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Difficult management of triple therapy for chronic hepatitis C in a patient on haemodialysis☆

Difícil manejo del tratamiento con triple terapia en paciente con hepatitis crónica C y hemodiálisis

We present the case of a 52-year-old patient with a 26-year personal medical history of chronic hepatitis C (HCV) infection. The patient was diagnosed with kidney failure secondary to non-proliferative glomerulonephritis and underwent a kidney transplant in 1991 with delayed graft failure in 2007, since which point he has been on haemodialysis. He has subsequently undergone surgery on three separate occasions due to iliac artery aneurysm and mitral valve disease, complicated by endocarditis in 2011, which is being treated with acenocoumarol.

He has been attending the gastrointestinal outpatient clinic since 2009. The patient is infected with genotype 1b and a liver biopsy revealed stage 3/6 fibrosis. Monotherapy was started with pegylated interferon (IFN) alpha-2a 135 μg/week, obtaining a biochemical and virological response throughout the 48 weeks of treatment, with recurrence 6 months after treatment was withdrawn.

Triple therapy was first contemplated in 2012. The degree of fibrosis was staged by elastography, which revealed 16.6 kPa (corresponding to F4 on the METAVIR score), and the IL28B polymorphism was identified as the CC genotype.

Triple therapy with telaprevir was started in February 2014 with the dose adjusted due to kidney failure: IFN 135 μg/week, ribavirin (RBV) 200 mg/day and telaprevir 750 mg/8 h. The lab tests at the start of treatment revealed thrombocytopaenia of 114×10^3/l, GPT 67 and creatinine of 10.7 mg/dl. The complete blood count conducted in week 4 showed a 5 g/dl fall in haemoglobin (Hb) levels (previous Hb level 15.6 g/dl), together with normal transaminase levels and a viral load (VL) <15 IU/ml.

Two packed red blood cell units and two platelet units were required for the first time in week 8 following a fall in Hb levels to 8.6 g/dl and thrombocytopaenia of 18×10^3/l, which led to IFN administration being postponed for one week (Fig. 1). The patient had an undetectable viral load at 12 weeks. Four further packed red blood cell units were transfused in the following weeks due to new episodes of anaemia (with Hb levels falling to 6.7 g/dl), and RBV was finally withdrawn in week 18.

Five months after initiating treatment, the patient was admitted with *Staphylococcus aureus* bacteraemia caused by the tunnelled haemodialysis catheter, with resolution of symptoms upon changing the catheter and administering intravenous antibiotics. Given the patient's clinical status, antiviral treatment was permanently withdrawn in week 21.

In the 3- and 6-month post-treatment follow-ups, the patient's blood levels had completely recovered, with normal Hb levels, an undetectable viral load and sustained viral response that the patient maintained.

The prevalence of chronic HCV infection is higher in patients with chronic kidney disease than in the general population. It currently stands at 5.6% in Spain, and prevalence increases as the number of years on haemodialysis increases.[1] As such, the Spanish Society of Nephrology recommends anti-HCV screening in these patients.[2]

The survival of haemodialysis patients is compromised by HCV,[3,4] which represents the fourth-highest cause of mortality and the main cause of post-kidney transplantation liver dysfunction due to the earlier onset of cirrhosis and the greater risk of liver cancer.[3,5,6]

Use of antiviral treatment in dialysis patients has been limited due to the adverse effects of IFN and RBV-induced haemolytic anaemia.[7,8]

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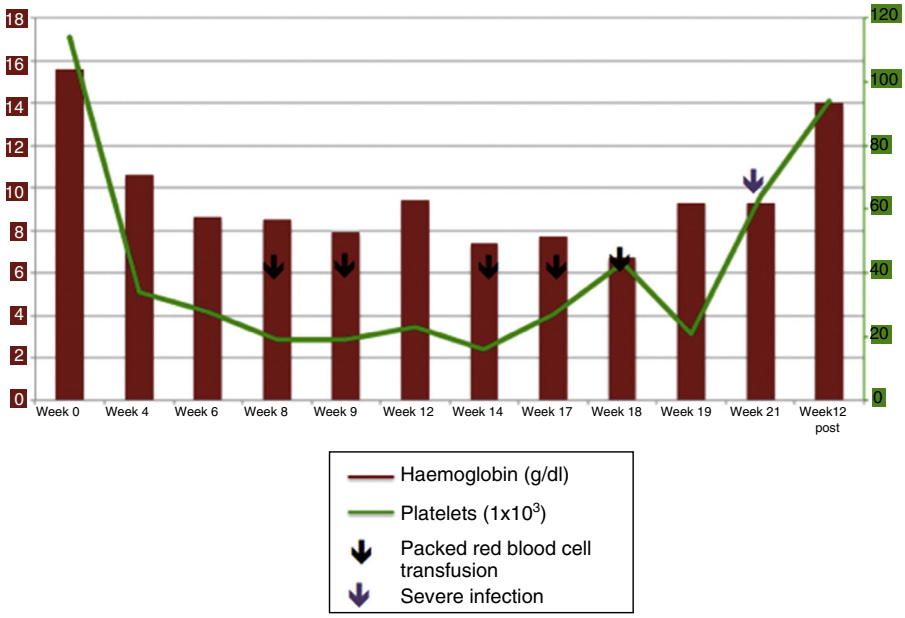

Figure 1 Bloods and transfusional requirements of our patient over time.

Over time, the use of pegylated alpha interferon, either alone or in combination with RBV, has shown low sustained virological response (SVR) rates and significant pharmacological intolerance, despite adjusting the dose in accordance with the glomerular filtration rate.[4,8] Improved SVR rates have been achieved with the use of direct-acting protease inhibitors in combination with IFN or RBV (around 70% at 48 weeks), without having to adjust the protease inhibitor dose as it is not primarily excreted by the kidneys.[9,10] However, it should be noted that severe adverse effects hinder its use.

In our case, the side effects (anaemia and thrombocytopaenia associated with sepsis) ultimately led to suspension of the treatment in week 21.

Despite advances having been made over the last 2 years with the introduction of triple therapy, the objective is to find IFN-free treatments with minimal side effects.[7] Numerous studies are currently ongoing to evaluate the response rates of such treatments in patients with kidney failure. With the exception of sofosbuvir, which would not have been indicated in this case owing to a creatinine clearance of less than 30 ml/min, the combination of ombitasvir/paritaprevir/ritonavir/dasabuvir would have been an appropriate treatment option as these drugs are not primarily eliminated by the kidneys, although they were not available at the time of treating our patient. Equally, elbasvir/grazoprevir, which are due to be released soon, would be a good option for this type of patient.

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Bacteraemia due to non-toxigenic *Vibrio cholerae*: The risks of eating seafood in a cirrhotic patient☆

Bacteriemia por *Vibrio cholerae* no toxigénico: los riesgos del consumo de marisco en un paciente cirrótico

Vibrio cholerae (*V. cholerae*) is a Gram-negative, curved, mobile, oxidase- and catalase-positive, facultative anaerobe bacillus commonly found in marine environments.[1] More than 200 different serogroups have been identified based on the nature of the lipopolysaccharide O-antigen of its wall, and epidemic cholera is caused by the O1 and O139 serogroups.[1] The non-toxigenic serogroups (non-O1 and non-O139) tend to be linked to the onset of self-limiting gastroenteritis after seafood consumption, particularly bivalve filter-feeding molluscs, with symptoms potentially as severe as cholera.[2,3] Notwithstanding its potential involvement in otitis externa, cellulitis and wound infection, the enteroinvasive potential of the non-toxigenic serogroups is limited and only affects hosts with particular comorbidities.[4]

We present the case of a 56-year-old male patient with type 2 diabetes mellitus and alcoholic liver cirrhosis with a Child-Turcotte-Pugh class of A6 (9 points on the MELD score), who had developed ascitic and oedematous compensation, oesophageal and gastric varices and thrombosis of the splenoportal venous axis as prior complications. The patient was taking spironolactone, furosemide, propranolol, tinzaparin and insulin glargine. He attended A&E having experienced the onset, 24 h previously, of dysthermia with a temperature measured at home of 38.5 °C, drowsiness, odynophagia and cough without expectoration, as well as loose bowel movements. The physical examination revealed an axillary temperature of 36.8 °C (after taking an antipyretic), blood pressure of 113/59 mmHg, a heart rate of 87 bpm and clinical signs of chronic liver disease. The lab tests revealed thrombocytopaenia (26.0×10^9 platelets/l), increased acute phase reactants (C-reactive protein 14.9 mg/dl; normal range: 0.1–0.5), hypertransaminasaemia (gamma-glutamyl transpeptidase [GGT] 114 IU/l, alkaline phosphatase 134 IU/l) and mildly impaired liver function tests (total bilirubin 2.7 mg/dl, INR 1.29). The white blood cell count was normal (4.7×10^9 leukocytes/l). An abdominal ultrasound only found a minimal number of ascites barely consistent with underlying chronic liver disease, while the chest X-ray revealed no consolidations. Assuming a possible diagnosis of respiratory tract infection, empirical treatment was started with levofloxacin (500 mg every 24 h) and the patient was discharged after obtaining two sets of blood cultures (BacT/ALERT® 3D system, bioMérieux, Marcy l'Etoile, France). After 24 h, a curved, lactose-and oxidase-positive Gram-negative bacillus was isolated in the MacConkey agar plate of one of the sets, which formed greenish colonies in the blood agar plate (Fig. 1). Using biochemical testing (MicroScan WalkAway® system, Siemens, California, USA), mass spectrometry (Bruker Daltonics, Bremen, Germany) and direct agglutination (BD Difco *Vibrio cholerae* Antisera, Becton Dickinson, Sparks, MD, USA), non-toxigenic *V. cholerae* was identified. The antibiogram confirmed susceptibility to aminopenicillins and trimethoprim/sulfamethoxazole. At that time the patient was asymptomatic and afebrile, so it was decided to maintain treatment with levofloxacin for 10 days. Upon questioning, the patient mentioned having eaten a large amount of shellfish a few days prior to symptom onset, including razor clams (*Ensis* spp.), steamed cockles (*Cerastoderma edule*) and mussels (*Mytilus galloprovincialis*), as well as grilled shrimp (*Aristaeopsis edwardsiana*). His partner, who had also eaten this seafood, coincidentally experienced mild gastroenteritis.

Although the clinical significance and public health impact of the non-toxigenic serogroups of *V. cholerae* (also known as non-agglutinating or non-choleric) was questioned for a long time, its involvement in outbreaks of diarrhoea in immunocompetent subjects after the consumption of contaminated seafood has been documented in several European countries.[2] A recent study demonstrated an elevated prevalence of non-toxigenic *V. cholerae* in prawns (17%) and mussels (9%) harvested off the Italian coast.[5] Given that it requires a temperate saline aquatic environment for optimal growth (>15 °C), it has been suggested that rising average sea temperatures as a result of global warming could explain the increased incidence of *V. cholerae* infection, including at more northern latitudes.[2,5]

The pathogenicity of non-toxigenic *V. cholerae* may be increasing due to the presence of a wide spectrum of virulence factors, including extracellular enzymes, enterotoxins and haemolysins.[5,6] As a result of iron overload and inhibited opsonophagocytosis and reticuloendothelial clearance (which favour bacterial translocation from the lumen of the gastrointestinal tract), liver cirrhosis is one of the most common comorbidities associated with the onset of enteroinvasive *V. cholerae* infections.[4,7] Examples of bacteraemia, spontaneous bacterial peritonitis and

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