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SUPPLEMENT ARTICLE

Prospects for Long-Acting Treatments for Hepatitis C

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In 2019, more than 4 years after the widespread availability of safe, oral, curative treatments, an estimated 58 million people were living with hepatitis C virus infections (PLWHC). Additional tools may enable those not yet reached to be treated. One such tool could be long-acting parenteral formulations of HCV treatments, which may allow PLWHC to be diagnosed and cured in a single encounter. Although existing highly effective oral medications might be formulated as long-acting parenteral treatments, pharmacological, regulatory, patent, and medical challenges have to be overcome; this requires the concerted efforts of PLWHC, researchers, funding agencies, industry, the World Health Organization, and other stakeholders.

Keywords. HCV; long-acting; glecaprevir; pibrentasvir; sofosbuvir.

CLINICAL AND PUBLIC HEALTH SIGNIFICANCE

In 2015, there were an estimated 71 million persons living with hepatitis C virus (HCV) (PLWHC), and there was an oral treatment that could cure infection in nearly everyone who received it. By 2019, the World Health Organization (WHO) estimated that there remained 58 million PLWHC, reflecting residual barriers to delivering curative oral treatment and preventing new infections [1]. New treatment strategies are clearly needed.

Long-acting treatments for HCV infection represent an important alternative approach. Because HCV can be cured in nearly all persons with 8 to 12 weeks of drug exposure, it may be possible to cure infection in a single encounter. Point-of-care diagnosis of HCV antibodies (and in some settings HCV RNA) is already possible. Thus, in comparison to HIV or hepatitis B virus treatment, a test-and-cure approach is possible and is especially appealing for implementation in public health. Single-encounter cure bypasses the need to establish medical infrastructure, such as had to be created to sustain human immunodeficiency virus (HIV) treatment in low-income regions and opens a range of possible implementation strategies (Table 1). For example, test-and-cure approaches could be deployed where harm reduction services are provided, in public health clinics, in pharmacies, and even by mobile delivery units. The latter could be especially important to bring treatment to the 58 million PLWHC who are not reached by existing health services. In low- and middle-income countries, infrastructure that has been established for HIV treatment and/or contraception delivery may present an opportunity for rapid rollout of a successful long-acting (LA) HCV product.

Long-acting treatments for HCV infection may also be important in correctional settings. In the United States, before direct-acting oral treatments, it was estimated that one-third of PLWHC had some contact with corrections each year. This fraction of all PLWHC who are in contact with corrections may have been even higher in 2022 because treatment has disproportionately been distributed to insured persons in medical care while new infections are tightly linked to illicit opioid use. Although precise estimates are lacking and vary by region, short-term facilities (jails) may be especially important points of contact with PLWHC. However, short-term facilities have not traditionally engaged in long-term medical care because approximately one-half of those incarcerated are released in 48 hours. Nonetheless, point-of-care testing and treatment for sexually transmitted infections such as chlamydia has already been successfully implemented in short-term facilities and may contribute to reducing the community burden of infection [2]. Even in long-term settings, there may be an operational advantage to a single-encounter cure compared with referrals to an infirmary for pill dispensing.

Notably, many of the key elements of a single-encounter cure of HCV infection have already been tested. Solomon and coworkers studied 399 PLWHC in 38 sites in Brazil, South Africa, Thailand, Uganda, and the United States using an approach of confirming HCV infection and then dispensing all pills at once and not monitoring thereafter, except to encourage adherence and check for cure. The rate of cure (95%) was similar to traditional approaches [3]. Because the visits were to encourage adherence and because at least some of the treatment failures were from poor adherence or loss to follow-up, the study also demonstrates not just the feasibility but also potential advantages of a long-acting treatment.

PATIENT AND STAKEHOLDER PERSPECTIVES

Because Solomon and coworkers showed that pills might alternatively be used in a single-encounter treatment strategy, it is important that PLWHC may prefer long-acting treatments

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Table 1. Possible Venues to Implement Long-Acting Single-Encounter Cures for HCV

Traditional clinics when preferred by people living with hepatitis C virus
Harm reduction service venues
Public health clinics
Pharmacies
Mobile delivery units
Long-term incarceration (prisons)
Short-term incarceration (jails)

for HCV infection to pills. In 1 study, 1140 PLWHC from North America, Europe, India, New Zealand, and Australia were asked what type of treatment they would prefer [4]. Persons were shown cards representing a typical injection, implant, or a gastric residence device and asked to compare their preferences to receiving treatment by one of those routes compared to taking 1 to 3 pills per day for 8 to 12 weeks. Only one-half (50.8%) indicated they most preferred to take 8 to 12 weeks of pills, and the remaining individuals preferred injection (37.7%), an implant (5.6%), or a gastric residence device (6%). Thus, even in high-income regions of the world and with the option to take pills, a substantial number of persons may prefer a long-acting treatment.

Clearly, additional studies are needed among PLWHC, not just in other settings but also to explore preferences in the possible approaches. For example, it is important to understand the range of acceptable platforms (injection volume, implant size/need for removal, patches). In addition, other views need to be considered, including those of pregnant women, children and their guardians, the medical providers, the ministries of health, correctional medicine providers, and organizations/foundations who might sponsor such approaches. Of course, the feasibility of various LA delivery systems will depend on the pharmacological properties of the candidate medicines (discussed in the following section). However, the overwhelming clinical and public health impact of a single-encounter cure provides an imperative to prioritize approaches such as injections and dissolvable implants that do not require close medical follow-up.

DRUG CANDIDATES FOR LONG-ACTING USE

There is precedent for long-acting treatment for HCV. Weekly injections of peginterferon alpha were used for a decade but replaced by safer and more effective direct-acting agents formulated as pills. Now, the potential applications of long-acting, single-encounter treatments of HCV are predicated on the safety and efficacy of those oral medications (Table 2). Current curative regimens require at least 2 drugs with 2 distinct mechanisms of action. We focus on the WHO-recommended treatments that are effective against all the HCV genotypes, obviating the need for expensive genotyping that is often not available in low-income settings nor at the point of care. These pangenotypic regimens include 12 weeks of sofosbuvir combined with NS5A inhibitors such as velpatasvir or daclatasvir (possibly ravidasvir) and 8 weeks of glecaprevir used with pibrentasvir.

Table 2. Characteristics of Pan-Genotypic HCV Treatments

Formulation	Regulatory status
Sofosbuvir 400 mg and velpatasvir 100 mg	Generic formulations of oral drugs exist
Sofosbuvir 400 mg and daclatasvir 60 mg	Generic formulations of oral drugs exist
Glecaprevir 300 mg and pibrentasvir 120 mg	Licenses extended to low- and middle-income countries

These regimens are extremely safe and effective, curing more than 95% of those treated, even persons with cirrhosis, and even in real-world situations with variable adherence. For example, 1 study considered 5552 PLWHC who were treated with sofosbuvir 400 mg and velpatasvir 100 mg, 20% of whom had cirrhosis. A sustained virologic response or cure was reported for 98.9% (another 6% were either lost to follow-up or did not finish medications) [5]. Similarly, a meta-analysis of real-world experiences with glecaprevir and pibrentasvir considered 12 531 PLWHC treated with glecaprevir and pibrentasvir in 18 cohorts [6]. Of those evaluated for cure, 96.7% had a sustained virologic response, which was 98.1% in the modified intent-to-treat analysis of 7001 persons. Serious adverse events were reported in 55 of 5522 patients and included pruritis, fatigue, and headache, which in 33 instances led to dose discontinuation. Zamor and coworkers also reported high cure rates even in those with lower adherence and less total drug exposure [7]. Notably, these HCV treatments have no hypersensitivity issues that might require oral pretreatment and obviate the single-encounter strategy.

Given the potential applications, it is important to consider the licensing and availability for low- and middle-income countries. The Medicines Patent Pool arranged with AbbVie, the patent holder and originator company, a license for glecaprevir and pibrentasvir to cover 96 low- and middle-income countries and for several generic manufacturers (Mylan, Arene Life Sciences, USV, and Remington Pharmaceuticals) to produce glecaprevir and pibrentasvir [8]. Likewise, the Medicines Patent Pool have executed a license agreement covering 112 low- and middle-income countries with Bristol Myers Squibb for daclatasvir, with 7 sublicences signed. Four of these generic manufacturers (Cipla, Hetero, Laurus, and Mylan) have received WHO Prequalification for daclatasvir products. For sofosbuvir-based treatment, there also are generic options with both daclatasvir and velpatasvir, including those made by Asegua Therapeutics as well as Mylan, Natco, and others [9]. The Global Fund lists prequalified suppliers for sofosbuvir combined with daclatasvir (eg, Cipla Ltd, Mylan) or sofosbuvir with velpatasvir (Gilead and Mylan) and others

prequalified to supply one or the other individually formulated medications [10]. Generic versions of these medications have been carefully studied and show comparable safety and efficacy to branded formulations [11]. The Medicines Patent Pool have also announced a license agreement with Tandem Nano Ltd for development of LA glecaprevir and pibrentasvir (an initiative that includes some of the authors of this paper). Nonetheless, regulatory challenges remain and may constrain development of long-acting treatments.

PHARMACOLOGICAL CONSIDERATIONS

Sofosbuvir-based treatments were the first all-oral pangenotypic treatments for HCV. Sofosbuvir is potent, safe, and has a high barrier to resistance. Sofosbuvir is a pro-drug that is initially hydrolyzed by cathepsin A, carboxylesterase 1, or other hydrolyzing enzymes depending on cell and tissue type and ultimately converted intracellularly to the active form, the triphosphate [12]. The triphosphate, referred to as GS-461203 or 007-TP in the literature, inhibits the NS5B HCV polymerase in hepatocytes. The primary form of the drug circulating in plasma is GS-331007, which is eliminated renally and has no antiviral activity. Sofosbuvir has not been evaluated as an implant or injectable to our knowledge, but other nucleotide phosphoramidate prodrugs, including tenofovir alafenamide, appear promising as potential long-acting agents. Several investigators are exploring implant-based delivery approaches for tenofovir and alternative enteric long-acting strategies for sofosbuvir [13, 14]. However, concentration targets to assess drug release with LA sofosbuvir preparations will need to be identified, which may prove challenging given the pharmacologically active triphosphate resides in the hepatocytes.

Injectable LA formulations using either an oil depot or aqueous particle dispersion, are among the most successful LA approaches to date. These approaches offer comparatively simple manufacture, which is important to ultimate product costs. However, sofosbuvir physicochemical properties do not align well with these cheaper formulation approaches, which require properties enabling either extremely high solubility in parenteral oils or extremely low aqueous solubility for formation of particle dispersions. The solubility does not lend well to those approaches, and more advanced (and costly) technologies may therefore be needed to develop sofosbuvir-based LA delivery formats. Other physiochemical properties of small molecules may also be important considerations for LA compatibility, but the field remains in relative infancy and much work is required to define those characteristics.

Glecaprevir 300 mg and pibrentasvir 120 mg are approved as an 8-week oral treatment for nearly all PLWHC. Glecaprevir inhibits the HCV NS3/4A protease. In oral dose-finding studies, greater than dose-proportional increases in plasma levels were noted up to 400 mg [15]. No obvious differences were detected in mean HCV RNA declines over 72 hours with doses from 100 mg (−4.1 log10 IU/mL) to 700 mg (−4.3 log10 IU/mL) [16]. Pibrentasvir inhibits the NS5A HCV replication complex. In oral dose-finding studies, pibrentasvir exposures increased in a greater than dose-proportional manner across a 1.5- to 120-mg range and became linear between 120 and 600 mg [17]. Oral doses of 40 to 400 mg produced similar reductions in HCV RNA [16]. Given high tolerability of the higher doses of glecaprevir and pibrentasvir, efficacy studies were done with a relatively limited range of doses and durations. Interestingly, aside from the most difficult to treat genotype 3 infections with/without cirrhosis, there appeared to be similar efficacy with lower doses of pibrentasvir (eg, 40 vs 120 mg) or glecaprevir (200 vs 300 mg). However, the data are few and variability in duration complicates interpretation. In a series of studies using the approved doses of 300/120 mg, durations of 8 weeks were shown to be equivalent to 12 weeks for nearly all persons, including those with compensated cirrhosis [18]. One study demonstrated high cure rates with just 6 weeks of treatment of glecaprevir and pibrentasvir in persons recently diagnosed with HCV [19]. Unlike most other current HCV direct-acting antiviral drugs, glecaprevir and pibrentasvir possess pharmacological properties that may lend well to simple and cost-effective parenteral LA formats using particle processing technologies. The aqueous solubilities, in vivo half-lives, and target plasma exposures for glecaprevir and pibrentasvir justify exploration of these drugs as LA injectables using technologies that have been effective for other indications.

CHALLENGES AND OPPORTUNITIES

Because the ideal physicochemical features such as water solubility differ for a parenteral versus an oral treatment, there may also be compounds with high potency that were not developed. Although those certainly should be considered for LA approaches, the requirement to demonstrate the safety of the parent compound is a disadvantage relative to those whose safety and efficacy has already been well established, including in real-world settings.

The pharmacokinetic profiles may differ for HCV drugs administered parenterally and with sustained prolonged administration versus oral administration. Because the portal blood drains to the liver, oral medications in general are first taken up by the liver and pro-drug transformation to active metabolites is enhanced at the target tissue, whereas with parenteral, long-acting administration, the drugs are likely to be delivered to the liver at a constant rate from the systemic compartment. Based on these differences, determining the pharmacokinetic-dynamic relationships with LA preparations are likely the more important goal than achieving plasma pharmacokinetic targets comparable to oral dosing. Studies in preclinical animal models and physiologically based pharmacokinetic modeling

will be important tools for predicting drug release, hepatic delivery, and establishing pharmacokinetic-dynamic relationships with LA agents.

Both sofosbuvir/velpatasvir and glecaprevir/pibrentasvir are US Food and Drug Administration–approved in children, and initial data reassure on the pharmacokinetics and safety of a sofosbuvir/NS5A combination in pregnant women, but LA approaches may bring added complexity that, although not insurmountable, will need to be addressed [20]. Dosing and tolerability may differ for infants and children and would need to be studied. Because the safety of the oral medications has not been fully established, there might be concerns that a woman might have prolonged drug exposure as the medications cannot be stopped if pregnancy occurs or is recognized after administration. Studies of the LA antiretrovirals, cabotegravir and rilpivirine, are in development for pregnant women and children with HIV. These studies may provide a platform for trials of long-acting HCV therapies in these populations. For a more comprehensive discussion of LA formulation in this context, please see in this supplement Abrams et al for use in infants and children and Olagunju et al for use in pregnant women.

There may also be explicit posological benefits of a LA delivery strategy relative to oral administration of HCV direct-acting antiviral drugs. For example, drug metabolism and active drug transport systems are a challenge for oral drug delivery, limiting the bioavailability of drugs administered via this route. Conversely, drugs delivered parenterally, transdermally, or via an implant may be expected to exhibit much higher bioavailability. Additionally, for antiviral drugs, the minimum concentration across the dosing interval that occurs immediately predose, is generally accepted to be the pharmacokinetic parameter that is best correlated with efficacy. Accordingly, dose optimization of orally administered drugs usually necessitates acceptance of a high maximum concentration to achieve a sufficient minimum concentration. Conversely, LA delivery formats aim to provide a flatter pharmacokinetic profile over a longer duration, which obviates daily peak to trough variation. Thus, LA injectable medicines almost exclusively require lower overall doses than their oral counterpart medicines when averaged across the treatment course, and it is fundamentally incorrect to use daily dose requirements as a surrogate of whether an LA format may be possible for a specific drug [21].

Many advances in medicine occur when economic and medical goals are aligned. Indeed, the development of safe, efficacious treatments for HCV is one of the most celebrated achievements of modern medicine (and the most lucrative). Given the differential focus on low- and middle-income countries and marginalized populations, the economic incentive to develop LA curative HCV treatments is less than for the initial oral approach. This and the complexities of patent protections of the parent molecules might impede the pace with which LA treatments are developed. Fortunately, the Medicines Patent Pool, WHO, and others have embraced this challenge by providing some solutions that have already demonstrated impact [22].

SUMMARY AND FUTURE DIRECTIONS

An LA HCV treatment that allows single-encounter cure could have enormous individual and public health impact. Being able to test and cure at a single encounter opens multiple strategies to implementing HCV cure. There remain pharmacologic, regulatory, and economic obstacles to this goal that still must be overcome. Key will be partnerships between PLWHC, researchers, funding agencies, industry, WHO, and other stakeholders. The net effectiveness of those partnerships will determine whether more than 50 million persons continue unnecessarily to live with HCV.

Notes

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