Sofosbuvir: the final nail in the coffin for hepatitis C?

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In *The Lancet Infectious Diseases*, Eric Lawitz and colleagues[1] report results from their randomised phase 2 trial, in which they showed a more than 90% cure rate of hepatitis C in patients given a combination of pegylated interferon alfa-2a (peginterferon), ribavirin, and sofosbuvir, a novel nucleoside inhibitor of the hepatitis C virus (HCV) NS5B polymerase. Among the 60 or so drugs under development for HCV, nucleoside inhibitors seem to be the most promising of the three classes of direct-acting antivirals currently in phase 3 trials (figure): NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors, which can be subdivided into nucleoside inhibitors or non-nucleoside inhibitors. Nucleoside inhibitors, namely sofosbuvir, seem to be best in terms of resistance profile, activity against all virus genotypes, adverse events, and antiviral potency. And as such, the emergence of sofosbuvir is an important milestone in the fight against hepatitis C.

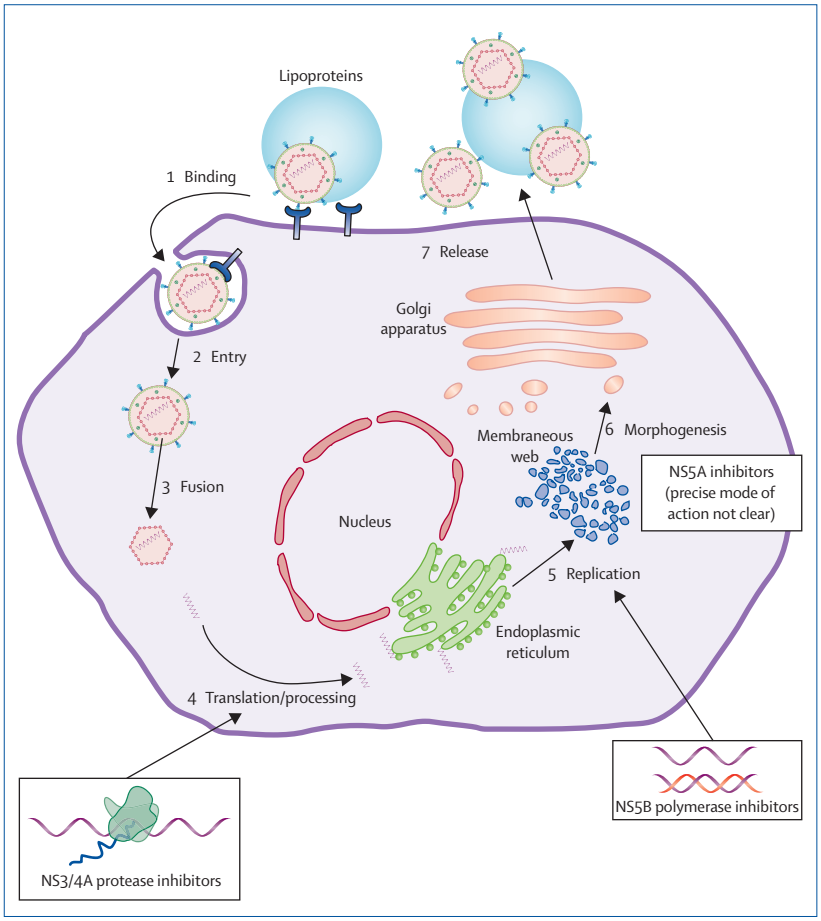

***Figure*: Life cycle of the hepatitis C virus and mode of action of the three main classes of direct-acting antivirals in phase 3 trials**
Image courtesy of Thomas Pietschmann, Twincore, Hannover, Germany.

The first such milestone was the approval of interferon alfa in the early 1990s.[2] The addition of ribavirin to interferon alfa in 1998 doubled response rates;[3] and once weekly peginterferon was introduced in combination with ribavirin in 2001.[4] In 2003, the protease inhibitor BILN 2061 (Boehringer Ingelheim, Ingelheim, Germany) provided the first proof of concept for direct-acting antivirals against HCV.[5] 8 years later, the protease inhibitors boceprevir and telaprevir were approved for treatment of HCV genotype-1.[6,7] Boceprevir and telaprevir improved sustained viral response rates (SVR) from about 40–44% to 68–75% in treatment-naive patients with genotype-1.[6,7]

SVR means patients are cured and has been associated with prevention of hepatocellular carcinoma and even improvements in overall mortality.[8] However, these protease inhibitors have several limitations: activity against genotype-1 only, dosing every 8 h, and many potentially serious drug interactions. Both protease inhibitors have to be given in combination with peginterferon plus ribavirin because monotherapy results in rapid emergence of drug-resistant variants, which explains why previous null-responders to peginterferon plus ribavirin had SVRs of only 30–40% when given triple therapy with peginterferon, ribavirin, and a NS3/4A protease inhibitor.[9] Boceprevir and telaprevir add to the adverse event profile of peginterferon plus ribavirin, especially in patients with cirrhosis—namely, a doubling of anaemia.[10,11]

A need for new drugs clearly exists. Ideally, novel direct-acting antivirals should fulfil the following requirements: oral administration once daily, few side-effects and drug interactions, short treatment duration, high barrier to resistance, and effectiveness against all major HCV genotypes. New drugs should also help in the development of an oral interferon-sparing regimen.[12]

Lawitz and colleagues' trial forms the basis for the phase 3 testing of sofosbuvir. The investigators not only showed high SVR with sofosbuvir but also the activity against HCV genotypes 1–3. No drug-resistant variants were seen with 400 mg daily sofosbuvir, and only two patients had viral relapse.[1] Therefore, a daily dose of 400 mg sofosbuvir was chosen as the dose for further

trials, including phase 3 trials. Sofosbuvir was safe and did not add notably to the adverse event profile of peginterferon and ribavirin. Limitations of the study were that only treatment-naive, non-cirrhotic patients were included.

Lawitz and colleagues showed that response-guided treatment for 24–48 weeks is not necessary,[1] and the findings of another phase 2 study (the ATOMIC study) suggested that a treatment duration of 12 weeks' sofosbuvir in combination with peginterferon plus ribavirin is sufficient, irrespective of baseline factors such as patients' IL28B status or viral load.[13] The ATOMIC trial enrolled more than 300 treatment-naive, non-cirrhotic patients with genotypes 1, 4, or 6, showing 87–89% SVR after 12 weeks or 24 weeks of sofosbuvir in combination with peginterferon plus ribavirin. Additionally, sofosbuvir has already been shown to be highly effective in protocols that do not include interferon alfa.[14] 12 weeks of sofosbuvir plus ribavirin resulted in 84–100% SVR in treatment-naive patients with HCV genotypes 1–3.[14] However, nine of ten patients with genotype-1 who had previously not responded to peginterferon plus ribavirin had a relapse without detection of drug-resistant variants. Thus, sofosbuvir plus ribavirin might be sufficient for easy-to-treat patients but more difficult-to-treat patients might need sofosbuvir in combination with peginterferon plus ribavirin or other direct-acting antivirals. In another trial,[15] sofosbuvir together with the experimental NS5A inhibitor daclatasvir (Bristol-Myers Squibb, NY, USA) showed excellent (>90%) SVR in patients with HCV genotypes 1–3.[15] Sofosbuvir is now being further developed in combination with ledipasvir (formerly known as GS-5885), Gilead Science's own NS5A inhibitor—both drugs are designed as a fixed-dose combination in one tablet. Thus, sofosbuvir seems to fulfil all the aforementioned requirements for new direct-acting antivirals. The key question is, therefore, does one pill fit all?

Certainly there are some important questions to be answered before we can call sofosbuvir the final nail in the coffin for hepatitis C. How effective and safe is the drug in patients with advanced liver disease, including those with decompensated cirrhosis? Does it prevent and treat HCV recurrence after liver transplantation? How effective is it in the treatment of difficult-to-treat HCV genotypes such as genotype 3?

In February this year, Gilead Sciences announced that patients with HCV genotype-3 are more difficult to treat than previously thought.[16] However, these data give hope for patients with chronic HCV infection, and, barring any unforeseen surprises, sofosbuvir should be approved by early 2014.

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1 Lawitz E, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infect Dis* 2013; published online March 15. http://dx.doi.org/10.1016/S1473-3099(13)70033-1.
2 Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. *Gut* 2006; **55:** 1350–59.
3 McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C: Hepatitis Interventional Therapy Group. *N Engl J Med* 1998; **339:** 1485–92.
4 Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358:** 958–65.
5 Lamarre D, Anderson PC, Bailey M, et al. An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus. *Nature* 2003; **426:** 186–89.
6 Poordad F, McCone JJ, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364:** 1195–1206.
7 Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; **364:** 2405–16.
8 van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; **308:** 2584–93.
9 Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; **364:** 2417–28.
10 Hezode C, Dorival C, Zoulim F, et al. Safety and efficacy of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin, in 455 cirrhotic non responders. Week 16 analysis of the French early access program (ANRS CO20-CUPIC) in real-life setting. *Hepatology* 2012; **56**: 51 (abstr).
11 Maasoumy B, Port K, Markova AA, et al. Eligibility and safety of triple therapy for hepatitis C: lessons learned from the first experience in a real world setting. *PLoS One* 2013; **8:** e55285.
12 Lange CM, Zeuzem S. Perspectives and challenges of interferon-free therapy for chronic hepatitis C. *J Hepatol* 2013; **58:** 583–92.
13 Kowdley KV, Lawitz E, Crespo I, et al. Sofosbuvir with peginterferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. *Lancet* 2013; published online March 15. http://dx.doi.org/10.1016/S0140-6736(13)60247-0.
14 Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med* 2013; **368:** 34–44.
15 Sulkowski M, Gardiner DF, Rodriguez-Torres M, et al. High rate of sustained virologic response with the all-oral combination of daclatasvir (NS5A Inhibitor) plus sofosbuvir (nucleotide NS5B inhibitor), with or without ribavirin, in treatment-naive patients chronically infected with HCV genotype 1, 2, or 3. *Hepatology* 2012; **56:** LB-2.
16 Gilead Sciences. Gilead 's sofosbuvir for hepatitis C meets primary endpoint in fourth pivotal phase 3 study. www.gilead.com/pr_1786260 (accessed Feb 19, 2013).