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**Oral combination therapy: future hepatitis C virus treatment?**

Commentary article on the following manuscript:

"Lancet. 2010 Oct 30;376(9751):1467-75. 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 et al.".

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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 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 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.

**Figure legends**

Figure 1: Early viral kinetic profile of danoprevir and RG7128 combination.

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