Journal of Clinical Virology 78 (2016) 27–30

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Case report

Direct-acting antiviral treatment in adults infected with hepatitis C virus: Reactivation of hepatitis B virus coinfection as a further challenge

Anne De Monte[a], Johan Courjon[b], Rodolphe Anty[c,d,e], Eric Cua[b], Alissa Naqvi[b], Véronique Mondain[b], Jacqueline Cottalorda[a], Laurence Ollier[a,*], Valérie Giordanengo[a,e,f]

[a] Department of Virology, Biological and Pathological Center, Centre Hospitalier Universitaire de Nice, France
[b] Department of Infectious Diseases, Centre Hospitalier Universitaire de Nice, France
[c] Digestive Center, Centre Hospitalier Universitaire de Nice, France
[d] Institut National de la Santé et de la Recherche Médicale (INSERM), U895, Team 8, Hepatic Complications in Obesity, France
[e] University of Nice-Sophia-Antipolis, Faculty of Medicine, France
[f] Institut National de la Santé et de la Recherche Médicale (INSERM), U1065, France

ARTICLE INFO

Article history:
Received 16 December 2015
Received in revised form 17 February 2016
Accepted 28 February 2016

Keywords:
HCV Direct-Acting Antivirals
HBV reactivation
HIV infection
NS3/4A protease inhibitors
NS5A inhibitors
NS5B polymerase inhibitors

ABSTRACT

Use of direct-acting antiviral drugs (DAAs) greatly improves management of adults infected with hepatitis C virus (HCV) whether patients are treatment-naive or unsuccessfully pre-treated. Several inhibitors of viral nonstructural proteins (NS3/4A protease, NS5A and NS5B polymerase) allow a rapid HCV clearance and increase rates of sustained virological response. Both the EASL and AASLD guidelines have recently published up-to-date recommendations for their use, addressing each HCV genotype and particular situations. However, management of patients coinfected with hepatitis B virus (HBV) has been developed by these guidelines with reference to cases of HBV reactivation reported during previous anti-HCV regimens containing interferon known active against both HBV and HCV. In the setting of the interferon-free HCV therapies with DAAs only, the possibility of HBV reactivation during treatment of hepatitis C is raised due to viral interferences in HCV/HBV coinfected persons. Herein, we report a case of early HBV reactivation during DAAs-based anti-HCV treatment (ledipasvir/sofosbuvir) in a patient having a resolved HBV infection and chronically infected with HCV genotype 4 and HIV. Moreover, we review similar recent cases of HBV reactivation in patients infected with HBV and HCV genotype 1 during treatment of hepatitis C by regimen incorporating other combination of DAAs (sofosbuvir/simeprevir or daclatasvir/asunaprevir). Due to the potential risk of early HBV reactivation in HCV/HBV-coinfected patients during interferon-free DAAs-based HCV therapies, altogether these cases highlight the necessity to closely monitor HBV coinfection, regardless its stage (chronic, occult, resolved), whatever HCV genotype or class of DAAs used.

1. Why this case is important?

Use of direct-acting antiviral drugs (DAAs) greatly improves management of adults infected with hepatitis C virus (HCV), whether patients are treatment-naive or unsuccessfully pre-treated [1].

Several inhibitors of viral nonstructural proteins (NS3/4A protease, NS5A and NS5B polymerase), allow a rapid HCV clearance and increase rates of sustained virological response. Treatments incorporating only DAAs have superseded most previous regimens containing peginterferon and ribavirin [1].

Recently, EASL and AASLD/IDSA societies provided up-to-date recommendations on HCV treatment [2,3]. These guidelines address each HCV genotype and particular situations, such as retreatment of persons in whom prior therapy has failed, or coinfection with human immunodeficiency virus (HIV). DAAs-based HCV treatment is also indicated in persons coinfected with HCV and hepatitis B virus (HBV). Due to interferences between these two viruses, there is a potential risk of HBV reactivation during therapy-induced

* Corresponding author at: Biological and Pathological Center, Laboratoire de Virologie, Hôpital Archet 2, 151 Route de St. Antoine de Ginestière, CS 23079, 06202 Nice Cedex 3, France. Fax: +33 492039219.
E-mail address: ollier.l@chu-nice.fr (L. Ollier).

http://dx.doi.org/10.1016/j.jcv.2016.02.026
1386-6532/

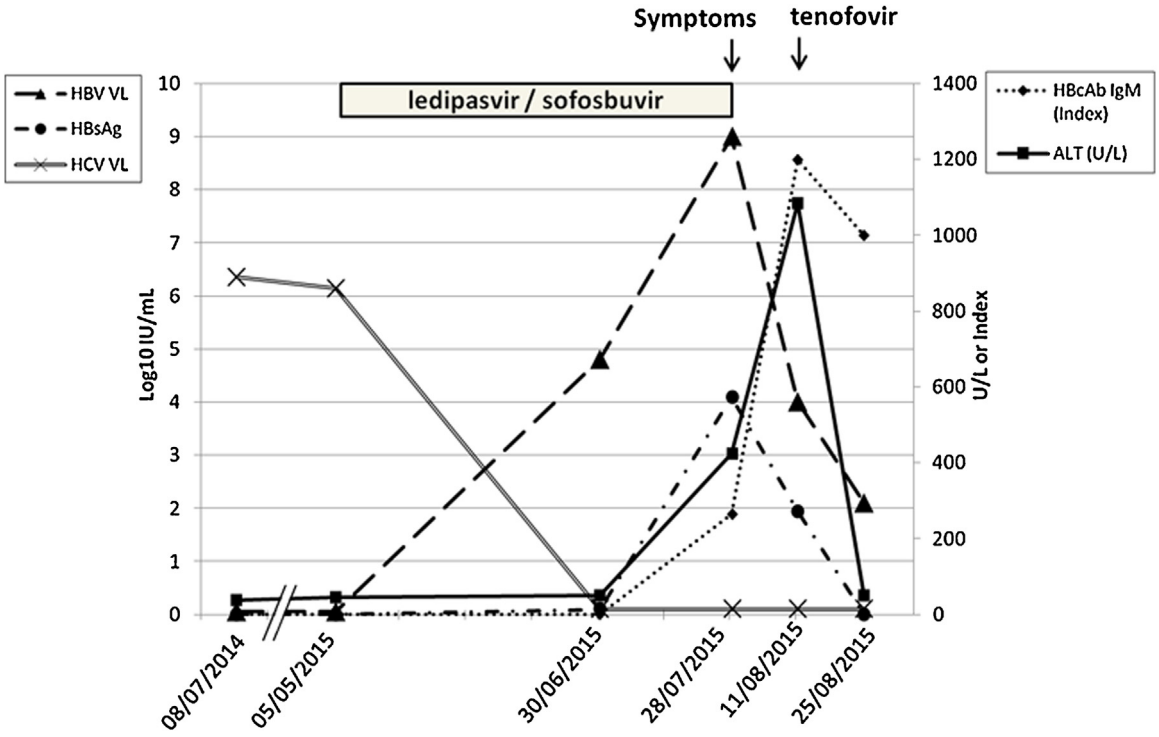

Fig. 1. Graphical illustration of HCV infection and HBV reactivation: HCV VL, HBV VL, HBsAg, HBcAb IgM and ALT over time.

HCV clearance. While AASLD/IDSA guidelines do not mention this risk, EASL guidelines raise this possibility referencing to what has been reported with previous HCV regimens containing interferon which is known active against HBV. Actually, in the setting of the interferon-free HCV therapies with DAAs only, the possibility of HBV reactivation remains unclear.

Herein, we first report the case of DAAs-based HCV treatment combining ledipasvir and sofosbuvir leading to HBV reactivation in a patient having a resolved HBV infection and chronically infected with HCV genotype 4 and HIV. Then, we review the few recent similar cases of HBV reactivation in HBV/HCV genotype 1-coinfected patients successfully treated by others classes of DAAs [4–6].

2. Case description

A HCV/HIV-coinfected 53-year-old man followed since 1988 in the Infectious Diseases Department of the Nice University Hospital presented for re-treatment of HCV genotype 4d infection. He was previously null responder to a bi-therapy incorporating peginterferon and ribavirin. Although liver stiffness was low (transient elastography using FibroScan = 7 kPa), HCV treatment was reconsidered because of cutaneous porphyria. Furthermore, his HIV infection (CDC class C3) was controlled since 2011, with a plasma viral suppression below the lower detection limit of the real-time RT-PCR amplification monitoring and a CD4+ lymphocyte count above 500/mm^3, thanks to highly active antiretroviral therapy (HAART) containing etravirine, raltegravir and darunavir/ritonavir.

The second HCV treatment combined inhibitors of NS5A and NS5B polymerase (ledipasvir/sofosbuvir) for 12 weeks. This regimen allowed to decrease HCV viral load (VL) from 1400,000 IU/mL (6.1 $\log_{10}$ IU/mL) to detectable below 12 IU/mL at weeks 8 and 12. Whereas treatment finished, dizziness, fever and jaundice began, and the patient presented the following week with increased levels of aminotransferases (ALT 1026 U/L, AST 758 U/L) and bilirubin (174 μmol/L). Abdominal ultrasound revealed hepatomegaly with heterogeneous echotexture.

HBV reactivation was then explored while other etiologies were ruled out. Indeed, this patient was known since 1995 with a history of HBV infection [hepatitis B surface antigen (HBsAg) negative, antibody to HBsAg (anti-HBs) below 5 IU/L, antibody to hepatitis B core (anti-HBc) positive, hepatitis B e antigen (HBeAg) negative and antibody to HBeAg (anti-HBe) positive] and he had to discontinue 14 months ago the tenofovir included in his HAART because of osteoporosis. Tests then detected HBsAg, HBcAb IgM and high HBV VL (960,000,000 IU/mL; 8.9 $\log_{10}$ UI/mL), whereas at the initiation of the DAAs treatment, HBsAg was negative and HBV DNA was undetectable. Tenofovir was reintroduced and HBV replication (drug-susceptible genotype D virus) was controlled (Fig. 1).

3. Similar and contrasting cases in the literature

Reactivation of hepatitis B is characterized by an abrupt reappearance or rise of HBV DNA levels in the serum of a patient with previously resolved or inactive HBV infection. This increase of HBV replication, or “viral breakthrough”, is often accompanied by a “biochemical breakthrough”, i.e. reappearance of disease activity or a flare of hepatitis in previously inactive or minimal disease [7]. To our knowledge, four cases of HBV reactivation have just been reported in patients infected with HCV, but not HIV, treated with DAAs only [4–6]. Their clinical characteristics are detailed in Table 1, in which patients have been arbitrarily numbered from 1 to 4.

All of these four patients were infected with HCV genotype 1, contrasting with our patient. Three of them were previously treated for their HCV infection by peginterferon/ribavirin with no sustained virological response. The DAAs-based HCV regimens incorporated another classes of inhibitors: anti-NS5B polymerase (sofosbuvir) plus anti-NS3/4A protease (simeprevir) for the 3 pretreated patients [4,5] and anti-NS5A (daclatasvir) plus anti-NS3/4A protease (asunaprevir) for the naive patient [6].

These four patients presented various state of HBV infection: inactive HBV carrier (HBsAg positive, seroconversion from HBeAg