Commentary

Is stronger better in curing hepatitis C virus infection?

Stanislas Pol

Hepatology Department, Hôpital Cochin and Center for Translational Research, Institut Pasteur, Paris, France

Correspondence to: Stanislas Pol, MD, PhD. Hepatology Department, Paris Descartes University, Assistance Publique-Hôpitaux de Paris, Hopital Cochin, Inserm U-1223, Institut Pasteur, Paris, France. Email: stanislas.pol@aphp.fr.

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Thanks to a better understanding of the hepatitis C virus (HCV) life-cycle, HCV direct-acting antiviral agents (DAAs) targeting the viral proteins implicated in the virus replication have been developed: they inhibit specifically the NS3/4A protease, the NS5B polymerase and the multifunctional NS5A replication complex (1). DAAs have revolutionized the treatment of HCV infection over the last 5 years. Oral interferon-free combinations of at least two DAAs showed high antiviral efficacy, easy dosing, fair tolerance, and manageable drug-drug interactions, whatever the combination for treatment duration of 8, 12 or 24 weeks according to the patients profile.

The combination of daclatasvir (DCV) (2) and asunaprevir (ASV) (3) has been the first interferon-free dual combination to support the evidence of this therapeutic revolution achieving a virologic cure of a viral chronic infection inducing mainly reversible hepatic and extra-hepatic manifestations. ASV is a first-generation NS3 protease inhibitor with activity against GT 1 and GT 4 (4), efficacy and safety in combination with pegylated interferon and ribavirin (P/R), and in DAA-only combinations with DCV, and DCV plus BMS-791325 (5).

In a sentinel cohort, an SVR was achieved in 9/10 GT 1a and 1b patients treated with DCV plus ASV in combination with P/R, while an SVR was achieved in 2/2 GT1b and 2/9 GT1a patients treated with DCV plus ASV (6).

Efficacy confirmed in an expansion cohort, with SVR rates >90% achieved in GT 1 prior null responder treated with DCV plus ASV and P/R (7).

These studies underlined the proof of concept of the efficacy of interferon-free and even ribavirin-free regimen but also evidenced some of the main limitations of the dual combination: the 24 weeks duration of therapy and the limited efficacy in genotype 1a-infected patients. A phase III trial with 24 weeks of interferon-free and ribavirin-free oral therapy with DCV and ASV in a significant number of patients demonstrated high and sustained antiviral activity and favorable tolerability in treatment-naïve and interferon-experienced patients with chronic HCV genotype 1b infection: SVR rates were achieved in around 90% of GT1b patients with or without cirrhosis (8), but there was a need for a 24-week course and the times in 2014–2015 were at a reduction of treatment duration and at pangenotypic combination. That is why a triple combination has been build combining DCV plus ASV plus a non nucleosidic polymerase inhibitor the beclabuvir which was developped in clinical trials including naïve or PR-experienced, cirrhotic and non cirrhotic patients (9).

The UNITY-2 was an open-label uncontrolled study in 112 naïve and 90 PR-experienced cirrhotic patients (compensated cirrhosis) infected by a genotype 1 (74% GT1a) who were given a 12 weeks course of a fixed-dose combination (FDC) of DCV (30 mg, lower than the standard 60 mg) plus ASV (200 mg) plus beclabuvir (75 mg), the so-called DCV-TRIO (9). SVR12 rates were 98% in naïve and 93% in experienced patients co-treated with ribavirin (N=55 and 45, respectively); rates dropped to 93% in naïve and 87% in treatment-experienced who were not receiving ribavirin (N=57 and 45, respectively). Conclusion is very encouraging regarding the high SVR12 rate achieve with the BMS-TRIO and has to be temperated.

The positive points are that: (I) results are excellent in GT1b-infected patients naïve or experienced patients with and without ribavirin (100% or 100%, 100% and 90%, respectively) without any negative predictor of non SVR (viral load, gender, age, IL28B); (II) baseline NS5 A resistance polymorphisms, detected in 10% of GT1a and 25% of GT1b poorly impacted SVR12 rate since they achieved 87% and 100% SVR12 rate, respectively; (III) thrombocytopenia (<100,000/mm^3) which mainly reflect portal hypertension

does not modify the SVR12 rate (94%) in the 53 patients.

On the contrary, the negative point was the lower SVR12 rate in GT1a-infected patients naïve or experienced patients with and without ribavirin: 97.4% or 91.4%, 90% and 87.5%, respectively, suggesting the need of ribavirin addition in GT1a-infected and experienced patients. Grade 3 or 4 liver abnormalities (ALT <5 UNL) occurred in 4 patients (2%), hyperbilirubinemia (>2.5 ULN) in 3 patients treated by ribavirin and lipase elevations in 6 patients suggesting drug toxicity but abnormalities resolved after discontinuation: a warning for another protease inhibitor-including combination has been made by the FDA for cirrhotic patients; the risk of hepatotoxicy of these drugs is class-related and observed with any protease inhibitor, which limit their use in decompensated cirrhosis and likely in "more advanced" compensated cirrhosis (<100,000/mm^3 or albumin lower than 35 g/L).

In summary, this FDC including the three classes of DAAs by adding the beclabuvir to the DCV/ASV dual combination clearly improves the previous SVR12 results of the dual combination which efficacy was mainly restricted to GT1b-infected patients and necessitated 24 weeks of therapy. But at a time of a trend for ribavirin-free regimen, the results in cirrhotic GT1a experienced patients are rather disappointing by comparison with the results of the sofosbuvir/ledipasvir results from the Ion program or the real-life, around 96% in cirrhotic patients for 12 weeks without ribavirin. The Astral or Polaris (Sofosbuvir and Velpatasvir combination for 12 weeks) or the 2nd generation ABT or MSD program (6, 8 or 12 weeks according to patients characteristics including the genotype) are all ribavirin-free, with superior and pangenotypic antiviral activity and limiting the relevance of this new combination which development has been withdrawn.

In summary, despite significant efficacy of the Trio, the competition is more and more critical with FDC, interferon-free, ribavirin-free, well tolerated and short duration and any development plan has now to take into account this very rapid wild competition.

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Footnote

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