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Review Article

Interferon-free direct-acting antiviral therapy for acute hepatitis C virus infection in HIV-infected individuals: A literature review

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ABSTRACT

Dramatic rises in hepatitis C virus (HCV) coinfection rates in human immunodeficiency virus (HIV)-infected individuals have been observed recently, largely attributable to increasing recreational drug use combined with increased testing for HCV. In the era of direct-acting antiviral (DAA) therapy, treatment of acute HCV infection in HIV-infected individuals with short durations of these drugs may potentially reduce the disease and economic burden associated with HCV infection as well as reducing the likelihood of onward HCV transmission. We performed an extensive literature search of PubMed, Embase and Google Scholar up to 05 September 2017 for clinical trials of acute HCV infection in HIV-infected individuals. In the studies identified, rates of sustained virologic response at 12 weeks post-treatment (SVR12) ranged from 21% with 6 weeks of therapy up to 92% with 12 weeks of therapy with sofosbuvir and ribavirin. Ledipasvir/sofosbuvir for 6 weeks achieved an SVR of 77%. No HIV-related events occurred regardless of whether patients were receiving antiretroviral therapy (ART) and DAAs were well tolerated. Data is currently limited with regards to optimal regimens and durations of therapy, which need to be tailored based on potential interactions with concurrent ART and consideration for the fact that patients with higher baseline HCV RNA levels may require an extended duration of treatment.

1. Introduction

Globally, hepatitis C virus (HCV) coinfection affects 5–10 million people living with HIV (PLWH) [1] and in certain populations, rates of HCV/HIV coinfection been found to exceed 90% amongst those who inject drugs [2–4]. Recent epidemics of acute HCV infection have been witnessed amongst HIV positive men-who-have-sex-with-men (MSM) [5]. A recent study also reported an increased prevalence of HCV infection in HIV-negative MSMs who were about to embark on HIV pre-exposure prophylaxis [6]. These surges in rates of HCV infection, which have been observed in several parts of the world, are becoming increasingly associated with sexualised recreational drug use known as 'chemsex' [7]. The rising numbers of tattooing (in prisons for example) and non-surgical cosmetic percutaneous procedures being performed in various settings (many of which are unregulated) could also be contributing to the increased rates of HCV transmission in both HIV positive and HIV negative individuals [8,9]. The first 6 months after acquisition of HCV has classically been recognised as the acute phase and only 15%–20% of people PLWH with acute HCV infection will spontaneously clear their HCV infection [10,11]. The European AIDS Treatment Network (NEAT) guidelines for acute hepatitis C in HIV-infected individuals suggest a viral kinetic model for HCV infection taking into consideration the fact that less than a 2 $\log_{10}$ IU/mL reduction in HCV RNA at 4 weeks after diagnosis and a positive HCV-RNA 12 weeks into acute hepatitis have both shown an association with progression to chronicity [12]. Individuals who exhibit these viral kinetics may therefore serve as primary targets for early therapeutic strategies. Once chronicity is established, as occurs in the majority of HCV-infected individuals, HIV/HCV coinfected patients demonstrate faster rates liver fibrosis progression [13], and are at an increased risk of developing cirrhosis and hepatocellular carcinoma compared to individuals not infected with HIV [14]. Development of cirrhosis occurs 12–16 years earlier in HCV/HIV coinfected individuals compared to HCV monoinfected individuals and once hepatic decompensation occurs, estimated median survival is only 13 months in coinfected patients [15]. Treatment of PLWH with acute HCV infection is important in preventing the development of chronic infection, preventing accelerated progression of liver disease and to minimise the risk of onward HCV transmission. Additionally, HIV/HCV coinfected individuals demonstrate reduced immunological responses to antiretroviral therapy (ART) compared to HIV monoinfected individuals [16].

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Prior to the recent, wider availability of direct-acting antivirals (DAAs), treatment of acute HCV infection in PLWH with interferon (IFN)-based therapy for 24 weeks' duration achieved significantly higher overall sustained virologic response (SVR) rates (up to 80%) compared to those seen with 48 weeks of interferon-based treatment (up to 40%) for chronic HCV infection in PLWH [17–19]. Currently used DAAs, available for the treatment of all 6 genotypes chronic HCV infection, offer improved SVR rates, shorter durations of therapy and lower incidences of adverse effects compared to previous IFN-based therapy [20]. Indications for the treatment of chronic HCV infection with DAAs are currently the same for monoinfected and HCV/HIV coinfected individuals and treatment duration ranges from 8 weeks to 24 weeks [21]. A recent large observational study found similar high rates of SVR with IFN-sparing DAA therapy for chronic HCV infection in HCV/HIV coinfected (n = 482) and HCV monoinfected (n = 1152) individuals (94% vs 97%) [22].

Based on findings that a minimum of 8 weeks therapy is needed to achieve optimal SVR rates in the treatment of chronic HCV infection, the most recent European Association for the Study of the Liver (EASL) guidelines recommend sofosbuvir (an HCV NS5B nucleotide polymerase inhibitor) combined with an NS5A inhibitor for a duration of 8 weeks in the treatment of acute HCV infection (with possible extension up to 12 weeks for PLWH and/or a baseline HCV RNA level >6.0 $\log_{10}$ IU/mL). The American Association for the Study of Liver Diseases (AASLD) recommends the same type and duration of DAA therapy for acute HCV infection as used in treating chronic HCV infection [21,23]. Treatment of acute HCV infection in PLWH reduces patient morbidity and the financial burden associated with longer term follow-up [19], therefore potentially shorter durations of therapy with these high cost DAAs could provide even greater health and economic benefits, provided maximal SVR rates are still achieved. We review the current literature on the use of DAAs for the treatment of acute HCV infection in PLWH.

2. Search strategy and selection criteria

A comprehensive literature search was performed using the MEDLINE/PubMed, Embase and Google Scholar databases up to 05 September 2017. Various combinations of the following keywords were used to identify relevant studies: 'acute HCV'; 'HIV and acute HCV'; 'HCV/HIV coinfection'; 'DAA'; 'NS5B inhibitor'; 'NS5A inhibitor'; 'NS3/4A inhibitor'; 'polymerase inhibitor' and 'protease inhibitor'. We searched the references of identified publications and utilised the PubMed 'similar articles' tool to identify any further relevant studies. Additionally; we searched for abstracts from recent conferences and clinicaltrials.gov for unpublished studies.

3. Types of therapy

The ability of HCV in an acute infection to escape host antiviral immune response mechanisms leads to viral persistence and chronic infection in the majority (80–85%) of HCV/HIV coinfected individuals [24]. Impairment of CD4+ T cells directed against HCV [25,26] and suppression of the antiviral activity of host type 1 interferons (alpha and beta) [27,28] are proposed mechanisms by which the virus escapes immune control. Exogenously administered interferon (IFN), in the form of pegylated-IFN (pegIFN) achieves SVR rates of 60–70% even as monotherapy in the treatment of acute HCV in PLWH [29] thus highlighting the impact of immunomodulators on viral clearance. The addition of ribavirin can increase SVR rates to approximately 80% [30]. Twelve weeks of triple therapy for genotype 1 acute HCV coinfection with pegIFN/ribavirin taken in combination with the HCV protease inhibitor boceprevir showed comparable rates of SVR12 with historical controls that received 24 weeks of pegIFN/ribavirin only (SVR12 86% vs 84%) [31]. In the CHAT study, where patients with genotype 1 acute HCV coinfection received pegIFN/ribavirin and the HCV protease inhibitor telaprevir for 12–24 weeks, similar SVR12 rates were also seen when compared to those that received pegIFN/ribavirin for 24–48 weeks (SVR12 78.9% vs 80%) [32]. However, due to the additional toxicities and the finding of telaprevir-induced selection of protease inhibitor resistance mutations associated with treatment non-response seen in their study, the investigators concluded that 'first-generation' protease inhibitors should not be used in treating acute HCV coinfection.

In PLWH, cellular mediated immunity is affected by both numerical and functional depletion of CD4+ cells [33] thus potentially compromising their ability to clear HCV in the acute phase. The CD4/CD8 ratio, which serves as a marker of immune dysfunction improves with ART but infrequently normalises in chronic HIV-1 infection even with long-term suppressive ART (29.4% estimated probability of CD4/CD8 normalisation at 5 years after starting ART) [34]. It has, however, been shown to have a significantly higher likelihood of restoration to normal levels when ART is initiated in the early stages of HIV-1 infection [35]. IFN-based re-treatment in HCV/HIV coinfected patients that had previously failed to achieve an SVR with IFN-based therapy for HCV, demonstrated significantly higher re-treatment SVR rates when patients were successfully HIV-1 RNA suppressed with ART [36]. In the current era where ART is now recommended for all PLWH [37], the significant numerical and functional restoration of CD4+ T cells that typically occurs with ART [33], will be seen in many more PLWH as increasing numbers of individuals receive ART earlier in the course of their HIV infection. This immune restoration may render the likelihood of PLWH achieving SVR following treatment of acute HCV coinfection with IFN-sparing DAA regimens on par with that of HCV monoinfected patients therefore negating the need for immunomodulatory agents.

IFN-sparing sofosbuvir-based regimens are licensed for and are highly effective in the treatment of all genotypes of HCV monoinfection and coinfection in patients with chronic hepatitis C and are well tolerated over a 12–24-week period [21]. There are no absolute contraindications to sofosbuvir itself (caution is advised in renal impairment) apart from in patients taking amiodarone. The four published studies to date using IFN-sparing DAA regimens in acute HCV coinfection have investigated the used of sofosbuvir-containing therapy (Table 1) [38–41]. There are three studies in progress for the treatment of acute HCV coinfection with DAA regimens not containing sofosbuvir (Table 2).

The purine nucleoside analogue ribavirin has been a major component in the success of HCV treatment in the era of pegIFN-based therapy [42,43] but with the high SVR rates achieved for chronic HCV with novel IFN-sparing DAAs its future role is less well defined. Even with IFN-sparing DAA regimens, however, there is still evidence that ribavirin hastens rates of decline in blood HCV ribonucleic acid (RNA) levels and reduces the likelihood of viral relapses [44]. It does still therefore remain an important component of therapy for chronic HCV infection, particularly in decompensated cirrhotic patients and in certain patients who have previously failed treatment with pegIFN-based and/or DAA-containing regimens [21,45]. Its role as part of IFN-sparing therapy for acute HCV infection in PLWH is not clear and needs further justification if it is to be an established component of future treatment regimens given that it is not free from side effects such as haemolytic anaemia [46] and adds further to their pill burden (albeit temporarily). A recent study of varying dual-DAA regimens for the treatment of chronic HCV infection in 323 PLWH reported that the use of ribavirin in addition to a dual-DAA regimen did not result in improved SVR rates (SVR12 of 92.7% with ribavirin vs 95.2% without ribavirin) [47]. However, if SVR rates are consistently found to be subopti-

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