telaprevir or boceprevir) will increase the sustained virologic response (SVR) rates from 40-44% to 68-75% in treatment-naïve patients infected with HCV genotype 1 [3,4]. This treatment is expected to become the new SOC at the end of 2011-beginning of 2012 in treatment-naïve and treatment-experienced

ACCEPTED MANUSCRIPT

patients infected with genotype 1. However, this therapy will be not be optimal for patients who are intolerant or have contra-indications to PEG-IFN or RBV, including for instance patients with decompensated cirrhosis or hemoglobinopathies. In the phase 3 registration trials, more than 10% of the carefully selected patients discontinued triple combination therapy prematurely due to adverse events. Moreover, the efficacy of the triple combination will be limited in treatment-experienced patients who did not respond to PEG-IFN and ribavirin by a more than 1 log drop in HCV RNA levels at week 4, with a high risk of treatment failure and the selection of HCV variants resistant to protease inhibitors [5,6]. Finally, triple therapy will most likely not be able to eradicate HCV in a number of so-called "difficult-to-treat" patients. Thus, PEG-IFN and/or RBV intolerant or poorly responsive patients could be the main beneficiaries of interferon-sparing HCV treatment regimens, and one cannot exclude that IFN-free regimens will become SOC first-line treatment for all patients with chronic HCV infection.

The main objectives of a regimen combining DAAs without IFN or ribavirin should be: a) to improve antiviral efficacy without increasing toxicity; b) to prevent the development of resistance by combining DAAs targeting different elements of the HCV life cycle and without cross-resistance; and c) to avoid drug-drug interactions without impairing safety. Although the present study met the short-term safety objective and direct interactions between the two drugs could be considered unlikely, it presents some limitations. Due to the short duration of administration of the study drugs, the long-term safety profile and the risk of late rebound due to viral resistance to the combination remain unknown. The goal of antiviral treatment is to cure HCV infection, as witnessed by the sustained virological response, characterized by an undetectable HCV RNA 6 months after the end of therapy. Because the patients were all treated with the combination of PEG-IFN and ribavirin after the two-week IFN-free regimen, the fact that the observed early pronounced antiviral activity of the combination of two DAAs could lead to HCV eradication has not been proven. However, interestingly, the early kinetics of HCV RNA levels with the DAA combination appeared to be similar to those reported in a previous study with a similar population receiving danoprevir in combination with PEG-IFN and ribavirin. The initial HCV RNA decline was rapid, especially during the first two days (first phase decline: -3.5 log on average with the highest drug doses in treatment-naïve patients), corresponding to the clearance of free HCV virions. The second slope was slower (HCV-RNA decline: -1.0 log per week on average), related to the loss of infected hepatocytes (Figure 1). Based on an estimated total body viral burden of 10^{11} virions, 8 to 12 weeks of DAA treatment could be sufficient to eradicate HCV infection

ACCEPTED MANUSCRIPT

in most patients, provided that no relapse occurs as a result of resistant variant selection. The possibility to cure HCV infection with DAA combinations without IFN (with or without ribavirin) should be assessed in future studies with longer treatment durations in both treatment-naïve and -experienced patients, as all-oral, IFN-free regimens should be effective in both patient populations.

Current and future trials will likely determine whether the IL28B genotype and IP-10 levels influence SVR when patients are treated with DAA combinations without IFN. The impact of RBV on the efficacy and safety of DAA combinations has to be established. Based on the observation of higher relapse and viral breakthrough rates in the RBV-sparing treatment arms in the telaprevir plus SOC studies [5,7] and on the fact that RBV could accelerate the second slope of viral decline and prevent breakthrough due to resistance when administered in combination with two DAAs with a low genetic barrier to resistance [8], the impact of RBV on efficacy and safety of combination DAA therapy has to be established. Although telaprevir has shown potent antiviral activity against HCV genotype 2, it has no effect on HCV genotype 3, suggesting that PEG-IFN and RBV will remain the SOC for non HCV genotype 1 patients [9]. However, other protease inhibitors, as well as nucleoside/nucleotide analogues and cyclophillin inhibitors, have shown antiviral potency against genotypes other than 1. Thus, IFN-sparing combination regimens could be studied in other patient populations than those included in INFORM-1.

Several trials of combination DAAs are ongoing in treatment-naïve or experienced patients. All studies include protease inhibitor, combined with either a NS5A, non-nucleoside NS5B, nucleoside NS5B inhibitor. The second DAA must be chosen carefully, as recent data suggest that the genetic barrier of combination therapy with a first-generation protease inhibitor and a non-nucleoside NS5B or an NS5A inhibitor is not higher than that of protease inhibitor monotherapy [8,10]. In contrast, the absence of occurrence of breakthroughs during this trial is probably related to the high barrier resistance of the danoprevir and RG7128 combination.

In conclusion, this proof-of-concept INFORM-1 trial has shown that the combination of danoprevir and RG7128 for up to 13 days results in a substantial biphasic HCV-RNA decline, without selecting HCV variants and with a satisfactory safety profile in both treatment-naïve or treatment-experienced patients infected with HCV genotype 1. Further trials with these drugs or other DAAs, with or without ribavirin are now needed to assess whether IFN-free regimens may provide high cure rates in the future.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Figure legends

Fig. 1. Early viral kinetic profile of danoprevir and RG7128 combination.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

References.

[1]. Poordad F. Big changes are coming in hepatitis C. Curr Gastroenterol Rep 2011;13:1906-1914.

[2]. Asselah T, Marcellin P. New direct-acting antivirals combination fot the treatment of chronic hepatitis C. Liver Int 2011;31(Suppl1):68-77.

[3]. Jacobson IM, McHutchison JG, Dusheiko GM, Di Bisceglie AM, Reddy R, Bzowej NH, et al. Telaprevir in combination with peginterferon and ribavirin in genotype 1 HCV treatment-naïve patients: final results of phase 3 advance study [abstract]. Hepatology 2010;52:427A.

[4]. Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir (BOC) combined with peginterferon alfa-2b/ribavirin (P/R) for treatment-naïve patients with hepatitis C virus (HCV) genotype (G) 1: sprint-2 final results [abstract]. Hepatology 2010;52:402A.

[5]. McHutchison JG, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhal NH, et al. Telaprevir for previously treated chronic HCV infection. N Engl J Med 2010;362:1292-1303.

[6]. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. HCV respond-2 final results: high sustained virologic response among genotype 1 previous non-responders and relapsers to peginterferon/ribavirin when re-treated with boceprevir plus pegintron (peginterferon alfa-2b)/ribavirin [abstract]. Hepatology 2010;52:430A.

[7]. Hézode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med 2009;360:1839-1850.

[8]. Zeuzem S, Buggisch P, Agarwal K, Manns MP, Marcellin P, Foster GR, et al. Dual, triple, and quadruple combination treatment with a protease inhibitor (GS-9256) and a polymerase inhibitor (GS-9190) alone and in combination with ribavirin (RBV) or PEGIFN/RBV for up to 28 days in treatment naïve , genotype 1 HCV subjects [abstract]. Hepatology 2010;52:400A.

[9]. Foster GR, Hézode C, Bronowicki JP, Carosi G, Weiland O, Verlinden L, et al. Activity of telaprevir alone or in combination with peginterferon alfa-2a and ribavirin in treatment-naïve, genotype 2 and 3, hepatitis-C patients: final results of study C209 [abstract]. J Hepatol 2010;52:S27.

[10]. Lok AS, Gardiner DF, Lawitz E, Martorell C, Everson GT, Ghalib RH, Reindollar R, et al. Combination therapy with BMS-790052 and BMS-650032 alone or with PegIFN/RBV

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

results in undetectable HCV RNA through 12 weeks of therapy in HCV genotype 1 null responders [abstract]. Hepatology 2010;52:877A

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT
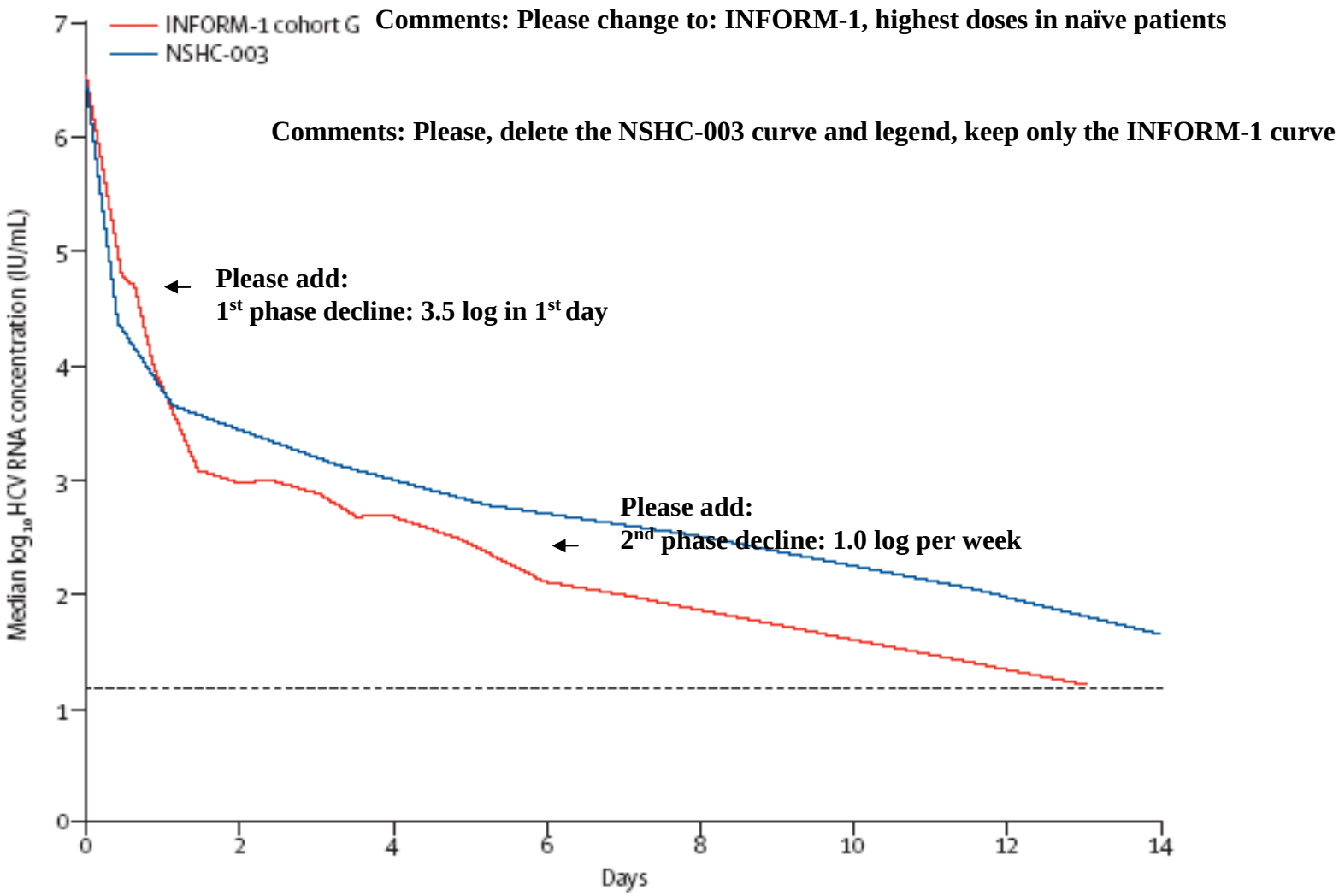
Figure 1