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Does HIV remain a risk factor for achieving sustained virological response (SVR) under DAA-based modern HCV therapy?

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In the era of dual HCV therapy, consisting of pegylated interferon and ribavirin combination therapy, significantly lower HCV cure rates have been reported in HIV/HCV coinfected subjects than in HCV monoinfected subjects (1). Indeed, perceived lower efficacy as well as the high burden of interferon and ribavirin associated adverse events, have limited the uptake of HCV therapies in this special patient population considerably (2). First pilot trials with direct acting antivirals (DAAs) in particular the first generation HCV protease inhibitors telaprevir and boceprevir however, showed similarly increased cure rates in HIV-coinfected HCV treatment naive patients as in treatment of HCV monoinfection with cure rates between 63-74% (3-4). However, these were highly selected small patient groups without advanced fibrosis or previous non-response to IFN-based therapy. Therefore, the question in the coinfection field clearly was how will these new treatment advances translate into more difficult-to-treat real world patient populations. In addition the high price of the new HCV compounds made their use in patients with low fibrosis stages rather unlikely clearly emphasizing the need for data in more difficult to treat patients with advanced fibrosis stages and higher treatment urgency. Fortunately the ANRS has supported and conducted a trial evaluating the efficacy and safety of a telaprevir based HCV therapy in HIV-HCV coinfected patients who previously failed a peg-interferon-ribavirin therapy (ANRS HC26 TelapreVIH) and also included patients with all fibrosis stages. The outcome of this trial is reported in this issue of Clinical Infectious Diseases and shows for the first time that even in much more difficult to treat patients the HCV cure rates can reach an impressive 80% (5). Most interestingly, SVR was not influenced by baseline fibrosis stage, IL28B genotype, antiretroviral regimen, HCV subtype, CD4 cell count, previous response to HCV treatment, HCV-RNA level or HCV-RNA decline at week 4 indeed suggesting that in

the setting of a DAA-based therapy all historic prognostic factors for achieving HCV cure become much less relevant. Looking at the high SVR rate obtained in this trial one could even speculate that SVR rates are even higher in coinfection than those from the CUPIC trial (a trial in previous HCV treatment failures with HCV mono infection and cirrhosis; Among patients given telaprevir, 74.2% of relapsers, 40.0% of partial responders, and 19.4% of null responders achieved SVR12) (6). Therefore, it is extremely important to highlight that HIV/HCV coinfected subjects with cirrhosis and previous non-response to PEG-IFN/RBV therapy as the most difficult-to-treat patients were excluded from the ANRS trial (because of the perception of very low response probabilities in this special patient group) thereby increasing the likelihood of SVR in this study population.

Another methodological limitation of the study is that telaprevir was administered trice daily, whereas now at least in monoinfection bid administration of telaprevir has become the new gold standard following the presentation of data demonstrating equal efficacy for the bid dose allowing for some treatment simplification (7). So far in HIV/HCV coinfection data from bid dosing has only been reported at conferences but also showing no differences in outcome for tid versus bid dosing (8).

With the rapid advent of interferon-free DAA combinations promising even much higher cure rates above 95% in shorter treatment durations without interferon and possibly even without ribavirin in the very near future the use of telaprevir or IFN as a component of HCV therapy may soon no longer play a role in the HCV armentarium and management plan. Under consideration of the high costs attached with these modern HCV therapies and the limited resources in many countries throughout the world however, it should not be forgotten that cure of HCV can be achieved with a 1st generation HCV protease inhibitor (such as Telaprevir) based triple therapy in 80% of

HIV/HCV coinfected individuals with previous treatment failure (unless they are cirrhotic non-responders) offering a chance to prevent the further progression of liver disease to cirrhosis or decrease the risk for the development of hepatocellular cancer. Ongoing price discussions can considerably delay treatment access and therefore first generation HCV protease inhibitors should at least be discussed where available and no other treatment options are in sight. Nevertheless, it has to be highlighted that this study also documents a considerably higher adverse event rate than observed in healthy non-cirrhotic HCV treatment naïve patient populations with 20% of patients discontinuing treatment for adverse events and 70% of patients requiring erythropoietin, blood transfusion or ribavirin dose reduction clearly underlining the challenges and complexity of the management of these patients when receiving PEG-IFN/RBV based DAA regimens (5).

As a consequence of the similar SVR rates in HCV mono and HIV coinfected subjects major guidelines such as the recent EASL updated HCV clinical practice guidelines no longer differentiate between HIV/HCV coinfected and HCV monoinfected patients (9). Indeed indication and treatment choices have become the same. Only remaining special issue is the need to check for drug-drug interactions between antiretroviral HIV drugs and HCV DAAs. In particular in combination with HCV protease inhibitors which are also metabolized through the cytochrome 450 pathways just as HIV NNRTIs or PIs drug interactions are common. Therefore, HIV drugs need to be checked for possible combinability through one of the drug interaction websites (for example see http://www.hep-druginteractions.org/). In conclusion, similar cure rates under modern DAA-based HCV therapy in HIV/HCV coinfection should prompt increased uptake of these improved HCV therapies in a

patient population with an even in the ART era higher risk for liver fibrosis progression.

Notes

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References

1 Lacombe K, Rockstroh JK. HIV and viral hepatitis co-infections: advances and challenges. Gut. 2012 May;61 Suppl 1:i47-58.

2. Rockstroh JK, Bhagani S. Managing HIV/hepatitis C co-infection in the era of direct acting antivirals. BMC Med. 2013 Nov 1;11:234.

3. Sulkowski M, Pol S, Mallolas, J, et al. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double blind, controlled phase 2 trial. Lancet Infect. Dis 2013; 13: 597–605.

4. Sulkowski M, Sherman K, Dieterich D, et al. Telaprevir in combination with peginterferon and ribavirin for chronic HCV genotype 1 infection in HIV-infected patients. Ann. Intern. Med 2013; 159: 86–96.

5. Cotte L, Braun J, Lascoux-Combe C, et al. Telaprevir for HIV-HCV coinfected patients failing peginterferon-ribavirin (ANRS HC26TelapreVIH): an open-label, single-arm, phase 2 trial. Clin Infect Dis 2014

6. Hézode C, Fontaine H, Dorival C, et al., CUPIC Study Group. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. Gastroenterology. 2014;147:132-142

7. Buti M, Agarwal K, Horsmans Y, et al. Telaprevir twice daily is noninferior to telaprevir every 8 hours for patients with chronic hepatitis C. Gastroenterology. 2014 Mar;146(3):744-753.

8. Hare B, Sherman KE, Talal A, et al. Simplified dosing and response-guided therapy using telaprevir combination treatment for genotype 1 HCV treatment-naïve or –experienced HIV co-infected patients: UNITE interim analysis. HEPDART 2013: Big Island, HI; abstract 64

9 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol. 2011 Aug;55(2):245-64.