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Editorial: interferon-free DAAs are a great boon for patients with hepatitis C and cryoglobulinaemia—Authors' reply

We would like to express our gratitude to Drs Atsukawa and Tsubota for their comments and the correct interpretation of the main messages that may be deduced from our study,[1,2] especially concerning the future challenges in the treatment of cryoglobulinaemic vasculitis (mixed cryoglobulinaemia syndrome, MCS), a HCV-related disease that is often under-estimated and not sufficiently known.[3]

The occurrence of MCS represents a condition that justifies careful prioritization of Interferon-free anti-HCV treatment. This appears to be the most effective as soon as it is carried out, whereas, when the therapy is too late and the patients have already developed severe damage (especially renal), MCS requires careful evaluation and accurate tailoring of non-aetiological therapies (e.g, anti-inflammatory and immunosuppressant) to be performed before, but also after, and sometimes concomitantly with anti-viral therapy.

The complex pathogenetic cascade that underlies this lymphoproliferative disorder, and that originates from the clonal expansion of specific B-cells (RF-B cells), may lead to the subsequent overcoming of points of no return whose identification would be important for the assessment of a rational approach to the patients. Above all, in case of the persistence of MCS symptoms and/or signs, it would be important to distinguish the causes indicating the risk of evolution of the lymphomagenetic process (the overcoming of points of no return), from those without this risk, such as the simple occurrence of irreversible tissue damage.[4]

In this light, it seems conceivable that a key factor for the correct interpretation of the persistence of MCS stigmata even after viral eradication, is the evaluation of the persistence of B cell clonal expansion. Various factors have been suggested as playing a key role in inducing clonal expansion, first the important and sustained activation of the B-cell compartment by both viral and host factors. Among the latter, special emphasis was placed on the binding of the viral E2 protein and the CD81 molecule on the surface of the B cells[5] and the effect of the B-cell-activating factor (BAFF)/B-lymphocyte stimulator (BLyS), especially in subjects harbouring particular genetic variants.[6] Such an important and persistent B-cell activation would cooperate to the lymphomagenetic process with B-cell anti-apoptotic factors including, first, the t (14; 18) translocation[7] and could possibly be correlated with an exhaustion of the B cells observed during MCS.[8] Consequently, it seems conceivable that the detection of persistent B cell expanded clones through sensitive methods, after HCV eradication, could help in understanding the condition that we are facing; this would be helpful in deciding the best approach to the patient (more frequent follow-ups and/or specific therapies).

In conclusion, following the demonstration of the positive effect of viral eradication in MCS patients, the most important future challenge is the identification of markers useful in assessing the best approach to patients that maintain clinical and/or immunological MCS stigmata after SVR.

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LINKED CONTENT

This article is linked to Gragnani et al and Atsukawa and Tsubota papers. To view these articles visit https://doi.org/10.1111/apt.14845 and https://doi.org/10.1111/apt.14899.

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Editorial: surviving your genes—the role of *PNPLA3* variation in end-stage liver disease

Nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) not only represent leading causes of chronic liver damage[1,2] but share significant pathophysiological pathways of disease.[3] Current evidence suggests that NAFLD has ostensibly incremented not only the burden of long-term complications of end-stage liver damage, including cirrhosis and hepatocellular carcinoma, but also liver- and non-liver-related mortality.

While it is difficult to accurately predict which NAFLD patients will clinically evolve more dramatically, it is clearly known that the presence and severity of liver fibrosis[4,5] are major determinants of the natural history of the disease. Other concurrent factors that may modify the clinical course of NAFLD predisposing to more aggressive and severe damage include age, sex, ethnicity, comorbidities, and genetic and epigenetic factors (Figure 1). The weight of each of these factors in determining the risk of progression to cirrhosis and decompensation in either NAFLD or ALD is only partially understood, particularly the size of the effect of the genetic influence.

In a recent issue of *AP&T*, Mandorfer and colleagues retrospectively evaluated the impact of the missense *PNPLA3*-rs738409 C>G variant on liver-related mortality in a cohort of patients with different underlying diseases and portal hypertension at the time of diagnosis.[6] The authors observed that homozygous status of the risk G-allele (rs738409-GG) substantially increased mortality rates among patients with NAFLD/ALD two-fold without influencing survival rates in patients with viral hepatitis. Altogether, these interesting results require some reflection. First, mortality rates were significantly influenced by *PNPLA3* variant only in the recessive model of inheritance, indicating that two copies of the G-allele seem to be required for increasing the risk of death. One might presume, however, that owing to the small sample size of the included cohort, the effect of the variant under the additive model, which is the model that has been largely replicated as a modifier of the presence of NASH and fibrosis,[7] could not be properly assessed. Second, while the authors have correctly adjusted their results by competing covariates, one might still argue what the specific role of *PNPLA3* variant is in determining mortality rates as the variant is undeniably a strong modifier of the severity of liver steatosis and fibrosis - the initial and final outcomes, respectively (Figure 1). The lack of association between the variant and a surrogate of steatosis may indicate the loss of a substantial proportion of functional organ mass in these patients with end-stage hepatic disease. In this particular scenario, it is difficult to explain the lack of effect of the *PNPLA3* variant on mortality due to viral hepatitis.

Finally, one might speculate that higher mortality rates in NAFLD/ALD are indeed explained by yet unexplored gene-by-gene interaction(s) with variant(s) located in gene(s) that may potentially modify the course of cirrhosis and portal hypertension, then amplifying the presence of deadly complications. For example, regulators of hepatic and systemic vasomotor activity, hemodynamic circulation and vascular remodelling, such as members of the angiotensin system,[8] might open further avenues for exploration novel gene-gene interaction networks and therapeutic options.

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