Case Report

Very short course of triple therapy including telaprevir for chronic hepatitis C: a possible strategy in selected patients

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ARTICLE INFO

Article history:
Received 21 August 2013
Received in revised form 4 September 2013
Accepted 6 September 2013

Corresponding Editor: Eskild Petersen,
Aarhus, Denmark

Keywords:
Anemia
Direct antiviral agents
Hepatitis C virus
Pegylated interferon
Ribavirin
Telaprevir

SUMMARY

The recent introduction of direct antiviral agents (DAAs) as a fundamental part of anti-hepatitis C virus (HCV) therapy has dramatically improved the possibility of cure for patients with genotype 1, but at the same time has increased the incidence of severe adverse events and the risk of reduced compliance. Here we present the case of a 72-year-old Caucasian male suffering from a genotype 1b HCV infection, with a previous history of virological breakthrough at the end of dual therapy with pegylated interferon and ribavirin at standard dosages. The patient was retreated with telaprevir-based triple therapy, and despite the early spontaneous interruption of treatment because of severe anemia and fatigue, he obtained a sustained virological response. This case suggests that in selected genotype 1 HCV-infected patients, primarily of subtype 1b, who require the interruption of anti-HCV therapy because of severe adverse events or reduced compliance, a successful treatment can be obtained even with a very short course of DAA-based triple therapy.

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1. Introduction

Hepatitis C virus (HCV) infection is a major health problem worldwide, causing severe complications such as cirrhosis and its sequelae, including end-stage liver disease and hepatocellular carcinoma. Dual anti-HCV therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV) can improve liver histology and also eradicate HCV. However, both of these objectives are more difficult to obtain for viral genotype 1 than for the other genotypes. The recent introduction of direct antiviral agents (DAAs) boceprevir (BOC) and telaprevir (TVR) into clinical practice has substantially improved the therapeutic outlook for patients with genotype 1 HCV infections; indeed, sustained virological response (SVR) rates have increased from approximately 35–50% for dual therapy to 63–75% for DAA-based triple therapy in treatment-naïve subjects and to 69–83% in relapsers; they are now satisfactory even in previous non-responders. Moreover, the use of DAAs may also allow a shortened duration of therapy, except in non-responder and cirrhotic patients, by virtue of a response-guided therapeutic strategy. This results in simplification of therapy, higher compliance, and a lower global cost of treatment.

However, subjects on either BOC- or TVR-based treatment develop significantly more adverse events than do those on dual therapy, and this can complicate treatment and sometimes lead to its discontinuation. In particular, patients with more advanced disease develop an increased incidence of moderate and also severe anemia, which have been found to be higher in the post-marketing surveillance than in the registered trials. Here we report the case of a treatment-experienced patient who was retreated with TVR-based triple therapy and who developed a severe anemia that induced him to interrupt all anti-HCV drugs early, but who obtained an SVR all the same.

2. Case report

In 2007, a 67-year-old Caucasian male with a medical history of absolute polycythemia, arterial hypertension, and metabolic syndrome, without other significant factors such as alcohol abuse or viral co-infections, suffered from an acute subtype 1b HCV infection, probably acquired in the hospital environment following either endoscopic retrograde cholangiopancreatography or subse-
quent cholecystectomy. He did not spontaneously clear his infection, remaining positive at 12 weeks after initial presentation. As a result he was treated with subcutaneous PEG–IFN alpha-2a plus oral RBV at standard dosages. Despite a rapid virological response (RVR), viral breakthrough occurred at the end of 24-week therapy; the patient was followed-up regularly in the subsequent years. In November 2011, a liver biopsy showing moderate nécroinflammatory activity and severe fibrosis (Ma
tavir A2/F3) and an unfavorable genotype in the IL28b genetic test (rs12979860 T/T) provided an indication for triple–anti–HCV therapy. In April 2012, the patient (now aged 72 years, weight 80 kg, body mass index 26.73 kg/m²) initiated subcutaneous PEG–IFN alpha-2b 120 μg/week, oral RBV 1200 mg/day, and oral TVR 2250 mg/day, in accordance with Named Patient Program use. Major baseline values were the following: HCV–RNA >7 log10 copies/ml, alanine transaminase (ALT) 73 IU/ml, and hemoglobin (Hb) 17.3 g/dl. At week 2, HCV–RNA was undetectable, ALT was 23 IU/ml, and Hb was 15.5 g/dl. Subsequently, the patient developed progressive fatigue, with Hb declining to 10.8 g/dl at week 4 and to 9.3 g/dl at week 5; in the meanwhile, the RBV dose was first reduced to 1000 mg/day and then subcutaneous erythropoietin alpha 40 000 units/week was started. At week 6, the patient was admitted to the hospital for worsening of both fatigue and anemia (Hb 7.9 g/dl), which required a red blood cell transfusion. At the beginning of week 7, he spontaneously suspended all anti–HCV drugs. During the following 4 weeks, Hb steadily rose to the normal range, and the fatigue progressively diminished and then subsided. HCV–RNA remained persistently undetectable throughout controls at 1, 3, 6, 9, and 12 months after discontinuation of anti–HCV therapy.

3. Discussion

Combination therapy with PEG–IFN and RBV produces an SVR in no more than 50% of genotype 1 HCV-infected patients, compared to 70–80% of patients infected with genotypes 2 and 3.1 This and other limitations of dual anti–HCV therapy, such as the long treatment duration (48–72 weeks) and the many side effects of both PEG–IFN and RBV, have resulted in the development of some new promising molecules named DAAs. The first – BOC and TVR – have just been introduced into clinical practice as part of triple anti–HCV therapy in combination with PEG–IFN and RBV.

Potential toxicity is one of the most important limitations of DAAs, in particular the risk of precipitating anemia that is caused by RBV, although by a different pathogenic mechanism. In registered trials, anemia occurred in approximately a third of patients treated with TVR-based triple therapy, whereas this figure has been found to be even higher in post-marketing surveillance studies, in particular in subjects with advanced fibrosis/cirrhosis. In one of these recent studies, independent predictors of severe anemia were primarily a baseline Hb level ≤13 g/dl, and secondarily, age ≥65 years, female gender, and no lead-in phase.2 Our male patient started from a pretreatment Hb level that was very high (17.3 g/dl) being known as polycythaemic, but he is elderly and did not undergo a lead-in phase. We believe that these latter negative factors do not explain per se why the patient suffered from a worsening fatigue with difficulty in all normal daily activities, such that he spontaneously decided to interrupt all anti–HCV drugs. Therefore, accurate monitoring of the Hb level throughout the entire duration of treatment, along with its early management, is of crucial importance in order to both maintain the maximal drug dosages and to limit the risk of therapy discontinuation due to toxicity. In light of this and other objectives (i.e., preventing drug–drug interactions and investigating patient adherence), a potential role for therapeutic drug monitoring could be assumed in the future in the field of triple anti–HCV treatment, as it is now for other anti-infective therapies (antibacterial, antifungal).3

Our patient presented with several baseline factors associated with a poor rate of SVR, i.e., advanced age, severe fibrosis, metabolic syndrome, high HCV–RNA, and IL28b T/T genotype; however he obtained a RVR as early as week 2, probably favored by the rapid decline in HCV–RNA that it is well known to occur during the first 2 weeks of TVR therapy.4 The severe anemia caused by concomitant RBV and TVR induced the patient to interrupt treatment after 6 weeks, however the possibility of obtaining an SVR was not impaired. To our knowledge, such a short duration of anti–HCV therapy has so far been evaluated only in treatment-naive genotype 1 patients with the favorable IL28B C/C polymorphism (rs12979860). These subjects, treated with a 6-week quadruple regimen containing two novel DAAs (GS-5885 and GS-9451) plus PEG–IFN and RBV, showed an SVR rate as high as 79% – although lower than in the 12-week arm (98%) – in particular in patients with a high baseline viral load and body mass index. Of note, fewer dose reductions and therapy discontinuations were observed in the 6-week arm.5

Well-designed studies including a rigorous selection of patients with their risk factors and a clear definition of treatment schedules and primary and secondary endpoints are required in order to draw firm conclusions, however the case we have reported here offers – in our opinion – some interesting starting points for future research. First, if TVR-based anti–HCV therapy needs to be stopped because of toxicity or reduced compliance, an SVR can still be obtained with as short as 6–8 weeks of treatment in selected genotype 1 HCV-infected subjects. Second, some characteristics carried by our patient (subtype 1b, absence of cirrhosis and viral co-infections, achievement of a RVR), along with other favorable factors (no previous anti–HCV therapy, IL28b C/C polymorphism, low baseline HCV–RNA) can identify those subjects who are candidates for a shorter anti–HCV treatment duration and, therefore, for a reduced exposure to potentially severe adverse events.

Conflict of interest: All authors who took part in this study declare that they have no financial or personal relationships with other people or organizations that could inappropriately have influenced (biased) their work.

Funding source: All authors who took part in this study declare that no sponsors had any role in the study design, in the collection, analysis, and interpretation of data, in the writing of the manuscript, or in the decision to submit the manuscript for publication.

Ethical approval: All authors who took part in this study declare that no ethical approval was required because personal patient details are not included in any part of the paper.

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