Persistent HCV-associated Cryoglobulinemic Vasculitis Following Virus Eradication after Direct-Acting Antivirals Therapy

M. Artemova, D. Abdurakhmanov, T. Ignatova, N. Mukhin.

To the Editor:

We read with great interest the article by Gragnani and Visentini et al., which shows that the majority of patients with hepatitis C virus (HCV)-associated mixed cryoglobulinemia vasculitis (MCV) treated by direct-acting antivirals (DAAs) achieved a sustained virological response (SVR) and complete clinical and immunological remission [1].

Several recent studies show a dissociation between virological and clinical responses to treatment with different interferon-free antiviral regimens [2, 3]. Here, we report a group of cases that demonstrate persistent mixed cryoglobulinemia (MC) or MCV after DAA treatment.

Nine HCV-positive Caucasian patients (females, mean age 59 years old, range 49-66 years) were consecutively recruited at the Hepatology Department of Tareev Clinic for Nephrology, Internal and Occupational diseases, Moscow, Russia. Four patients had asymptomatic cryoglobulinemia, and five had moderate-stage MCV. Between January and November 2015, the patients started anti-HCV treatment with DAAs (five patients - asunaprevir+daclatasvir, four patients - sofosbuvir+daclatasvir for 24 weeks). Therapy was well tolerated, and no severe adverse events occurred. The rate of SVR12 was 100%. The clinical efficacy and virological response were evaluated during a post-therapy follow-up of at least 20 weeks.

We found no correlation between the virological response and cryoglobulins production. Three patients (of four) still exhibited asymptomatic cryoglobulinemia. Five patients had moderate-stage MCV; therefore, we did not propose addition of rituximab (RTX) concurrently with DAA treatment. Meanwhile, persistence of MCV was observed in two patients. One patient experienced a reappearance of severe skin purpura with ulceration and a 50% cryocrit level increase compared to the pretreatment level at 8 weeks after treatment. The other patient with moderate-stage MCV also demonstrated no improvement, including: skin lesions, high MC serum levels and a 30-fold rheumatoid factor increase after 36 weeks of follow up. We particularly focused on searching for malignant B-cell

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/hep.28981

lymphoproliferative disease as one of the reason for the persistence of MC and MCV, which was later ruled out.

According to the recommendations, RTX should be considered when treating patients with severe HCV-associated MCV, i.e., active glomerulonephritis, skin ulcers or refractory peripheral neuropathy [4]. However, persistent vasculitis symptoms observed in moderate MCV patients after successful HCV treatment, suggest that therapeutic approaches for this subgroup of patients require further improvement to achieve a complete clinical response.

1. Gragnani L, Visentini M, Fognani E, Urraro T, De Santis A, Petraccia L, et al. Prospective study of guideline-tailored therapy with direct-acting antivirals for hepatitis C virus-associated mixed cryoglobulinemia. Hepatology 2016;64:1473-1482.

2. Sollima S, Milazzo L, Peri AM, Torre A, Antinori S, Galli M. Persistent mixed cryoglobulinaemia vasculitis despite hepatitis C virus eradication after interferon-free antiviral therapy. Rheumatology (Oxford) 2016; 55:2084-2085.

3. Cornella SL, Stine JG, Kelly V, Caldwell SH, Shah NL. Persistence of mixed cryoglobulinemia despite cure of hepatitis C with new oral antiviral therapy including direct-acting antiviral sofosbuvir: A case series. Postgrad Med 2015;127:413-7.

4. Pietrogrande M, De Vita S, Zignego AL, Pioltelli P, Sansonno D, Sollima S, et al. Recommendations for the management of mixed cryoglobulinemia syndrome in hepatitis C virus-infected patients. Autoimmun Rev 2011;10:444-54.