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Commentary

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

Michael J. Sofia

OnCore Biopharma, Inc., 3805 Old Easton Rd, Doylestown, PA 18902, United States
The Blumberg Institute, 3805 Old Easton Rd, Doylestown, PA 18902, United States

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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.

E-mail address: mikes@oncorebiopharma.com

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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

replication capacity of the double mutant was even further reduced.

In the clinic, the primary S282T mutation has not been identified as a pre-emergent variant, and only in one case has this mutated virus been observed upon treatment with sofosbuvir (Jacobson et al., 2013; Rodriguez-Torres et al., 2013). In this case, sofosbuvir was given as monotherapy in a Phase 2b trial, and a single GT2b patient harboring the mutated virus was observed after relapse 4 weeks post-treatment, but was no longer detectable at post-treatment week 12 (Gilead Sciences, 2013). In GT3a Phase 3 patients, the treatment-emergent L159F and V321A NS5B mutations were observed, but no detectable shifts in phenotypic susceptibility to sofosbuvir were seen (Gilead Sciences, 2013). In hepatocellular carcinoma patients awaiting liver transplantation, who received up to 48 weeks of sofosbuvir and RBV, the L159F NS5B substitution was detected in subjects who experienced virologic failure (Gilead Sciences, 2013). However, the clinical significance of the L159F and V321A NS5B substitutions is not known at this time. Therefore, based on current data, patient relapse after cessation of sofosbuvir-containing therapy has not been associated with resistant virus.

3. What opportunity exists for a better nucleos(t)ide to treat hepatitis C?

With sofosbuvir fast becoming the backbone of the standard of care, a next-generation nucleos(t)ide therapeutic would probably have to overcome the hurdle of a superiority, or at least a non-inferiority clinical study. To assess the possibility of developing a next-generation nucleos(t)ide agent, I will consider four aspects of this question: potency and efficacy, toxicology, pharmacokinetics and viral resistance. I will not address the ongoing debate regarding competitive drug pricing of new market entrants, as this falls outside the scope of this discussion.

3.1. Potency and efficacy

Is sofosbuvir sufficiently potent and efficacious to address the needs of a broad spectrum of HCV patients? What improvement would a next-generation nucleos(t)ide have to exhibit to be competitive? Potency relates to dose, efficacy and toxicity. Typically, the more potent a compound, the lower the dose and the lower the chance of dose-limiting toxicity. Sofosbuvir is a potent HCV polymerase inhibitor, which has translated into rapid kinetics of viral load decline in the clinic, although early viral load decline kinetics seen with nucleos(t)ides are less dramatic than observed for other DAAs such as NS5A inhibitors (Guedj et al., 2014). Several nucleotide HCV polymerase inhibitors (PSI-352938, IDX184 and INX189) that have been shown to be significantly more potent *in vitro* have been evaluated in early clinical trials, but none has produced more rapid or deeper viral load declines than sofosbuvir (Guedj et al., 2014; Lalezari et al., 2009; McGuigan et al., 2010; Patti et al., 2011; Reddy et al., 2010; Zhou et al., 2011).

Sofosbuvir has been shown to be equipotent across all HCV genotypes *in vitro*. However, this *in vitro* pan-genotypic profile does not appear to completely translate into the human clinical setting. The most obvious comparisons can be made in patients harboring GT1, 2 or 3 viruses. It is still not clear why sofosbuvir, or for that matter most HCV DAA, exhibits genotype differences in the clinic (Pol et al., 2014; Tapper and Afdhal, 2013). This lack of understanding of what drives the clinical manifestations of differential drug response across genotypes makes it difficult to re-engineer a molecule to overcome these disparities. A nucleos(t)ide that does not exhibit such genotype differences in the clinic would certainly have a competitive advantage. However, the combination of sofosbuvir with a second potent DAA such as an NS5A or protease inhibitor appears to smooth out genotype variability (Koff, 2014; Sulkowski et al., 2014). This two-drug combination has the potential to provide the pan-genotypic effect clinically.

Since it is widely accepted that, because of concerns about duration of viral suppression and resistance, a single agent is not sufficient to effect HCV-cure, the only competitive advantage that a more potent, next-generation nucleos(t)ide could potentially provide is delivery of true pan-genotypic results when combined with RBV. The other possibility for improved efficacy relates to treatment duration. Sofosbuvir combinations currently require either a 12-week (GT1, 2, and 4) or 24-week (GT3) duration of therapy. The possibility of reducing treatment duration would certainly add value to a new agent. Such a reduced treatment duration has been studied for sofosbuvir in combination with ledipasvir, for which 8 weeks on treatment delivered SVR12 rates comparable to the standard 12-week regimen (Koff, 2014; Kowdley, 2014). Even a 6-week treatment duration seems possible with a 3-drug DAA combination (Kohli et al., 2014). Concerning sofosbuvir and dose-limiting toxicity, none has been observed and therefore, attempting to address this in a second-generation agent would present no clear advantage. When considering potency/efficacy, a next generation nucleos(t)ide would therefore need to deliver a clear advantage in either genotype coverage or duration of therapy to compete with existing sofosbuvir-containing regimens.

3.2. Toxicity

It goes without saying that a drug's toxicological profile and manifestation of adverse events can make or break its acceptance in the marketplace, and can provide opportunities for new agents to carve out a competitive position. An example can be seen within the HCV space itself. Telaprevir and boceprevir launched a new era in the treatment of patients with chronic hepatitis C, demonstrating improved cure rates and reduced treatment duration. However, they both carried the baggage of significant toxicities and demonstrated adverse events, both in clinical trials and post-approval. Being aware of new, more tolerable drugs approaching the end of clinical studies, patients began to refuse treatment and doctors began to "warehouse" patients.

As noted above, a review of sofosbuvir's toxicological profile and reported clinical adverse events indicates that this drug is surprisingly free of toxicity. To date, all reported *in vitro* and *in vivo* animal studies have shown sofosbuvir to be devoid of any of the typical toxicity signals seen for nucleos(t)ides which were identified as potential problems for several other nucleotide-analog HCV inhibitors that had entered clinical studies (Arnold et al., 2012). The fact that sofosbuvir is a uridine analog, and that uracil is an RNA base, may help explain its lack of effect on host DNA polymerases. The cardiovascular toxicity that has plagued other nucleotide analogs has not been seen with sofosbuvir. Clinical studies have shown sofosbuvir to be generally safe and well tolerated, and most of the reported adverse events can be ascribed to the well-established side effects of co-administered agents RBV and Peg-IFN. Drug discontinuations due to adverse events have been rare. From a toxicology and adverse events assessment, it is therefore unclear where an opportunity might exist for a next-generation agent to improve upon sofosbuvir. The best possibility would be to achieve a non-inferiority toxicity and adverse event profile.

3.3. Pharmacokinetics

As a nucleotide prodrug, sofosbuvir is designed to selectively deliver the parent drug, 2′-F, 2′-C-methyluridine 5′-monophosphate, to the liver (Sofia et al., 2010). This strategy takes advantage

of liver first-pass metabolism to remove the pro-moieties, thus revealing the 5′-monophosphate. The parent drug is effectively trapped inside hepatocytes for subsequent conversion to the active nucleoside triphosphate. The prodrug strategy is also intended to improve oral bioavailability for the parent molecule, which would probably not be absorbed orally. Application of this liver-targeting strategy has the advantage of minimizing systemic exposure of sofosbuvir and its parent drug, and consequently minimizing any possible systemic side effects.

The major systemic by-product of this liver-targeting strategy is the inactive uridine nucleoside, which is cleared predominantly in the urine. Consequently, one limitation presented by sofosbuvir may be associated with patients diagnosed with severe renal impairment. Patients taking drugs that are potent intestinal P-glycoprotein inducers could also pose a problem, because sofosbuvir interacts with P-glycoproteins. An opportunity therefore exists to find a next-generation nucleos(t)ide that overcomes the problems associated with severe renally-impaired patients and compatibility with drugs that are also P-gp inducers.

3.4. Viral resistance

The existence of pre-emergent viral variants and the inherently highly error-prone replication process make drug resistance a significant concern for HCV DAA therapy, However, the resistance picture for sofosbuvir appears quite manageable. The major resistant variant (S282T) was shown to be very unfit, and was never observed on dual- or triple-therapeutic regimens, and other, less prevalent variants had a much reduced replicative capacity. It appears that even for the small number of patients who exhibit S282T-associated breakthrough after therapy, re-treatment with sofosbuvir can clear the virus.

Sofosbuvir's high barrier to resistance has made it the ideal backbone in combination therapies. Combinations with NS5A or NS3/4 protease inhibitors have been sufficient to mitigate the low barrier to resistance associated with these other therapies, and have led to exceptionally efficacious treatment regimes (Afdhal et al., 2014a,b; Gane et al., 2014; Koff, 2014; Sulkowski et al., 2014). However, it would certainly be of value to identify a nucleos(t)ide that does not share sofosbuvir's resistance profile, which would allow for an alternative nucleos(t)ide therapy, in the event that sofosbuvir resistance becomes a problem. Such a nucleotide has been identified, and was shown to be quite potent as an inhibitor of viral replication in the clinic. This nucleotide (PSI-352938, GS-938) is similar to sofosbuvir, in that it contains the signature 2′-F, 2′-C-methylfuranose sugar construct, but it has a guanine base in place of the uracil, and it also employs a different phosphate prodrug strategy (Lam et al., 2010a, 2011). Unfortunately, the clinical development of this compound was terminated due to liver enzyme elevations (Sofia, 2013). The nucleoside R1626 also exhibited a unique resistance profile relative to sofosbuvir, but its development was also terminated as a result of severe clinical adverse events (Zeuzem et al., 2010). Although sofosbuvir resistance appears to be of minimal concern, the greatest opportunity for a next-generation agent would be to have an orthogonal resistance profile.

Based on this analysis, it appears that a next-generation nucleos(t)ide HCV polymerase inhibitor would have to exhibit a potent, non-differentiated pan-genotypic profile, especially improved efficacy against GT3 virus, and no limitations for patients who have severely compromised renal function or are being administered agents that are P-glycoprotein inducers. A nucleos(t)ide having an orthogonal resistance profile relative to sofosbuvir would also be preferred. Based on what we currently know, is there an agent with such a profile?

Substantial work over the past 15 years has gone into the discovery and development of nucleoside and nucleotide HCV polymerase inhibitors. No less than fifteen nucleos(t)ide inhibitors have entered clinical trials (Table 1), but only sofosbuvir has received both US FDA and EU marketing approval (Alios, 2014; Idenix, 2014; Sofia, 2013; Sofia et al., 2012). With the exception of R1626 and RG7348 (Nieforth et al., 2012), which are 4′-azidocytidine nucleosides, most if not all of the other agents appear to share a common structural motif, a 2′-β-*C*-methylfuranose with either a 2′-α-hydroxyl or a 2′-α-fluoro substitution (Table 1). Since the occurrence of life-threatening hematological toxicity associated with the 4′-azidocytidine nucleoside R1626, significant concern about compound class-related toxicity has reduced interest in this chemotype (Zeuzem et al., 2010).

For the extensively studied 2′-β-methyl nucleos(t)ides, both natural and modified purine and pyrimidine bases have been investigated. A review of the 2′-C-methyl class reveals that the nucleotide prodrug derivatives have proven to be more potent and efficacious than the nucleosides (Sofia et al., 2012). The purine derivatives are also more potent than the pyrimidine versions (Sofia, 2013). The high attrition rate in this class has largely been due to clinical safety issues, but several compounds have been discontinued because of poor PK characteristics. The safety issues have ranged from severe cardiovascular toxicity to gastrointestinal and potential liver toxicity (Table 1). The PK limitations shown by some of these 2′-methyl nucleos(t)ides have been attributed to poor oral bioavailability or variable PK profile across a patient population (Table 1). Consequently, because of the high attrition rate and the success of the uridine nucleotide prodrug sofosbuvir, a majority of the recent clinical stage entrants into the HCV NS5B nucleos(t)ide inhibitor arena contain the uridine nucleotide

Table 1
Nucleoside and nucleotide HCV polymerase inhibitors that have entered clinical development.

Compound	Class	Nucleobase	Phase of development	Development status	Issues
NM283	2′-Methyl	Cytosine	II	Discontinued	GI toxicity
R1626	4′-Azido	Cytosine	II	Discontinued	Hematological toxicity
PSI-6130	2′-Methyl-2′-F	Cytosine	I	Discontinued	PK
Mericitabine (RG7128)	2′-Methyl-2′-F	Cytosine	III	Active	–
Sofosbuvir (GS-7977, PSI-7977)	2′-Methyl-2′-F	Uracil	Marketed	FDA & EU approved	–
GS-938/PSI-352938	2′-Methyl-2′-F	Guanine	II	Discontinued	Liver enzyme elevation
IDX-184	2′-Methyl	Guanine	II	Discontinued	Potential cardiotoxicity
INX-189	2′-Methyl	Guanine	II	Discontinued	Cardiotoxicity
RG7348	4′-Azido	Uracil	I	Discontinued	Lack of efficacy
ALS-2158	2′-Methyl-?	Adenine	I	Discontinued	Lack of efficacy
VX-135/ALS-220	2′-Methyl-?	Uracil	II	Active	–
ACH-3422	2′-Methyl-?	Uracil	II	Active	–
GS-6620	2′-Methyl	Adenine	I	Discontinued	PK
IDX-20963	2′-Methyl-?	Uracil	IND	Hold	Preclinical toxicity
IDX-21437	?	Uracil	I/II	Active	–

prodrug motif (Table 1). Based on available resistance data showing a common S282T resistant phenotype, the majority of these recent clinical agents again resemble sofosbuvir, in that they appear to employ a 2′-C-methylfuranose sugar moiety (Popa et al., 2013; Yang et al., 2013).

With striking similarity to sofosbuvir, can nucleotides now in clinical development sufficiently differentiate themselves from it? Renal clearance is a major pathway for nucleos(t)ide elimination, and this is the case for sofosbuvir's major metabolite, the uridine nucleoside. Consequently, the probability is high that the kidneys will be a major clearance route for the more recent nucleotide prodrug clinical entrants. This fact would limit their ability to differentiate themselves from sofosbuvir in patients with severe renal impairment. The newer nucleotide prodrugs also display a similar resistance phenotype to sofosbuvir. Differentiation based on efficacy in GT3 patient populations or the potential for reduced duration of therapy cannot be adequately assessed with data available at this time.

Based on the common structural class and current information, it is anticipated that the sofosbuvir follow-on agents will, to a large extent, mirror sofosbuvir's profile. The questions can therefore be raised whether "just another sofosbuvir" will benefit patients, and whether such a "me-too" nucleotide without distinguishing characteristics will address the limitations of current nucleotide therapy. Clinical studies will clearly answer these questions, but patients will be best served by innovative research that addresses their needs and identifies new, structurally distinct nucleos(t)ides that present an orthogonal resistance profile to sofosbuvir.

Disclosure

Michael J. Sofia, Ph.D. is the principle co-inventor of sofosbuvir and former Senior Vice President of Chemistry at Pharmasset, Inc., where he led the efforts in the discovery and early development of sofosbuvir. He is also a former Senior Vice President of Chemistry and Senior Advisor at Gilead Sciences, Inc.

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