Successful treatment of hepatitis B virus infection and related cryoglobulinaemic purpura with nucleoside/ nucleotide analogues

Sirs,

The term cryoglobulinaemia indicates the presence in the serum of one (monoclonal cryoglobulinemia) or more (mixed cryoglobulinemia) (MC) immunoglobulins, which precipitate at temperatures below 37°C and re-solubilise with heating (1). Orthostatic purpura (as expression of small vessel vasculitis), weakness, arthralgia/arthritis, glomerulonephritis, peripheral neuropathy, and Raynaud's phenomenon are the main clinical manifestations related to MC (1,2). Laboratory test shows a hepatitis C virus (HCV) infection in 70-100% of MC patients in different countries (1). Antiviral therapy is a cornerstone for the management of HCV-related MC and has the strongest biologic rationale (3).

An association between hepatitis B virus and MC was reported since 1977 but at that time an HCV co-infection could not be excluded since laboratory tests for HCV detection were unavailable (4, 5).

At present, HBV-related cryoglobulinaemic vasculitis is considered rare and very few cases treated with nucleoside or nucleotide analogues were reported (6-9). We have recently successfully treated 2 cases of HBV-related cryoglobulinemic purpura (which retrospectively satisfied the recent international classification criteria) (10) respectively with tenofovir and entecavir.

Case 1. A 65-year-old Caucasian woman came to our attention in May 2004 with an 8-year history of HBV-related HBe negative Hepatitis B and type III cryoglobulinemia with severe orthostatic purpura (OP), effectively treated with interferon alfa2b 5MU T.I.W. and metylprednisolone (MTP) 8 mg daily for the last two years. High levels of rheumatoid factor (RF) were persistently detected. C4 resulted inconstantly lowered. HCV-antibodies and HCV-RNA repeatedly tested on plasma were absent.

In June 2005 we decided to switch to Pegylated interferon alfa2a 180 mcg a week which was stopped on June 2006 on the patient's request. In July a 25.000 UI/ml viral replication was detected and at the end of the same month OP reappeared. Cryocrit was 2%. MTP 16 mg/daily was re-instituted, obtaining the OP remission. In August, a weekly dose of Pegylated interferon alfa2a 180 mcg was newly prescribed and MPS was reduced to 8 mg. In October 2006 lamivudine 100 mg/daily was also added, when the purpura persisted although it decreased

In January 2007, due to loss of sensitivity of the lower limbs and gait difficulty, an EMG was performed showing sensory-motor polyneuropathy.

In October 2009, the patient autonomously stopped Pegylated interferon, therefore when she came to clinical control it was decided to switch the oral therapy to tenofovir disoproxil fumarate 245 mg every other day according to calculated creatinine clearance. Considering that the patient had other diseases requiring drugs, lamivudine was discontinued after two months of combined therapy and metylprednisolone was reduced to 4 mg/daily and stopped after 3 further months. At that time, purpura was absent and polyneuropathy was stable at clinical examination and EMG. At present, viral replication, cryoglobulinaemia, rheumatoid factor and purpura are undetectable. C3 and C4 are normal. The sensory-motor neuropathy is unchanged.

Case 2. A 49-year-old, Caucasian man presented in June 2009 with a 15-year history of HBV-related chronic hepatitis. He reported the appearance of a mild OP on his legs for 6 months. Weakness and paresthesias localised in the lower limbs coexisted although EMG was normal. Blood tests showed: increase of transaminases (ALT 357 UI/ml; n.v. <40), platelets 112.000/ml; positivity of HBs antigen, anti-HBc and anti-HBe antibodies, HBV-DNA 663.000 UI/ml. A type II MC (by immunefixation method) and a cryocrit of 6% were also detected. ANA, anti-ENA antibodies, anti-DNA antibodies, and ANCA were absent. High levels of RF and lowered C4 were persistently found. Echotomography of the abdomen disclosed a picture suggestive of fatty liver. Entecavir was prescribed at the dose of 0.5 mg/daily. It was preferred to lamivudine in order to reduce the onset of viral resistance. A significant reduction of viraemia and disappearance of cryoglobulins from serum were obtained after only 1 month of therapy. After a further month, purpura completely remitted. Transaminases, platelets, RF, C4 and viremia normalised in 12 months. Purpura remains in sustained remission. Cryoglobulins are absent in serum.

As for the HCV-related cryglobulinaemic vasculitis, our experience and other few data published on this topic demonstrates that HBV-related cryoglobulinaemic purpura favourably responds to antiviral treatment with nucleoside/nucleotide analogues, also when resistant to interferon which was not able to induce a virological response; however, studies based on large series of patients are needed. Difficulties concerning the use in chronic administration of these molecules are related to costs, patient compliance and possible long-term side effects.

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Competing interests: none declared.

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