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Hepatitis C and HIV Co-Infection: New Drugs in Practice and in the Pipeline

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Abstract

HCV/HIV coinfection continues to represent a serious health issue with risk of liver disease progression and development of hepatocellular carcinoma. Pegylated interferon with ribavirin is approved for treatment but results are suboptimal and tolerability poor. First-generation HCV protease inhibitors appear to significantly improve HCV treatment response in the setting of HIV infection. Interactions with HIV protease inhibitors have been documented, but the significance of this in terms of adverse reactions and HCV or HIV viral breakthrough remains uncertain. Next generation agents hold the promise of even better efficacy, with improved dosing schedules and perhaps decreased risk of drug:drug interactions.

Keywords

HCV; Protease inhibitors; HIV; AIDS

Introduction

In the era of modern combination antiretroviral therapy (ART) for HIV, leading to marked decreases in AIDS and related complications, chronic hepatitis C virus (HCV) associated liver disease has become a major cause of morbidity and mortality among persons with HIV [1].

It has been well established that HIV infection modifies HCV natural history [2]. Persons with HIV/HCV coinfection have higher rates of hepatic fibrosis compared to HCV monoinfected persons [3]. They are also less likely to clear HCV viremia and have higher levels of HCV RNA [4]. Successful treatment of HCV may decrease the risk of developing cirrhosis, end stage liver disease, hepatocellular carcinoma (HCC) and in HIV-infected patients have the added benefit of reduced risk from ART-induced hepatitis. Public health benefits include decreased risk of transmission of HCV [5]. The currently (FDA) approved treatment for HCV in the U.S., in the setting of HIV/HCV coinfection, consists of pegylated interferon alfa 2a (PegIFN) plus ribavirin (RBV). The treatment cycle is 48 weeks and is dependent on HCV genotype.

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Prior HIV/HCV studies demonstrated that rates of sustained virologic response (SVR) were significantly lower in patients with HIV/HCV coinfection versus HCV mono-infection. In the ACTG 5071 trial comparing PegIFN alpha 2a/RBV versus standard interferon/RBV, patients with HIV/HCV genotype 1 on PegIFN/RBV achieved SVR of 14 %, vs. 6 % for patients receiving standard interferon/RBV [6]. Seventy-three percent of genotype 2/3 patients treated with PegIFN/ribavirin achieved SVR. In the APRICOT trial, 40 % of HIV/HCV-infected patients on PegIFN alpha 2a/RBV achieved SVR versus 12 % on standard interferon/RBV but lower rates were again observed in genotype 1 subjects [7]. The RIBAVIC trial comparing PegIFN alpha 2b/RBV vs. standard interferon/RBV yielded similar results [8]. There appears to be no significant statistical difference in efficacy and adverse events between PegIFN alpha 2a and PegIFN alpha 2b in HIV/HCV [9]. A meta-regression analysis by Shire et al. provided a pooled overall rate of SVR in co-infected patients (all genotypes) of approximately 33 % [10].

First-Generation Direct-Acting Antivirals (DAAs)

DAAs and HCV-Mono-infected Patients

Considering the low rates of SVR for HCV, there has been a push towards combination therapy with direct acting antivirals (DAAs), which have yielded higher rates of SVR and shorter durations of therapy in a subset of patients. The two HCV NS3/4A serine protease inhibitors (PIs), boceprevir (BOC) and telaprevir (TVR), were approved for treatment of genotype 1 chronic HCV in conjunction with PegIFN and RBV in mid-2011. These approvals were based upon five phase 3 trials that were performed in both treatment naïve and treatment experienced HCV-mono-infected patients. Review of data derived from these trials forms the basis for discussion of treatment in the co-infected population.

There were two phase 3 trials in treatment-naïve HCV genotype 1 patients that utilized telaprevir. The ADVANCE trial was a multicenter, randomized trial that compared two dosing durations of telaprevir, 12 or 8 weeks, with PegIFN/RBV to a PegIFN/RBV control arm. Patients were treated using a response-guided therapy (RGT) schema for the telaprevir containing arms. Those with extended rapid viral response (eRVR, defined below) received 24 weeks of PegIFN/RBV with the DAA; all others took PegIFN/RBV for 48 weeks. The overall SVR rate in the three treatment arms was 75 % in the 12-week arm, 69 % in the 8-week arm, and 44 % in the PegIFN/RBV controls [11•]. The other phase 3 trial, ILLUMINATE was designed to determine the efficacy of the RGT algorithm. Extended rapid viral response was defined as having no detectable virus at weeks 4 and 12 of triple drug therapy. Patients with eRVR were randomized to either 24 or 48 weeks of total therapy following 12 weeks of telaprevir/PegIFN/RBV. Nearly two thirds of patients were eligible for RGT with shorter therapy. The overall SVR rate was 72 %, but the shorter therapy arm SVR rate was 92 %. This was statistically equivalent to longer therapy and clearly demonstrated the utility of RGT in HCV mono-infected patients [12•].

There was one phase 3 trial for treatment-naïve patients using boceprevir. Patients were randomized to one of three arms including a boceprevir-containing RGT (28 or 48 weeks total treatment) arm, a non-RGT arm (48 weeks total treatment) or a control arm with 48 weeks of PegIFN/RBV. All patients in the experimental arms received a 4 week lead in of PegIFN/RBV prior to the addition of boceprevir. If a subject was HCV RNA negative at week 8 they were considered eligible for shorter treatment in the RGT arm. Boceprevir was part of a triple therapy regimen for 24 weeks in the shorter duration patients and was administered for 48 weeks in all others. The overall SVR rates were 63 % in the RGT arm, 66 % in the 48 week treatment duration arm and 38 % in the PegIFN/RBV control arm. The study further divided patients into a black and non-black cohort and overall responses were better in the non-black subgroup [13•].

With respect to both drugs in studies of treatment-experienced patients, those with prior treatment relapse did very well, but those with prior partial (or null response defined as no response to prior PegIFN/RBV treatment in the telaprevir trial) had lower SVR rates. However, rates in these patients were still significantly better than those seen in PegIFN/RBV controls [14, 15].

These HCV PI-based combination therapies come with their own unique limitations including increased risk of toxicities, increased cost and complicated dosing regimens. Both telaprevir and boceprevir have been associated with increased risk of anemia. A high proportion of patients in the boceprevir phase 3 trials required use of erythropoietin (43 %) [13•]. The telaprevir trials did not permit use of growth factors and anemia was managed by reduction of dose of both ribavirin and pegylated interferon [11•, 12•]. When telaprevir was utilized, rash was a common finding, though an infrequent cause of drug discontinuation. Serious rashes were described [16]. Both PIs increase the total cost of treatment, have complex treatment algorithms and require frequent dosing with high pill burden which raises concerns about medication compliance and tolerability. Both PIs are associated with significant drug–drug interactions and have limited utility with non-genotype 1 HCV.

DAAs and HCV/HIV Co-infected Patients

The availability and improved efficacy of HCV DAA regimens raises the issue of use of these first-generation HCV PIs in HCV/HIV co-infected patients. These patients were excluded from the registrational trials described above. However, phase 2 trials of these agents and others are underway in co-infected patients, and new data have recently been presented that shed light on the safety and efficacy profile of DAAs in those with HIV infection (Fig. 1).

In an ongoing Phase 2b trial investigating the role of boceprevir, 100 HCV/HIV co-infected participants with previously untreated HCV genotype 1 were randomly assigned to receive boceprevir 800 mg TID or placebo plus PegIFN alfa-2b plus weight based RBV. All subjects started with a 4-week lead-in period of PegIFN/RBV, followed by boceprevir or placebo plus PegIFN/RBV for 44 additional weeks. There was no RGT schema utilized in this study. All subjects were on stable ART with undetectable HIV RNA. Median CD4 count was approximately 580 mm³. The majority of patients had HCV genotype 1a (65 %) and were male (70 %). Median age was 44 years. Not surprisingly, most had high HCV RNA and 5 % had compensated cirrhosis. Patients were limited to ART regimens containing a boosted HIV protease inhibitor or raltegravir plus 2 nucleoside/nucleotide reverse transcriptase inhibitors or a few other agents. Efavirenz was not allowed due to prior drug–drug interaction data that suggested that efavirenz would decrease the boceprevir minimum serum concentrations. The majority of participants had undetectable HCV RNA 12 weeks (SVR 12) after completion of boceprevir plus PegIFN/RBV versus PegIFN/RBV alone (61 % versus 27 %). There were reports of 2 HCV relapses in subjects receiving boceprevir and 1 in the control group. HIV breakthrough was uncommon and observed in a few patients in both arms. This observation is highly relevant to the discussion of other drug–drug interactions described below. Rates of serious adverse events were similar (21 % and 17 %). Subjects who received boceprevir were at least 10 % more likely than those in the control group to report anemia (41 % versus 26 %), fever (36 % versus 24 %), weakness (34 % versus 24 %), loss of appetite (34 % versus 18 %), diarrhea (28 % versus 18 %), vomiting (28 % versus 15 %), dysgeusia (28 % versus 15 %), and neutropenia (19 % versus 6 %) [17].

Data were also presented regarding safety and outcomes of a phase 2b trial using telaprevir in combination with PegIFN alfa 2a 180 mcg and weight-based RBV in 60 treatment-naïve HCV/HIV co-infected patients with HCV genotype 1. This study was divided into two parts, based upon ART status. Part A included 13 HCV/HIV co-infected subjects who had CD4 T-

cell counts of at least 500 cells/mm³ and were not yet taking ART. Part B included 47 people on ART; 24 took efavirenz (EFV) plus tenofovir and emtricitabine, while 23 took ritonavir boosted atazanavir (ATZ/r) with either lamivudine or emtricitabine. Participants on ART had HIV RNA <50 copies/mL. Median CD4 counts in Part A and B were 690 cells/mm³ and 562 cells/mm³, respectively. Most patients were male (88 %) and over half were infected with HCV genotype 1a (68 %). Median age was 46. The majority of patients had high HCV RNA viral loads at baseline and 10 % had advanced liver fibrosis or compensated cirrhosis. Patients were randomly assigned to receive either telaprevir or placebo in combination with PegIFN/RBV for both parts of the study. Triple therapy was continued for 12 weeks, followed by PegIFN/RBV for an additional 36 weeks. There was no RGT option for eRVR patients in this trial. Subjects randomized to telaprevir and on EFV during this study received a higher dose of telaprevir (1,125 mg every 8 h) based on prior drug–drug studies. HCV RNA was undetectable at week 4 (RVR) and week 12 (complete early virologic response-cEVR) in 70 % and 68 % of subjects who received telaprevir compared to those in the control arm, 5 % and 14 %. Overall rates of SVR 12 were 74 % for the triple therapy arm compared to 45 % in the control arm. Thus, early responses with the addition of telaprevir translated into higher rates of SVR. Rates of SVR 12 among participants not taking ART were 71 % and 33 %, respectively. Patients on EFV and ATV/r based ART regimens who received telaprevir achieved SVR 12 rates of 69 % and 80 %, compared to 53 % for both regimens without telaprevir. Three subjects on telaprevir experienced HCV RNA breakthrough while on treatment, 1 subject on telaprevir and 2 on placebo experienced HCV relapse. The combination therapy tolerability profile paralleled data observed in genotype 1 HCV monoinfected patients. Three subjects on telaprevir discontinued study drug due to serious adverse events versus none in the placebo arms. Rates of adverse events were higher with telaprevir versus placebo. Adverse events that occurred at least 10 % more often among those receiving telaprevir compared to placebo included pruritus (39 % vs 9 %), headache (37 % vs 27 %), nausea (34 % vs 23 %), rash (34 % vs 23 %), fever (21 % vs 9 %), and depression (21 % vs 9 %). Rates of anemia were 18 % in both groups. There was no evidence of HIV RNA breakthrough in either arm. While CD4 counts fell in both arms, CD4 cell percentages did not change [18].

PI/ART Drug–Drug Interaction Studies

Serious concerns for drug–drug interactions between DAAs and ART exist, as many of these agents share metabolic pathways such as cytochrome p450 (CYP450). Boceprevir is metabolized by aldo-ketoreductases and is an inhibitor of CYP3A4 but probably not a substrate of that pathway. In healthy volunteers, boceprevir concentrations were decreased 44 % with efavirenz, and 19 % with low dose ritonavir (100 mg bid at steady state) [19]. Boceprevir reduced mean trough concentrations of ritonavir boosted atazanavir, lopinavir and darunavir by 49 %, 43 % and 59 %, respectively. Mean reductions of 34–44 % and 25–36 % were observed in AUC and C_{max} of atazanavir, lopinavir, and darunavir. Boceprevir AUC was not altered by boosted atazanavir, although AUC of boceprevir was decreased by 45 % with ritonavir-boosted lopinavir and 32 % with ritonavir-boosted darunavir. Based on this data, coadministration of boceprevir with ritonavir-boosted HIV PIs is not recommended in routine clinical practice until these combinations are evaluated in the context of clinical trials [20, 21]. Interestingly, data from the boceprevir phase 2 trial described above does not appear to substantiate concerns generated in the healthy volunteer trials. As noted above, there was no HIV RNA breakthrough signal noted when boceprevir was combined with boosted atazanavir, lopinavir, or darunavir. The reasons for this are unknown but are probably multifactorial in nature; most patients have enough reserve barrier to resistance breakthrough that observed reductions in boosted PI concentration does not cause loss of viral control. Additionally, PegIFN has intrinsic antiviral activity against

HIV and this was added to regimens protecting HIV control even when PI concentrations may have been reduced [22].

Telaprevir is a cytochrome P450 3A4 (CYP 3A4) substrate. Telaprevir blood concentrations are reduced by ritonavir boosted fosamprenavir, darunavir, lopinavir, and to a lesser extent, atazanavir [23]. Efavirenz reduces blood concentrations of telaprevir, which can be partially offset by use of higher doses (1,125 mg every 8 h vs 750 mg every 8 h). Despite this increased dose, coadministration of telaprevir with EFV still led to an 18 % reduction in telaprevir AUC and 25 % reduction in telaprevir C_{min} [23]. Telaprevir also reduced concentrations of darunavir and fosamprenavir.

The FDA considers HIV/HCV co-infected patients as a special population for HCV drug development and mandates studies addressing drug–drug interactions and safety [24]. At this time, clinicians must make treatment intervention decisions without availability of complete data regarding background ART interactions with the approved DAAs. Use of raltegravir with a tenofovir/emtricitabine backbone appears to entail the lowest risk of significant drug–drug interactions. Telaprevir was used effectively with efavirenz but at an altered dose which is not approved nor provided by specialty pharmacies. Complex regimens in patients with underlying HIV resistance should probably not be utilized until additional carefully monitored trials are performed.

Resistance

All antiviral therapy has the potential to select for viral resistance. HIV and HCV have similarities and differences in the probability, pathogenesis, and clinical implications for development of resistance. These viruses have rapid replication of their nucleic acid using polymerases which are error prone and have high mutation rates which create nucleotide variations. Unlike HCV, HIV has a complementary DNA strand during at least part of its replication cycle and an archive of viruses can be established by integration of viral and host DNA, a circumstance not present with HCV replication. Thus, selection of antiviral resistance may have lower long-term consequences for HCV than HIV, although there are limited data regarding the clinical significance of resistance with DAAs. Based on population sequence analysis data, there are a small percentage of patients with baseline resistance mutations with HCV; the proportion of dominant resistance mutations does not appear to be increased among HCV/HIV co-infected patients when population sequencing is performed [25]. Resistant variants are detected in most instances in which there is more than a 1 log increase in HCV RNA in patients taking DAAs, though in most patients those variants cannot be detected 1–2 years after treatment is stopped. Resistance appears to be more likely for HCV genotype 1a vs 1b; rate of reversion to wild-type HCV is slower [26, 27]. There is a need for more research to determine if individuals who develop viral resistance while taking a DAA can have a clinically meaningful response to future agents with similar resistance mechanisms.

IL28B Gene Polymorphisms in HCV/HIV Co-infected Patients

The nucleotide sequence located upstream from the gene for IL28B or lambda IFN3 on chromosome 19 affects the likelihood of resolution of HCV and achieving SVR with PegIFN/RBV. At least 7 single nucleotide polymorphisms are highly predictive of these outcomes including the C or T allele at position rs 12979860 which is generally accepted as the best marker of viral clearance. The CC genotype is found more than twice as frequently in persons who have spontaneously cleared HCV than in those who progressed to chronic HCV [28]. Rates of SVR in chronic genotype 1 with PegIFN/RBV are 69 %, 33 %, 27 % in Caucasians who have CC, CT, and TT genotypes; rates among African American are 48 %, 15 %, 13 % [29]. The prognostic predictive value of these genotypes is also observed among

HCV/HIV co-infected patients, and is greater than that associated with degree of hepatic fibrosis, age or baseline HCV RNA [30]. HCV RNA levels may also be influenced by IL28B polymorphisms [31]. There is continued interest in the value of IL28B as a pretreatment predictor of response to PegIFN in combination with DAAs although predictive value will be reduced as overall response rates increase with DAA regimens. HCV monoinfected Caucasian patients randomized to receive boceprevir with PegIFN/RBV had rates of SVR 80–82 %, 65–71 %, and 55–59 % in patients with CC, CT, and TT genotypes [32]. HCV monoinfected Caucasian patients randomized to receive telaprevir with PegIFN/RBV similarly had SVR rates of 84–90 %, 57–71 %, and 59–73 % with CC, CT, and TT genotypes [33].

The DAA Pipeline: Implications for the HCV/HIV Co-infected Patient

There is a rich pipeline of new agents that target HCV or host-factors required by HCV. The pipeline includes next-generation HCV NS3/4A PIs, polymerase inhibitors (nucleos(t)ide and non-nucleoside agents), NS5A inhibitors, entry inhibitors, cyclophilin inhibitors, and microRNA antagonists. Few of these have been evaluated in those with HCV/HIV co-infection to date.

A novel cyclophilin inhibitor, alisporivir was originally developed as an antiretroviral agent. It had low levels of activity against HIV but is being investigated in phase 2 and 3 clinical trials with and without PegIFN/RBV in patients with HCV genotypes 1, 2, and 3 [34, 35]. Early studies included patients with HCV/HIV co-infection [35]. Results from a phase II study of 300 HCV genotype 1 treatment-naïve patients who were treated with alisporivir plus PegIFN/RBV reported a 76 % SVR 24 rate in the group that was treated for 48 weeks compared to 55 % in the group that received PegIFN/RBV. The rates of SVR 24 (undetectable HCV RNA 24 weeks after completion) were 53 % in the fixed 24-week alisporivir triple arm and 69 % in the alisporivir RGT arm. Alisporivir doubled the likelihood of SVR in patients with IL28 B TT gene pattern. Rates of RVR were 24 %, 28 %, 23 % in the alisporivir 48 week, 24 week and RGT arms compared to 8 % in the standard therapy arm. Rates of relapse were 15 %, 39 %, and 16 %, respectively. Viral breakthrough was present in 5 % in all alisporivir arms compared to 6 % in control arm [36]. Alisporivir appears to be active against all HCV genotypes, well tolerated and can be dosed once daily. Adverse events were similar to PegIFN/RBV. Hyperbilirubinemia is a frequent adverse event related to alisporivir, although it appears to be transient, reversible and not associated with hepatotoxicity or cholestasis [37]. More serious cases of pancreatitis have been described and led to an FDA hold on development at this time (Assoc Press, April 19, 2012).

In difficult-to-treat HCV genotype 1 prior PegIFN/RBV null responders, a phase 2a trial was performed with a combination of Bristol-Myers Squibb (BMS) DAAs BMS 650032-PI, BMS-0790052, a first-in-class NS5A replication complex inhibitor (daclatasvir). This trial included 21 genotype 1 null responders and compared once daily BMS-790052 plus twice daily BMS-650032 versus PegIFN/weight based RBV/BMS-650032/BMS-790052 for 24 weeks. Most participants were male and about 90 % had IL28 genotype CT or TT. The results were notable as 4 of 11 (36 %) achieved SVR12 and SVR24 in the all oral regimen compared to 10 of 10 (100 %) SVR 12 in participants who were on quad therapy. One patient had SVR12 but not SVR 24. Resistance to both BMS agents was seen in the 6 subjects who had HCV viral breakthrough. Most adverse events were mild to moderate (fatigue, neutropenia, ALT elevations) and there were no serious adverse events [38]. In preparation for studies in HCV/HIV co-infected patients, drug–drug interaction studies in healthy volunteers were recently reported. With efavirenz, daclatasvir cMax was lowered 67 %. Cmax was increased 35 % when administered with boosted atazanavir. There was little

pK effect when daclatasvir was combined with tenofovir. A phase 3 trial in HCV/HIV using daclatasvir is in progress (NCT01471574).

Next-generation protease inhibitors tend to have greater potency, longer half-life (which permits less frequent dosing intervals), a higher barrier to resistance and perhaps more pan-genotypic activity. Several promising agents are entering trials in HCV/HIV co-infected patients. These include, but are not limited to TMC-435 (NCT01479868), BI201335 (NCT01399619).

Nucleos(t)ide inhibitors have become prominent as either single agents or as part of a strategic backbone due to high barriers of resistance that have been observed in this class. These agents have a high likelihood of interaction with the nucleos(t)ide backbone of HIV regimens. Therefore, pK studies are very important for this group. The most promising agent in this group to date, PSI (now GS)-7977 is under evaluation in an ongoing pK study with efavirenz, tenofovir, zidovudine, lamivudine, atazanavir, ritonavir, tenofovir, and emtricitabine (NCT01565889).

Conclusions

Clearly, the goal of future therapy is to move towards interferon-free regimens with greater tolerability in the HCV/HIV co-infected population. Success may be limited by high viral loads and the complexities associated with drug–drug interactions with antiretroviral regimens. However, considerable progress has been made and the next few years should provide a clearer picture of the treatment landscape in this important group.

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Fig. 1. Treatment response to first-generation DAAs. (BOC SVR 12 data not inclusive as four subjects who achieved SVR 4 had not yet reached SVR 12 timepoint). *DAA* direct acting antiviral; *P* pegylated interferon; *R* ribavirin; *ART* antiretroviral therapy