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Commentary

Beyond sofosbuvir: What opportunity exists for a better nucleoside/nucleotide to treat hepatitis C?

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ABSTRACT

Sofosbuvir is a liver-targeting uridine nucleotide prodrug inhibitor of the hepatitis C virus (HCV) RNA-dependent RNA polymerase recently approved by the FDA and EU regulators for treatment of patients infected with genotype 1, 2, 3 and 4 virus. The request for regulatory approval of the fixed-dose combination containing sofosbuvir and the NS5A inhibitor ledipasvir is also under review. Preclinical and clinical studies have shown that sofosbuvir is effective, safe and well tolerated. Review of sofosbuvir's preclinical and clinical profile reveals a drug that has the potential to become the backbone of standard of care. Pursuit of a next generation nucleos(t)ide HCV inhibitor that could compete with sofosbuvir would need to address whatever limitations sofosbuvir exhibits. These include reduced efficacy in genotype 3 patients and use in severe renally impaired patients or those patients currently on drugs that are inducers of P-glycoprotein. However, it has been shown that reduced efficacy in genotype 3 is largely eliminated when sofosbuvir is combined with another oral DAA. Next-generation inhibitors would also benefit by enabling a reduced duration of therapy and an orthogonal resistance profile. The more recent group of nucleos(t)ides in clinical development maintains similarities to sofosbuvir, in that they are uridine nucleotide prodrugs. The question therefore remains whether these new agents will be sufficiently differentiated from sofosbuvir to provide any additional benefit to patients. This paper forms part of a symposium in *Antiviral Research* on "Hepatitis C: next steps toward global eradication."

1. Introduction

On December 6, 2013, sofosbuvir was approved by the US Food and Drug Administration as the first nucleotide therapy for the treatment of hepatitis C, and it received European Union approval in January, 2014. These approvals also marked a milestone in the treatment paradigm for patients infected with the hepatitis C virus (HCV). For the first time, a subset of genotype (GT) 2 and 3 patients can be treated with an all-oral interferon (IFN)-free regimen and no longer have to weather the debilitating side effects associated with 24 or 48 weeks of IFN injections. Now these patients will only need to take a single 400 mg pill of sofosbuvir and an oral dose of ribavirin (RBV) for 12 or 24 weeks to eradicate their infection with a high probability of success (Jacobson et al., 2013). Even patients with GT1 or 4 infection will experience the benefits presented by sofosbuvir, in that they will now see their treatment duration reduced to 12 weeks when IFN and RBV are combined with a single daily dose of sofosbuvir. For GT1 IFN-intolerant patients, sofosbuvir/RBV alone can also be prescribed (Lawitz et al., 2013). These benefits extend to cirrhotic patients, and patients awaiting liver transplants because of HCV infection (Charlton et al., 2013; Curry et al., 2013; Koff, 2014). It is anticipated that IFN-free combinations of direct-acting antivirals (DAA) that include sofosbuvir as the backbone will soon be available to patients, with some delivered as fixed-dose combinations (Fontana et al., 2013; Gane et al., 2014; Hoofnagle and Sherker, 2014; Lawitz et al., 2014).

The optimism about sofosbuvir and its benefits for patients is also fueled by the overwhelming clean safety profile exhibited by this drug (Jacobson et al., 2013; Koff, 2014; Lawitz et al., 2013). To date, sofosbuvir has been well received in the marketplace of the western world, and access to this game-changing drug in the developing world has become a topic of much discussion (Callaway, 2014; Herper, 2014; Staton, 2014). With the clear efficacy and safety benefits demonstrated by sofosbuvir, one might ask whether there is a need for another nucleos(t)ide antiviral for hepatitis C, and what added characteristic that agent would need to demonstrate to warrant its development and eventual regulatory approval.

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2. Sofosbuvir

In an attempt to address this question, a review of sofosbuvir's profile is warranted. Sofosbuvir is a phosphoramidate liver-targeted prodrug of the 2′-F, 2′-C-methyluridine-5′-monophosphate, and exists as a single pure diastereomer (Sofia et al., 2010). It is a potent inhibitor of the HCV RNA-dependent RNA polymerase with and EC_{90} = 0.42 μM in the HCV GT1b replicon. It also has equipotent pan-genotypic activity across HCV GT1-6 and in the JFH-1 infectious clone (Hebner et al., 2012; Lam et al., 2010b, 2012). Sofosbuvir was shown not to be a substrate for human DNA polymerases, RNA polymerases or mitochondrial polymerases (Arnold et al., 2012; Lam et al., 2010b). Combination studies with IFN and a wide variety of DAAs, including NS5A inhibitors, NS3/4 protease inhibitors, non-nucleoside NS5B inhibitors and other nucleos(t)ide inhibitors demonstrated additive or synergistic effects (Hebner et al., 2012; Zennou et al., 2010). Animal and human pharmacokinetic (PK) studies showed that sofosbuvir was rapidly converted to the 2′-F, 2′-C-methyluridine-5′-monophosphate and subsequently on to the active triphosphate in the liver, with little to no sofosbuvir observed in systemic circulation (Babusis et al., 2013; Martel-Laferriere and Dieterich, 2012; Sofia et al., 2010a,b). The human PK study results strongly support a liver-targeting mechanism and validate the PK and metabolism results demonstrated in animals.

Sofosbuvir presents an unusually clean safety profile for a nucleotide therapeutic. *In vitro*, sofosbuvir exhibits no cytotoxicity, mitochondrial toxicity, or bone marrow toxicity when dosed at multiples above the effective dose (Lam et al., 2010b; Sofia et al., 2010). Animal toxicology studies and preclinical animal pharmacology studies were reported to show no significant drug related findings. Sofosbuvir was also not genotoxic when studied in a battery of *in vitro* or *in vivo* tests, nor did it show effects on embryo-fetal viability or on fertility when studied in rats. In a wide range of human clinical trials, in which over 2000 patients were dosed, sofosbuvir was deemed to be exceptionally safe and well tolerated, with no reported drug-related adverse events (Jacobson et al., 2013; Koff, 2014; Lawitz et al., 2013).

Sofosbuvir and its major metabolite, the uridine nucleoside, were shown not to be substrates or inducers of CYP450 enzymes, but sofosbuvir was observed to be a substrate for P-glycoprotein and breast cancer resistant protein (BCRP). Drug–drug interaction studies did not identify any limiting combinations that would restrict sofosbuvir's use in patient populations typically infected with HCV such as HIV infected patients, transplant recipients or recovering drug addicts (Gilead Sciences, 2013; Karageorgopoulos et al., 2014; Koff, 2014; Mathias et al., 2012). Pharmacokinetic analysis also showed that liver cirrhosis, common in HCV-infected patients, had no clinically relevant effect on sofosbuvir exposure.(Gilead Sciences, 2013) No food effects were observed with oral sofosbuvir administration and no accumulation of the drug or its major metabolite was noted (Rodriguez-Torres et al., 2013).

The clinical efficacy of sofosbuvir in HCV-infected patients was demonstrated in a widely diverse patient population, that included Caucasians, African-Americans, Hispanics, Asians, males, females, non-cirrhotics, cirrhotics, treatment-experienced, null responders and patients of all age groups. Clinical efficacy was also demonstrated across the spectrum of HCV genotypes. Sofosbuvir has now been approved for use in GT1, 2, 3 and 4-infected patients. In a treatment-naïve or previously IFN-treated GT2 patient population, SVR12 was achieved in 93% of patients. For GT2 IFN-intolerant, ineligible or unwilling patients, sofosbuvir (400 mg) + RBV for 12 weeks produced an overall SVR12 of 93% (Jacobson et al., 2013). For GT3 IFN-intolerant, ineligible or unwilling patients, 12 weeks of sofosbuvir + RBV led only to an SVR12 of 61% (Jacobson et al., 2013; Koff, 2014). In a treatment-experienced patient population (relapsers and non-responders) an SVR12 of 86% was achieved for GT2 patients, compared with an SVR12 of 30% for GT3 patients. Extending therapy to 16 weeks increased cure rates to 94% (GT2) and 62% (GT3) (Jacobson et al., 2009).

In the treatment-naïve or previously IFN-treated patient study, a 24-week course of therapy increased SVR12 rates to 84% in the GT3 group (Gilead Sciences, 2013). Overall, in GT2 populations, patient status (treatment-naïve, cirrhotic or treatment-experienced), had no impact on cure rates; however, in GT3 populations there was an obvious difference in SVR response rates, dependent on status. Experienced GT3 patients responded less well than naive, and treatment-experienced cirrhotics (SVR12 60%) responded less well than non-cirrhotics (SVR12 85%) (Gilead Sciences, 2013; Jacobson et al., 2013).

In GT1 or 4 patients, sofosbuvir + RBV alone was not sufficient to deliver acceptable cure rates. However, a sofosbuvir + peg-IFN/RBV combination therapy for 12 weeks delivered an excellent overall response rate (SVR12) of 90% (GT1 89%, GT4 96%) (Lawitz et al., 2013). SVRs in this study were not particularly sensitive to IL28B status or the presence or absence of cirrhosis. In a small cohort of GT5 and 6 patients, the SVR12 was 100%.

Even in difficult-to-treat patients, sofosbuvir has demonstrated high cure rates. In a GT1, mostly African-American population exhibiting various stages of liver fibrosis and a high CT/TT IL28B allele frequency, a 24-week course of sofosbuvir + RBV delivered SVR12 rates in the 90% range (Osinusi et al., 2013). HIV/HCV co-infected patients who were HIV virologically suppressed showed a promising response to sofosbuvir + RBV-containing therapy, when administered for 12 or 24 weeks. These co-infected patients demonstrated SVR12 rates of 76% (GT1, 24 weeks), 88% (GT2, 12 weeks) and 92% (GT3, 24 weeks) (Gilead Sciences, 2013; Koff, 2014). Co-administration of sofosbuvir with a number of antiretroviral agents had no effect on HIV status (Karageorgopoulos et al., 2014). In recently reported clinical trials in liver transplant patients with severe HCV recurrence who were treated with sofosbuvir + RBV ± PegIFN, an overall SVR12 of 56% was achieved, with accompanying marked clinical improvement and improved liver function tests (Charlton et al., 2013; Curry et al., 2013; Koff, 2014).

Recently reported studies evaluating IFN-free combinations of sofosbuvir with either an NS5A inhibitor (ledipasvir or daclatasvir) or a protease inhibitor (simeprevir), with or without RBV, have shown exceptional results (Afdhal et al., 2014a,b; Fontana et al., 2013; Gane et al., 2014; Kowdley et al., 2014; Schinazi et al., 2014; Sulkowski et al., 2014). These studies demonstrated that two-drug combinations with sofosbuvir as the backbone produce very high cure rates (SVR12 95–100%) in HCV-infected patients across genotypes, and that RBV is not needed to achieve these high rates. The drug combinations were well tolerated, with no treatment-ascribed adverse events. A NDA for the sofosbuvir/ledipasvir fixed-dose combination was recently submitted.

The emergence of clinical resistance has always been a concern for nucleos(t)ide therapies, but thus far sofosbuvir has proven to be largely immune from this problem. In the laboratory, the S282T amino acid change in the HCV polymerase has been identified as the primary resistance mutation (Lam et al., 2010b, 2012; Tong et al., 2014). This substitution confers approximately a 2- to 18-fold reduction in susceptibility in cell culture, but also reduces viral replication capacity by 89–99%, making the mutant virus very unfit for survival. Recently, a novel double mutation (L159F/L320F) which conferred low level resistance to sofosbuvir was identified in the laboratory, but it is not represented in GenBank (Tong et al., 2014). Each of the single mutants, L159F and L320F, demonstrated a low replication capacity relative to wild-type, and the