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HIV protease inhibitors in combination with boceprevir: are drug–drug interactions the same for all patients?

The new direct acting agents, boceprevir (BOC) and telaprevir (TVR), have been approved for the treatment of chronic hepatitis C virus (HCV) genotype 1 infection in the USA and in Europe in 2011. Sustained virological response (SVR) rates up to 75% have been reported in phase III trials for triple therapy examining efficacy and safety of either BOC or TVR in combination with pegylated interferon and ribavirin in HCV monoinfection [1,2]. Improved treatment outcomes have also been reported for HIV/HCV-coinfected patients reaching SVR rates of up to 70% in pilot trials [3,4]. BOC and TVR are HCV protease inhibitors sharing similar metabolic routes with HIV protease inhibitors. Both are substrates and inhibitors of the cytochrome P450-3A system as well as a substrate of p-glycoprotein. BOC is additionally a substrate of aldo-ketoreductase [5]. Unfortunately, due to these complex drug–drug interactions, triple therapy is substantially limited in HIV/HCV-coinfected individuals. Indeed, recently the European Medicines Agency and the Food and Drug Administration have warned against the coadministration of BOC with the commonly available HIV protease inhibitors, as significant drug–drug interactions, which not only decrease the level of BOC but also lead to relevant decreases in the respective HIV protease inhibitor, have been reported [6–8]. Particularly, in patients with extensive prior HIV resistance and accumulation of resistance mutations, in which HIV protease inhibitor drug levels may be of great importance, the risk of resistance development and virological failure may be increased. However, most data on pharmacokinetic interactions of BOC and HIV protease inhibitors derive from pharmacokinetic studies in healthy volunteers and so far no data are available from HIV/HCV-coinfected patients with different stages of liver disease receiving BOC and HIV protease inhibitors.

Here, we report on two patients who prior to the 'Dear Healthcare Professional' letter received BOC containing HCV triple therapy in combination with a HIV protease inhibitor because prior drug interaction studies with 100 mg of ritonavir and BOC suggested that despite small alterations in drug level this would be clinically feasible [9,10]. Patient 1 was on darunavir 800 mg/ritonavir 100 mg once-daily monotherapy due to extensive nucleoside and nucleotide reverse transcriptase inhibitor resistance when HCV triple therapy with BOC was started. Liver disease had progressed to liver cirrhosis confirmed in FibroScan (Echosens, Paris, France) with a liver stiffness of 34 kPa. Trough concentration of darunavir was measured at week 5 of HCV triple therapy in the reference range with 3777 ng/ml (reference trough concentration 2400–4600 ng/ml). HIV-RNA was below detection limit (<40 copies/ml) at all times and HCV-RNA became negative at week 10.

Patient 2 had previously undergone chemotherapy for non-Hodgkin's lymphoma and was on a simplified emtricitabine once daily and fos-amprenavir 700 mg/ritonavir 100 mg twice-daily regimen. Using FibroScan, a liver stiffness of 32 kPa suggested liver cirrhosis prior to start of HCV triple therapy. Fos-amprenavir trough level was measured at week 8 of HCV triple therapy with 1699 ng/ml lying in the normal reference range (reference trough concentration 750–2500 ng/ml). HCV-RNA was measured with less than 12 IU/ml at week 11 and HIV viral load was below the detection limit of less than 40 copies/ml at all times.

Our clinical data suggest that, potentially, drug levels of HIV protease inhibitors that are coadministered with BOC may be within the normal range in patients with advanced liver disease. Indeed, various pharmacokinetic studies of HIV protease inhibitors in HIV/HCV-coinfected patients with advanced liver disease suggested higher protease inhibitor levels with more advanced stages of liver fibrosis [11]. According to the product label, dose reduction is even recommended for fos-amprenavir in patients with liver cirrhosis [12]. Many patients suffering from more advanced liver fibrosis are in particular need for triple HCV therapy, but may have acquired prior HIV resistance depending on a HIV protease inhibitor as a corner stone of their second-line or third-line therapy to maintain HIV suppression. Coadministration of HCV protease inhibitors may not be possible because of the reported HIV protease inhibitor/HCV protease inhibitor drug–drug interactions. However, our findings suggest that, indeed, in advanced liver disease, normal levels of HIV protease inhibitors may be found during HCV triple therapy. Unfortunately, BOC levels could not be determined in our patients as no standardized assays are currently in place. As BOC levels have been shown to decrease with HIV protease inhibitor administration, this remains of concern but may also be changed in patients with more advanced liver disease. Therefore, clearly more pharmacokinetic studies are urgently required in HIV/HCV-coinfected patients with more advanced liver fibrosis in order to better understand

the true amount of drug interactions between BOC and commonly used HIV protease inhibitors and possibly make HCV triple therapy accessible for a wider number of HIV/HCV-coinfected patients in desperate need of these drugs.

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Limitations of proposed novel trial design

We read with interest the article by Mani *et al*. [1], which proposes a novel trial design for new antiretroviral drugs intended to be used in treatment-experienced HIV-infected patients on a failing regimen. The new design is primarily motivated by the small current number of patients with multidrug-resistant virus causing difficulties in recruiting to trials for which this is an inclusion criterion. The new design has two phases. In the first phase, patients experiencing virological failure are randomized to receive the investigational drug or placebo for 10–14 days, while remaining on the failing regimen; the primary assessment of efficacy (virological response) takes place at the end of this phase. In the second phase, the background regimen is reoptimized for all patients, and those who received placebo in the first phase are also switched to the investigational drug, with follow-up continuing to 24 weeks. The rationale for this design is to provide evidence on safety and efficacy, while minimizing the chance of resistance developing to the new drug or additional resistance to the background drugs. We have several concerns about this new trial design and the implication in the article that it could replace traditional phase 3 trials (a control group maintained for a minimum of 48 weeks) currently required for licensing by regulatory agencies [2].

As all participants would receive the new drug after 10–14 days, the randomized safety evidence elicited by the new design is limited to acute adverse reactions. Thereafter, judgement is required in assigning the causality of each adverse reaction to an individual drug, which is recognized to be very difficult in the context of combination therapy [2]. Thus, only highly specific adverse reactions which have been previously unobserved

in all of the other background drugs can be reasonably attributed to the new drug. Such reactions, if they exist at all, are likely to be rare, and may well not be observed in the proposed sample size of 200–300 patients over 24 weeks of observation. Another weakness of the proposed design is that it leaves unanswered the critical questions of the durability of efficacy and the emergence of resistance because, again, there is no control group to reliably assess these factors. Furthermore, phase 2 dose-ranging monotherapy studies assessing short-term virological response would also usually be conducted, and the added value of similar information in treatment-experienced patients, who may or may not have viral cross-resistance to the investigational drug, is unclear.

The authors acknowledge these limitations of the proposed design and the need for 'confirmatory' or 'other' trials [1]. However, if approval was granted on the basis of evidence from the proposed trial design, there is no guarantee that larger and longer trials would be conducted. Phase 3 trials should attempt to reflect the way in which the investigational drug will be used in clinical practice, including the drugs with which it is likely to be coadministered, while acknowledging that different considerations may apply in licensing and academic-led trials. In contrast, the proposed trial design assesses the investigational drug in an artificial way, namely adding it to a failing regimen. We are also not persuaded by the arguments in the article about protecting patients from unknown toxicities and losing future treatment options. The stringent monitoring of phase 3 trials, including the regular unblinded assessment of the data by an Independent Data Monitoring Committee, ensures that the minimum number of patients are exposed to a drug which may have suboptimal efficacy or an unacceptably high rate of serious side effects. Indeed, there is strong ethical argument against rolling out new drugs in clinical practice in potentially large numbers of patients, without this being underpinned by a traditional phase 3 trial [3].

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Conflicts of interest

None declared.

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Novel clinical trial designs for the development of new antiretroviral agents

We thank Dunn *et al.* [1] for their comments on our article. The article [2] reports an expert discussion on antiretroviral drug development at a time when the great majority of patients, including most who have experienced virological failure once or more, have licensed treatment options that if, adhered to, will help achieve durable virological suppression. As discussed in the article, traditional large-scale comparative trials like those pivotal for the licensure of raltegravir or etravirine are therefore difficult to conduct. There remains, however, a small group of patients for whom a likely suppressive treatment regimen may not be available, and for whom new agents that are efficacious against viral strains with multiple resistances to existing drugs would be of value. Due to the relative scarcity of patients without remaining treatment options, and to the recognized risk of aggravating drug resistance with incompletely suppressive regimens, drug development in this population is a challenge. As a first point of response to the comment by Dunn *et al.* [1], we note that the proposed study design discussed at the meeting principally addresses a population that would not be recommended for study in traditional 24–96 week placebo controlled trials according to present European or US regulatory and clinical guidance [3,4].

Dunn *et al.* [1] question whether the efficacy assessment in the proposed study adds value, over and above that obtained in phase 1/2 dose ranging monotherapy studies. In this context, we note that investigational agents that might be studied according to the proposed design are most likely to be new agents of existing drug classes. Thus, the primary efficacy objective of the randomized phase would be to assess in-vivo antiviral potency against a range of viruses with different genotypic resistance

mutation patterns relevant to the drug class, and possibly conferring cross resistance to the new agent. Traditional monotherapy dose-ranging studies are generally performed in treatment-naive patients, and this information would not be obtained in such studies. If 'functional' monotherapy (add-on) studies in drug-class experienced patients failing their present regimen were performed in phase 1/2, these might be designed as smaller, pilot-type studies of a similar design as the randomized phase of the proposed pivotal study.

Dunn *et al*. [1] rightly note that the proposed study would not provide randomized evidence of the durability of response. In this context, an assumption of the rationale for the proposed design is that, if an antiretroviral drug showed reasonable short-term potency against a certain viral resistance strain, available experience indicates that it would be highly likely to contribute to the long-term durability of response to a combination regimen, provided that the other agents had different mechanisms of action and did not select for similar drug resistance mutations. The second, nonrandomized phase of the proposed study would provide observational data on the durability of response, to be analyzed in relation to estimated optimized background therapy activity. Furthermore, it would provide information on emerging resistance mutations to the new agent in case of failure. As was discussed at the meeting, in order to generate randomized comparative data on the contribution of the new agent to the durability of response, the agent could be investigated in traditional, reasonably sized studies, which would likely have a noninferiority design. The meeting deliberations, which were prompted by the present treatment landscape, noted that such studies would most readily be conducted in treatment naive or lightly treatment experienced patients. Also, in such studies, rates of emerging drug resistance in case of viral failure would provide valuable information on the barrier to resistance of the agent.

Finally, Dunn *et al*. [1] pose valid questions concerning the lack of randomized evidence on safety with the proposed study design. Neither the meeting nor our report systematically covered the issue of what supporting safety data would be required to bring a drug to market in the context of pivotal trials of the kind proposed. The size of the safety database, as well as the trials in which this may be generated, may differ depending on the range of treatment populations that are targeted in the drug development program. This will need to be further defined by regulatory agencies, if the proposed path is followed.

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Acute congestive heart failure and death secondary to itraconazole therapy

Itraconazole is routinely used to treat histoplasmosis in HIV-infected patients. Congestive heart failure (CHF) is a recognized complication of itraconazole therapy. We report a patient with disseminated histoplasmosis and probable HIV cardiomyopathy who developed acute CHF and fatal asystole while being treated with itraconazole.

A 22-year-old man was diagnosed with asymptomatic HIV infection and prescribed zidovudine, lamivudine, and lopinavir/ritonavir. CD4 cell count was 150/μl and HIV viral load was 35 000 copies/ml. There was no history of opportunistic infection or heart disease and no sign of cardiac dysfunction on examination. Chest radiograph (CXR) showed no cardiac enlargement or

evidence of pulmonary congestion. The patient did not return for follow-up care and did not take prescribed antiretroviral medications.

He presented 14 months later with a 2-week history of fever, chills, dyspnea, and cough. He was unemployed and denied use of illicit drugs, alcohol, or tobacco. Examination revealed a temperature of 102.6°F, blood pressure 99/68, pulse 122 beats/min, and respiratory rate 22 breaths/min. The buccal mucosa had several shallow oral ulcerations. Examination showed a grade 2/6 systolic murmur with a third heart sound, bibasilar crackles of the lungs, bilateral jugular venous distention, and 2+ pitting edema of the legs.

CXR demonstrated cardiomegaly and bilateral pulmonary interstitial infiltrates. Complete blood count showed white blood cell count of 1200/ml, hematocrit of 19.2%, and platelet count of 20 000/ml. A serum multichemistry panel showed Na of 128 mEq/l, K of 5 mEq/l, blood urea nitrogen of 59 mg/dl, creatinine of 3 mg/dl, alkaline phosphatase of 322 units/dl, and albumin of 1.3 g/dl. Random serum cortisol level was 31.8 mg/dl. Thyroid function tests were normal. CD4 cell count was 10/μl. Illicit drugs were not detected by urine screening. Quantitative urine histoplasma antigen levels (by ELISA) were high at 22.47 ng/ml (MiraVista Diagnostics, Indianapolis, IN, USA).

The patient was admitted to the ICU and transfused with two units of packed red blood cells, and received intravenous albumin. 3 mg/kg/day of empiric liposomal amphotericin B and prophylactic atovaquone (there was a history of allergy to sulfa drugs) were begun. Transthoracic echocardiogram (TTE) showed an ejection fraction of 45% and no valvular abnormalities or pericardial effusion. Bronchoalveolar lavage demonstrated a few small intracellular yeast structures morphologically suggestive of *Histoplasma capsulatum*. Two sets of blood cultures subsequently grew *H. capsulatum*.

The patient experienced rapid improvement in symptoms and resolution of fever, tachycardia, and hypotension. His leg edema resolved, his chest examination cleared, and his third heart sound disappeared. After 8 days, he was transferred out of the ICU, and antifungal therapy was changed to itraconazole suspension (200 mg three times daily for 2 days followed by 200 mg twice daily). He was not receiving any gastric acid inhibiting agents.

After 5 days of itraconazole therapy, dyspnea acutely developed. Examination showed bilateral jugular venous distention, diffuse pulmonary rales, an S3 cardiac gallop, and 3+ edema of the legs. Brain natriuretic peptide (BNP) was elevated at 3200 pg/ml (normal <100 pg/ml). CXR demonstrated worsening cardiomegaly, bilateral pulmonary congestion, and moderate pleural effusions. Repeat TTE showed decrease in ejection fraction to 30%. Serial electrocardiograms and measurements of cardiac enzymes did not show evidence of myocardial ischemia.

Returning to the ICU, supplemental oxygen as well as intravenous furosemide, morphine sulfate, and nitroglycerine were administered. Asystolic cardiac arrest ensued and, in keeping with the patient's advanced directives, no resuscitation was attempted. Autopsy was not performed.

Itraconazole is widely used for the treatment of disseminated histoplasmosis, usually after initial 'induction' therapy with amphotericin B [1]. Disseminated histoplasmosis is a common opportunistic infection in HIV-infected patients in endemic areas. HIV cardiomyopathy is a common complication of advanced HIV infection, and left-ventricular systolic dysfunction has been reported in 10–40% of patients with HIV infection [2]. Clinically important HIV cardiomyopathy is less common, but has been reported in up to 10% of patients [3]. Sudden cardiac death has accounted for 13% of all deaths in 2860 consecutive patients with HIV followed for 9 years [4].

Itraconazole therapy-associated development of CHF has been reported in 58 patients, including 13 fatal outcomes [5]. A black box warning has been added to itraconazole prescribing information for onychomycosis therapy by the US Food and Drug Administration [6]. As this warning does not apply to the use of itraconazole in systemic fungal infections, clinicians are expected to exercise clinical judgment when considering the use of itraconazole in patients with systemic fungal infection and CHF.

In studies of animals and healthy human volunteers, itraconazole has been demonstrated to have a possible negative inotrophic effect [7]. Other antifungal azoles do not appear to share itraconazole's cardiac effects and have been used in patients with itraconazole-induced CHF [7]. Because many HIV-infected patients presenting with disseminated histoplasmosis are young and lack traditional cardiac risk factors, therapy with itraconazole may be initiated without documenting normal cardiac function.

The patient we report likely had underlying HIV cardiomyopathy represented by abnormal cardiac examination findings, cardiomegaly on CXR, and reduced ejection fraction on TTE. There was no history of prior cardiac disease or traditional cardiac risk factors, but he did have advanced HIV infection, which is a recognized risk factor for HIV cardiomyopathy [8]. After initial improvement, the administration of itraconazole likely resulted in exacerbation of myocardial dysfunction with a reduction in ejection fraction and overt acute CHF leading to asystole.

Underlying HIV cardiomyopathy in patients being considered for itraconazole therapy might be detected

by screening with TTE and possible serum BNP levels. Alternative antifungal agents, such as amphotericin B, posaconazole, or voriconazole, should be considered if evidence of cardiomyopathy is discovered. Patients receiving treatment with itraconazole should be carefully followed for any evidence of the development of CHF.

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