HHS Public Access

Author manuscript

Curr Opin Infect Dis. Author manuscript; available in PMC 2017 August 01.

Published in final edited form as:

Curr Opin Infect Dis. 2016 August ; 29(4): 373–380. doi:10.1097/QCO.0000000000000281.

Post-exposure Prophylaxis after Hepatitis C Occupational Exposure in the Interferon-free Era

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Abstract

Purpose of review—Healthcare personnel are at risk for occupational exposures to bloodborne pathogens. Primary prevention remains the first line of defense, but secondary prevention measures known to be effective should be implemented when percutaneous exposures occur. Hepatitis C virus (HCV) is a major infectious cause of liver-related morbidity and mortality. Chronic HCV treatment has changed dramatically, with many all-oral directly acting anti-HCV antiviral (DAA) regimens now available. Evidence for the use of DAAs as post-exposure prophylaxis (PEP) after occupational exposures to HCV is summarized here.

Recent findings—Little new evidence supports the use of antivirals in acute HCV infection. Several preliminary studies have examined the use of DAAs or host target agents (HTAs) in chronic HCV treatment. Effective HCV PEP requirements likely include pan-genotypic activity and a high barrier to resistance. One investigational DAA has shown promising results as an efficacious option for all genotypes in chronic HCV treatment and may ultimately represent a potential HCV PEP agent.

Summary—Insufficient supporting data exist to endorse the use of DAAs for PEP after HCV occupational exposures; additional studies examining efficacy, duration, and cost-effectiveness are needed. Development of more oral drugs possessing a high barrier of resistance and equal activity against all HCV genotypes is anticipated.

Keywords

Keywords: Bloodborne pathogens; post-exposure prophylaxis; HCV; direct acting antiviral agents

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Disclosure statement: Neither HYH nor DKH have any disclosures

Conflicts of Interest: There are no conflicts of interest

Introduction

Healthcare personnel continue to be at risk of acquiring bloodborne pathogens such as HIV, Hepatitis B virus (HBV) and HCV as a result of occupational exposures. The Centers for Disease Control and Prevention (CDC) estimates that over 380,000 percutaneous-related injuries occur annually among hospital employees and approximately half of such exposures go unreported [1-3]. Primary prevention remains the most important strategy for averting occupational infection with bloodborne pathogens. When exposures do occur, secondary prevention with exposure-specific PEP should be offered to healthcare personnel when existing scientific evidence supports the use of PEP. Recommendations for HIV and HBV PEP have been recently updated, whereas similar guidelines for HCV exposures remain unchanged [4-6]. No vaccine, intravenous therapy or other chemoprophylaxis is currently recommended for HCV PEP. However, the FDA approval of several new antiviral DAAs has dramatically changed the landscape of chronic HCV management [7]. Treatment options now include all-oral regimens with shorter durations and fewer adverse effects than interferon (IFN)-based therapy [8]. In this context, we consider the role that these new agents may ultimately have in the management of HCV occupational exposures.

Hepatitis C Epidemiology

HCV is a major cause of chronic liver disease and liver transplantation. Globally, the prevalence of HCV is 3% with 130-150 million people estimated to have chronic infection and approximately 500,000 deaths per year attributed to HCV-related liver disease [9]. The most recent National Health and Nutrition Examination Survey (NHANES) estimate of the prevalence of HCV infection in the United States is 2.5-4.7 million [10, 11]. HCV is the leading cause of liver transplantation and, since 2007, has surpassed HIV as a cause of death in the United States [12, 13].

The risk of developing HCV infection after a parenteral exposure is estimated at 1.9%. Whereas this risk is much lower when compared with similar exposures to HBV, the number of HCV patients accessing the U.S. healthcare system appears to be increasing [14]. With no existing vaccine available, occupational exposure to HCV remains important.

Hepatitis C Lifecycle and Pathogenesis of Infection

Understanding the HCV lifecycle has allowed development of drugs that have inhibitory actions targeted at various steps of the viral lifecycle. Antivirals currently on the market or in clinical development have two main targets of inhibition: HCV protein maturation (NS3-4a protease inhibitors) and HCV RNA synthesis (NS5a and non-nucleoside inhibitors, nucleoside/nucleotide analogues, and host target agents) [15]. HCV, a positive-stranded RNA virus lacking a latent form, replicates its genome directly into RNA using an error-prone RNA polymerase. The importance of the viral species heterogeneity resulting from such error was magnified by the selection of resistant viral variants that occurred during monotherapy with the first-generation HCV protease inhibitors, a class of DAAs with a low barrier to resistance. Selection of resistant viral variants does not usually occur when using drugs with a high barrier to resistance, but cross-resistance within a drug class can occur.

Each of the currently approved DAAs has differing barriers to resistance and differing activity against each viral genotype. We now understand that successful antiviral regimens require a combination of drugs from different classes in order to increase the barrier to resistance and achieve lasting sustained virologic response (SVR).

Management of Hepatitis C Occupational Exposure

Adherence to standard precautions remains the cornerstone of preventing occupational exposures [16]. Secondary prevention practices that have documented efficacy should be implemented when exposures occur after primary prevention fails. Any employee who sustains a workplace injury associated with risk for a bloodborne pathogen infection should receive immediate first aid. Further management recommendations such as cleansing the injury site, reporting exposures to occupational health, urgent evaluation of the exposure source for HIV, HBV, and HCV, and evaluation of the exposed healthcare worker for preexisting bloodborne pathogen infections, are unchanged [4-6, 17].

Diagnostic testing recommendations specific to HCV exposure are also unchanged. Healthcare personnel who sustain occupational exposures to HCV should be tested for HCV antibody and for HCV RNA (by polymerase chain reaction [PCR]). This initial testing should be performed within 48 hours of exposure to document pre-existing HCV infection [8]. Current U.S. Public Health Service guidelines recommend repeat serological testing at 6 months [6]. Many U.S. institutions have adopted a repeat testing frequency for both anti-HCV antibody and HCV RNA based upon either a “pre-emptive” or “watchful waiting” management strategy [18]. The first strategy, implementation of IFN therapy after detection of repeatedly positive HCV-RNA assays in the exposed healthcare worker, is based upon accumulated evidence that the treatment of acute HCV infection is more successful than chronic HCV. Proponents of “watchful waiting,” in which patients diagnosed with acute HCV are closely monitored for 3-4 months for persistent viremia before IFN is started, cite evidence that 20-40% of patients who develop acute HCV spontaneously clear their infections [19]. Both of these approaches aim to diagnose and treat acute infections before they progress to chronic HCV, a diagnosis with a poorer prognosis; however, the urgency of treating acute infection may be reduced with the notable success of oral DAAs in chronic infection. Current American Association for the Study of Liver Diseases (AASLD) guidelines recommend that if acute HCV infection is treated, the same genotype-specific regimens and duration as those approved for chronic infection should be used [8].

Hepatitis C Post-exposure Prophylaxis

PEP for occupational exposures to bloodborne pathogens is treatment given to healthcare personnel in the time period immediately following exposure and has the goal of preventing infection with specific pathogens. This approach is distinguished from the “pre-emptive” or “watchful waiting” strategies which involve the treatment of a pathogen after infection has occurred.

The rationale for PEP administration after occupational exposures to HIV has been previously described [20]. Understanding the sequence of events of early HIV infection has

provided data suggesting that early chemoprophylaxis may limit viral proliferation and dissemination within localized infected dendritic cells. Subsequent animal and human studies have demonstrated the efficacy of HIV PEP and it is now widely accepted practice in the U.S. [4].

Less persuasive evidence exists for the use of PEP after occupational exposure to HCV. Previous case reports of IFN therapy given after needlestick injuries were either unsuccessful or unconvincing [21, 22]. A more recent pilot study examined the efficacy of four weeks of weekly peginterferon (PegIFN) administered to 44/51 enrolled healthcare personnel following percutaneous or mucous membrane exposures to HCV-positive sources [23]. No cases of HCV transmission occurred in any of the healthcare personnel, including 162 who did not enroll in the study. Because of the overall absence of HCV transmission, the authors concluded there was “little evidence to support prophylaxis against hepatitis C in healthcare workers.” Given the relatively low infection rate associated with occupational exposures to HCV (i.e., approximately 2%) and the very high costs associated with the administration of DAAs, the strategy of monitoring for infection and then treating acute infection may be more cost-effective. In addition, the genotype-specific antiviral activity of DAAs makes PEP impractical when the source patient's genotype is not known.

One recent letter published in *Hepatology* raised many important questions about HCV PEP in the DAA era [24]. As in the case for HIV, careful thought should be given to the pathogenesis of early vs. late HCV infection when considering the use of chemoprophylaxis. Clinical features such as age <40 years, female gender, and jaundice are associated with spontaneous viral clearance during acute infection [19]. However, the majority of people who have acute HCV infection are asymptomatic, making this stage of HCV infection difficult to identify. Nearly all of the existing evidence for DAA use is based upon experience in chronic HCV treatment; to our knowledge, no published trials or case reports describe the use of these agents either as PEP or as primary therapy for acute HCV infection. In this context, based upon our understanding of treatment during late infection, an effective HCV PEP regimen would presumably require a combination of at least two drug classes with the following requirements: (1) “pan-genotypic” activity against all HCV genotypes, (2) a high barrier to resistance, (3) easy tolerability, and (4) treatment duration that is considerably shorter than the currently approved 12-24 week treatment regimens. Decreased adherence (either due to non-compliance or treatment duration) may result in resistant HCV viral variant selection. None of the current DAAs are approved specifically for PEP, but several approved or investigational agents may have a potential role in HCV PEP and are worthy of discussion.

Oral DAAs

Sofosbuvir, a nucleotide analogue that acts as a false substrate for the HCV RNA polymerase, is the only FDA-approved DAA with documented pan-genotypic activity and a high barrier to resistance [15]. Sofosbuvir in combination with ribavirin is recommended as one option for treatment-naïve patients who have chronic infections caused by genotypes 2, 3, and 4, and as an alternative regimen for those infected with genotypes 5 & 6 [8]. The treatment duration and recommendation to include IFN varies by genotype. High SVR rates

were reported in genotype 1 patients when given with IFN for 12 weeks, but sofosbuvir/ribavirin (with or without IFN) is not recommended for use in genotype 1 because it is inferior to other recommended oral IFN-free regimens [8, 25]. The genotype-specific varying results of these trials and the lack of evidence for an entirely IFN-free regimen do not support the use of sofosbuvir/ribavirin as optimal HCV PEP chemoprophylaxis.

Velpatasvir, an investigational pan-genotypic NS5A inhibitor, has recently been evaluated as a once-daily fixed-dose combination pill that also contains sofosbuvir. In January 2016, the FDA granted priority review to Gilead Sciences' New Drug Application for the use of sofosbuvir/velpatasvir in chronic HCV genotypes 1-6 [26]. Three recent studies have evaluated this combination in previously treated and untreated patients both with and without cirrhosis. ASTRAL-1 is a phase 3, double-blind, placebo-controlled international trial comparing 12 weeks of sofosbuvir/velpatasvir to placebo in genotypes 1, 2, 4, 5, and 6 patients [27]. Regardless of genotype, SVR12 rates were greater than 98% (99% in individuals with cirrhosis) in those receiving sofosbuvir/velpatasvir. ASTRAL-2 and ASTRAL-3 are phase 3, randomized, open-label studies examining 12 weeks of daily sofosbuvir/velpatasvir vs. sofosbuvir/RBV for 12 weeks (genotype 2) or 24 weeks (genotype 3) [28]. Both studies demonstrated high SVR12 rates in patients treated with sofosbuvir/velpatasvir compared to sofosbuvir/RBV, although a greater difference was noted among genotype 3 patients (95% vs. 80%). In all three trials, patients receiving sofosbuvir/velpatasvir had rare virologic failure and experienced an overall low adverse event rate. Taken together, the results of the three ASTRAL studies suggest that sofosbuvir/velpatasvir is a highly efficacious and well-tolerated pan-genotypic DAA. Whereas the overall number of both genotype 5 and black patients were under-represented in these studies, the combination of sofosbuvir/velpatasvir is promising. We await further investigational studies of this combination.

Host Target Agents

Successful HCV replication depends upon interactions with human cellular components such as enzymes or small RNAs. Host target agents (HTAs) block viral replication via inhibition of these components; because they target human structures, HTAs can exhibit both pan-genotypic antiviral activity and a high barrier to resistance [15]. Cyclophilin A is a proline isomerase whose interaction with NS5A is essential for HCV replication [29, 30]. Originally discovered as the target of the immunosuppressive drug cyclosporine, animal studies have demonstrated lower levels of HCV replication in cyclophilin A-deficient mice [29]. Three cyclophilin inhibitors currently in clinical development include alisporivir, SCY-635, and NIM811. Although early clinical trial data on alisporivir in genotype 2 and 3 infections are promising, a trial in patients infected with genotype 1 was placed on partial clinical hold due to reports of pancreatitis [31, 32].

SCY-635, an oral cyclosporine A analog, stops HCV replication by blocking NS5A and cyclophilin A interactions [33]. A previous phase 1b study examined 15 days of SCY-635 dose escalation in 20 genotype 1 patients [34]. Serial IFN and HCV RNA serum levels revealed the greatest HCV RNA reduction in patients with IL28B genotype receiving SCY-635 300 mg TID. Another study evaluated the addition of SCY-635 to PegIFN for 28

days in 10 treatment naïve genotype 1 patients without cirrhosis [35]. By week 24, 63% of patients who received SCY-635/ PegIFN experienced undetectable HCV RNA; by contrast, none of the patients treated with PegIFN alone had a 2 $\log_{10}$ HCV RNA decline. Similar HCV RNA declines were observed in a small safety and pharmacokinetic study of the addition of the cyclophilin inhibitor NIM811 to PegIFN [36]. Whereas the results from these 3 studies suggest that SCY-635 or NIM811 could restore human immune responses to IFN treatment, they likely have less relevance in the IFN-free regimen era. The role of cycophilin inhibitors in hepatitis C and other liver diseases has been recently reviewed [37]; future studies could elucidate their role as an addition to oral treatment regimens [38]. At the current time, no evidence supports the use of either of these agents for chemoprophylaxis.

MicroRNAs are small noncoding RNAs involved in posttranscriptional gene expression regulation via binding site regions on messenger RNAs [39]. MicroRNA-122 is found in the human liver and stimulates HCV protein translation by direct interaction with the HCV genome, resulting in accelerated small ribosomal-HCV RNA binding [40]. Miravirsen is an injectable microRNA-122 inhibitor associated with HCV viral suppression in chimpanzee and human phase 1 studies [41]. A subsequent phase 2b study evaluating the safety and efficacy of 29 days of miravirsen given to 36 treatment-naïve genotype 1 patients demonstrated dose-dependent serum HCV RNA reductions [42]. Some animal studies have demonstrated that decreased levels of microRNAs could be associated with cancer. A recent phase 2a study in 16 chronic HCV patients treated with 4 weeks of miravirsen showed decreased microRNA-122 levels without significant reduction in other microRNA levels [43]. While interesting, the use of an injectable drug for several weeks as HCV PEP is less desirable than oral options.

Conclusion

In summary, the treatment of HCV has rapidly evolved and the highly successful cure rates using IFN-free oral DAA combination regimens has tremendous potential to significantly reduce liver-related morbidity and mortality. From a public health standpoint, PEP could possibly help decrease the transmission of HCV and spare infected patients both the inconvenience and costs associated with additional weeks of treatment. However, data supporting the utility of PEP after HCV occupational exposures is lacking.

One reason that the DAAs may not have been used in the PEP setting is that these agents can effect a complete cure in most instances – even when longstanding, chronic HCV infection is detected. Conversely, PEP for occupational exposures to HIV may prevent an infection that cannot be subsequently cured with directly acting therapies. Because PEP use would treat approximately 100 HCV-exposed individuals for every two who become infected following occupational exposures, the “watchful waiting” strategy may actually make most sense. The DAAs, as a group, are expensive, so this latter approach may be cost-effective as well.

Without doubt, clinical trials are needed to evaluate, in the post-exposure setting, the feasibility, duration, appropriate regimens, and cost effectiveness of PEP vs. monitoring for infection and treating acute infection when identified. At this point in time insufficient

evidence exists to support the use of DAAs or HTAs as HCV PEP. We await further data and/or the future development of oral drugs that possess a high barrier of resistance and broad activity against all HCV genotypes.

Acknowledgments

None

Financial Support: None

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** of outstanding interest

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Key Points

1. Hepatitis C is a major global cause of liver-related morbidity and mortality and healthcare workers remain at risk for occupational exposures to this bloodborne pathogen
2. Successful chronic HCV treatment requires the use of DAA regimens composed of a combination of drugs from different classes to increase the barrier to resistance and achieve lasting sustained virologic response
3. No published data exist supporting the use of DAA or HTA regimens either for PEP or as primary therapy for acute HCV infection
4. Effective HCV PEP regimens likely require the use of oral combination regimens that have pan-genotypic antiviral activity and a high barrier to resistance
5. More evidence supporting the feasibility, duration, appropriate regimen, and cost effectiveness is needed before HCV PEP could be recommended.

Table 1

New and/or investigational agents with HCV anti-viral activity

Agent Class	Drug Name & Duration	Study	Population	Results	Virologic Relapse	Most Common Adverse Events
Oral DAA	Velpatasvir/sofosbuvir 12 weeks	ASTRAL-1[27] (phase 3, randomized†, double- blind, placebo-controlled)	- 624 TA/116 PA - 68% TN/32% TE - GT 1-2 & 4-6 - 19% cirrhosis	**SVR 12** - 99% TA (618/624) - 0% PA (0/116)	- <1% 2/624 TA - <4% 4/624 ORF TA	- 2% (15/624) SAE * - headache, fatigue, nasopharyngitis, nausea ** - <1% hematologic abnormalities in TA
	Velpatasvir/sofosbuvir gt;12 weeks	ASTRAL-2[28] (phase 3, randomized, open-label, active comparator‡)	- 134 TA/132 AC - 85% TN/15% TE - GT2 - 14% cirrhosis	**SVR 12** - 99% TA (133/134) - 94% PA (124/132)	- 0% TA 0/134 - 5% PA 6/132	- 1% TA/2% AC SAE - fatigue, headache, nausea (more common in AC group) - 0% TA/5% AC hemoglobin <10 g/dL - 0% TA/2% AC grade 2/3 hyperbilirubinemia
	Velpatasvir/sofosbuvir 12 weeks	ASTRAL-3[28] (phase 3, randomized, open-label, active comparator‡)	- 277 TA/275 AC - 74% TN/26% TE - GT3 - 30% cirrhosis	**SVR 12** - 95% TA (264/277) - 80% AC (221/275)	- 4% TA 11/276 - 14% AC 38/272	- 2% TA/5% AC SAE - fatigue, headache, nausea (more common in AC group) - 0% TA/4% AC hemoglobin <10 g/dL - 0% TA/1% AC grade 2/3 hyperbilirubinemia
Cyclophilin Inhibitor	Alisporivir +/- PegIFN & +/- RBV 24 weeks	VITAL-1[31] (phase 2b, randomized, open-label, parallel-group with 4 TAs vs PegIFN + RBV)	- 300 TAs/40 AC - 100% TN - GT2&3 - 0% cirrhosis	**SVR 12** - 77-85% TAs (242/300) - 63% AC (25/40)	- 7-11% TAs (n=26) - 25% AC (n=10)	- 6% SAE - ILI symptoms, anemia, TG elevations (> in IFN arms) - 0% neutropenia, thrombocytopenia in IFN-free ALV-based arms - hyperbilirubinemia, jaundice (>in ALV-based arms) - 0% pancreatitis
	Alisporivir + PegIFN + RBV 24 or 48 weeks	ESSENTIAL II (phase 3, randomized,	- 813 TAs/268 PA	**SVR 12** - 69% TAs (558/813)	- 13-18% TAs (n=101)	- trial stopped early due to reports of pancreatitis

Curr Opin Infect Dis. Author manuscript; available in PMC 2017 August 01.

Agent Class	Drug Name & Duration	Study	Population	Results	Virologic Relapse	Most Common Adverse Events
		placebo-controlled, with 3 TAs vs. placebo + PegIFN/RBV)[32]	- 100% TN - GT1 - 12% cirrhosis	- 53% PA (139/265)	- 26% PA (n=47)	- 6-9% SAE - anemia, headache, fatigue, pyrexia, neutropenia, thrombocytopenia, hyperbilirubinemia, hypertension°
	SCY-635 15 days	phase 1b, randomized, double-blind, placebo-controlled, multi-dose escalation[34]	- 17 TA/3 PA - 40% TE - GT1	**Change in Plasma HCV RNA levels (IU/mL)** - Minimal change in 300 & 600 mg TA or PA - 0.84- 5.47 log_{10}IU/ml decrease in 900 mg TA	n/a	- 0 SAE - elevated serum CPK, headache, hypokalemia, elevated liver function tests, and nausea (>in TAs)
	SCY-635 (4 weeks) + PegIFN/RBV (48 weeks)	phase 2a, randomized, double-blind, placebo-controlled[35]	- 8 TA/2 PA - 100% TN - GT1	**SVR 24** - 63% TA - 0% PA	- not available	- 0% SAE - neutropenia and anemia
	NIM811 14 days	randomized, double-blind, placebo-controlled, dose-escalation[36]	- 65 TA/19 PA - GT1 - TE and TN	**HCV viral load log_{10} change at day 14** - 0 log_{10} change in NIM811 alone - 2.85 log_{10} reduction in NIM811 + PegIFN - 0.56 log_{10} reduction in PegIFN alone	n/a	- 0% SAE - neutropenia, diarrhea, nausea, vomiting, ILI symptoms, myalgias, headache - malaise, fever, headache in PegIFN arms
MicroRNA	Miravirsen 29 days	phase 2a, randomized, double-blind, placebo-controlled [42]	- 27 TA/9 PA - GT1 - 100% TN	**Mean HCV RNA log_{10} IU/ml reduction through week 18** - 1.2-3.0 log_{10} TA/0.4 log_{10} PA ***	n= 9	- 1 SAE - 8-10% mean increase in platelet counts in TA - No other clinically significant hematologic abnormality - Headache, fatigue, nasopharyngitis, nausea, rash, diarrhea, myalgia, ILI symptoms, pruritus

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Agent Class	Drug Name & Duration	Study	Population	Results	Virologic Relapse	Most Common Adverse Events
						- 6 injection-site events in TAs
	Miravirsen 4 weeks	phase 2a, randomized, double-blind, placebo-controlled[43]	- 12 TA/4 PA - GT1 - 100% TN	**microRNA-122 levels at week 10/12** - median 552-fold lower in TA - no significant reduction in other microRNA levels Mean HCV log_{10} change - 1.4 log_{10} IU/ml lower in TA	n/a	n/a

TE, treatment-experienced; TN, treatment-naïve

TA, treatment arm; PA placebo arm

GT, HCV genotype

ORF, other reason for failure (loss to follow-up, consent withdrawal, death)

SAE, serious adverse event; ILI, influenza like illness

ALV, Alisporivir

†Patients with GT5 were assigned to TA; ‡sofosbuvir/ribavirin x 12 weeks (ASTRAL-2), x 24 weeks (ASTRAL-3)

*No single SAE occurred in >1 patient

**No significant difference in rate of any AE between TA and PA (78% & 79%)

***12 patients started PegIFN + RBV during follow up

°Occurring in >25% patients in any group and/or ≥ 10% more frequently in ALV treatment groups

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