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Daclatasvir: a team player rather than a prima donna in the treatment of hepatitis C

Alessio Aghemo,[1] Raffaele De Francesco[2]

With the introduction of direct-acting antivirals (DAA), the treatment for chronic hepatitis C is evolving at an astonishingly rapid pace.[1] Among DAAs, HCV NS5A inhibitors show substantial promise as anti-HCV therapeutics. NS5A inhibitors in clinical development include daclatasvir (DCV), ledipasvir, ombitasvir and MK-8742.[2] With in vitro anti-HCV activities in the low picomolar range, these represent the most potent class of DAAs to target HCV. The HCV NS5A protein is known to function in multiple aspects of the HCV life cycle, including roles in viral replication and assembly, as well as complex interactions with cellular factors. Not being associated with any measurable enzymatic activity, NS5A was not considered 'druggable' for a very long time. In fact, the first small-molecule NS5A inhibitors were discovered by random screening using the HCV replicon system. The initial lead compounds had only moderate potency, but subsequent medicinal chemistry efforts resulted in the discovery of drugs with unparalleled antiviral activity that are characterised by highly symmetrical dimeric structure.[3] The most studied of these 'palindromic' NS5A inhibitor class is DCV[4] (formerly BMS-790052), a DAA active against a broad range of HCV genotypes for which regulatory approval both in interferon (IFN)-containing or IFN-free regimens is currently being sought. Sequencing of replicons resistant to DCV and related compounds identified NS5A as their molecular target.[5 6] In particular, variants of NS5A M28, Q30, L31 and Y93 were found to be the most common mutations conferring broad resistance to this class of antivirals. Y93, the hallmark resistance mutation for NS5A inhibitors, is found near the protein–dimer interface. The highly symmetric structure of DCV and other NS5A inhibitors suggests a binding interaction with NS5A in which the inhibitor interacts across the dimer interface, making simultaneous contacts with both protein monomers.[7] This could, at least partly, explain the extraordinary potency observed for this inhibitor class. In spite of a very fast progress through clinical development, the exact mechanism DCV and related agents interfere with the HCV life cycle has just started to be elucidated. Importantly, it has been very recently suggested that NS5A inhibitors act by a dual mode of action, involving

[1]Division of Gastroenterology and Hepatology, A.M. and A. Migliavacca Center for Liver Disease, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy; [2]Fondazione INGM, Istituto Nazionale di Genetica Molecolare "Romeo ed Enrica Invernizzi", Milan, Italy

Correspondence to Dr Alessio Aghemo, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milano, Via F. Sforza 35, 20122 Milan, Italy; alessio.aghemo@policlinico.mi.it

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both suppression of viral RNA synthesis as well as inhibition of viral release.[8] In particular, DCV and its relatives have been shown, on one hand, to block HCV RNA replication by preventing the proper formation of the so-called 'membranous web', which is the site where functional HCV RNA replication factories are found.[7] On the other hand, they have been demonstrated to potently and rapidly inhibit intracellular virion assembly independently of the inhibition of RNA replication, thus providing an explanation for the very fast and profound antiviral response observed in the clinic. DCV has been studied as a component of IFN containing regimens in a triple therapy regimen in combination with Ribavirin (Rbv) or in a quad therapy regimen in combination with Rbv and the HCV NS3 protease inhibitor asunaprevir (ASV). In the Phase IIb COMMAND-1 study, Hezode and colleagues evaluated the safety and efficacy of Pegylated IFN (PegIFN)/Rbv and DCV in previously untreated HCV-1 and HCV-4 patients.[9] Three hundred and ninety-five patients were randomised to receive either PegIFN/Rbv/DCV 20 mg (A), PegIFN/Rbv/DCV 60 mg (B) or PegIFN/Rbv/Placebo (C). Treatment was guided by on-treatment virological response in groups A and B, where patients who achieved HCV-RNA <25 IU/mL at weeks 4 and 10 (protocol-defined response: PDR) were rerandomised at week 12 of treatment to another 12 weeks of PegIFN/Rbv±DCV. On the other hand, patients who did not achieve a PDR received a total of 48 weeks of treatment that included 36 weeks of PegIFN/Rbv. The overall message of COMMAND-1 is that the addition of DCV increased sustained virological response (SVR) rates to 59% (A) and 60% (B) compared with 38% in the placebo arm (C). In the 72% of patients who achieved a PDR, the SVR rates were high 71%–79%, and were not affected by DCV intake from week 12 to 24 of treatment. These figures are not a major breakthrough for HCV-1 treatment, as they are very similar to the efficacy rates reported by real-life data on the first-generation NS3 protease inhibitors, Telaprevir (TVR) and Boceprevir (BOC), which achieved 68% and 56% SVR rates, respectively, in cohorts of patients enriched with factors associated with treatment failure, such as advanced fibrosis, older age and concomitant comorbidities.[10 11] Where DCV shows an advantage over TVR/BOC is in terms of safety and tolerability profiles, which was one of the main clinical problems with TVR and BOC.[12] Indeed, in the COMMAND-1 study, the DCV arms were comparable with the placebo arm in terms of discontinuation (4% group A vs 4% group B vs 10% group C), and serious adverse events rates (7.5% group A vs 8% group B vs 8% group C), with no specific safety signals associated with DCV.

In spite of the potent antiviral activity, the genetic barrier to resistance for the first-generation NS5A inhibitors—such as DCV—is low, especially for genotype 1a. This was reflected in the COMMAND-1 study by lower SVR rates in HCV-1a (55%–57%) than in HCV-1b (76%–77%) patients, and higher rates of on-treatment virological failure (21% vs 8%) which were characterised by selection of DCV-associated resistant variants. Pre-existence, emergence and persistence of resistance variants in patients who failed DCV-containing treatment is not a novelty and has already been reported by several in vitro and in vivo studies. Strikingly, in a study of genotype 1a HCV patients treated with DCV in combination with the NS3 protease inhibitor ASV, NS3 resistance variants generally decayed fast, but NS5A resistance variants persisted throughout the 48 weeks of observation, suggesting a high fitness of NS5A resistance-associated variants and a possible clinical nightmare in the re-treatment of these patients.[13] This is the reason why DCV is best fit for combination regimens with other DAAs in IFN-free regimens, rather than for triple therapy with PegIFN/Rbv.

DCV has been studied extensively in combination with other DAAs such as the NS3 protease inhibitors ASV, Simeprevir, the NS5B nucleotide polymerase inhibitor Sofosbuvir (SOF) and the NS5B non-nucleoside polymerase inhibitor (BMS-791325).[2] In terms of pill burden, efficacy and side effect profile, the combination with the NS5B nucleotide polymerase inhibitor SOF appears to be the ideal DCV including IFN-free regimen. SOF compliments DCV perfectly as it adds a high genetic barrier to resistance, a potent antiviral effect and pangenotypical activity which allow for extremely high rates of SVR even in HCV-1a patients. This was demonstrated by a study where 132 HCV-1a and 35 HCV-1b patients received DCV/SOF for 12–24 weeks with or without Rbv, the overall SVR rates were 98% in HCV-1a and 100% in HCV-1b.[14] European recommendations on the treatment of HCV have accepted this data as strong evidence that the combination of DCV plus SOF is an optimal treatment regimen for HCV-1 patients, also suggesting this combination for patients with HCV genotype 4 where no formal trial has been published yet.[15] Previous evidence of in vitro and in vivo potent antiviral activity of both DAAs on HCV genotype 4 as well as findings from the COMMAND-1 study, where DCV in HCV-4 patients increased SVR rates from 50% in the placebo group to 95% in the DCV arm, support this recommendation and identify DCV as a valid treatment option for genotype 4 patients as well.

Contributors AA and RDF conceived and wrote the manuscript.

Competing interests AA: Advisory Board: AbbVie, Gilead Sciences. Speaker Bureau: AbbVie, Gilead Sciences, Janssen, Merck.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Aghemo A, De Francesco R. *Gut* 2015;**64**:860–862.
Received 15 August 2014
Accepted 19 August 2014
Published Online First 5 September 2014

▶ http://dx.doi.org/10.1136/gutjnl-2014-307498

Gut 2015;**64**:860–862.
doi:10.1136/gutjnl-2014-307958

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Gut 2015 64: 860-862 originally published online September 5, 2014
doi: 10.1136/gutjnl-2014-307958

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