Cryoglobulinemic vasculitis in the era of direct-acting antiviral drug

We thank Moiseev et al for their interest in our work regarding sofosbuvir and ribavirin in hepatitis C virus (HCV)-associated mixed cryoglobulinemia vasculitis (VASCUVALDIC study)1 and to bring new elements for discussion.

Moiseev et al emphasise that treatment with immunomodulatory or immunosuppressive therapy (including rituximab) may have contributed to the impressive results of the VASCUVALDIC study. We have to stress that with the advent of new direct-acting antiviral (DAA) drugs (ie, sofosbuvir plus ribavirin), up to 87.5% of patients achieved complete clinical remission while only 17% of patients required the use of rituximab and glucocorticosteroids associated with antiviral therapy.1 In comparison, first-generation protease inhibitors (telaprevir or boceprevir) plus peginterferon and ribavirin allowed 70% complete clinical remission with 43% of patients requiring the use of immunosuppressants associated with antiviral therapy.2 So, this clearly shows that DAAs reduce the need for glucocorticosteroids and immunosuppressants and with higher efficacy. However, we still recommend the use for immunosuppression in patients with severe cryoglobulinemia glomerulonephritis or nervous system disease. Our results demonstrate a rapid virological response and clinical improvement. The HCV viral load dropped dramatically within 4 weeks of treatment, and 83% of patients had undetectable HCV RNA at week 8, a typical feature found with DAA agents. A rapid clinical improvement of cryoglobulinemia vasculitis symptoms was simultaneously achieved.

We agree with Moiseev et al that long-term follow-up of patients with HCV cryoglobulinemia vasculitis is crucial. In VASCUVALDIC study, one clinical relapse was observed in a patient who was virological relaper.3 After long-term follow-up, we observed only one additional relapse in a patient who developed purpura despite a sustained virological response. There was no evidence of B cell lymphoma. The purpura resolved spontaneously.

DAA offers many other advantages. Their safety profile is much better than previous anti-HCV regimen. Serious adverse events were observed in 8% of patients treated with sofosbuvir and ribavirin.4 By comparison, treatment with peginterferon and ribavirin5 and more recently with first-generation protease inhibitors (boceprevir or telaprevir) in combination with peginterferon and ribavirin2 had shown very high rates (up to 50%) of serious side effects. Interferon α has also well-known potential to exacerbate autoimmune disease states and to induce vasculitis in some patients.4 5 DAAs allow a short treatment duration (usually 12 weeks and up to 8 weeks in selected patients), convenience (as few as one pill a day), a very high response rate and a favourable safety profile with few adverse events. Therefore, DAAs (without ribavirin) may increase the tolerance profile and response rates in cryoglobulinemia vasculitis and should be the basis of therapy in these patients.

Whether rituximab will continue to play an important role in the treatment for HCV-associated cryoglobulinemia vasculitis, particularly in severe kidney or nervous system disease is still an open question? Gragnani et al6 have recently reported 44 consecutive patients with HCV-associated cryoglobulinemia vasculitis treated by sofosbuvir-based DAA therapy (individually tailored). All 44 patients were virological responders and 93% improved clinically. Rituximab was only used in 4.5% of cases in a recent Italian study. The results from VASCUVALDIC 2 study (NCT02856243) will provide important information regarding this point.

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