While \textit{IFNL4} variant was strongly associated with a sustained virological response in both HCV genotypes 1 and 4, and thus confirmed previous findings by Prokunina-Olsson \textit{et al.} and Bibert \textit{et al.}, the study confirms a strong linkage between ss469415590 and rs12979860 variants ($\rho = 0.988$) compared with the modest correlation between rs8099917 and \textit{IFNL4} ($\rho = 0.598$). These findings therefore do not support an additional clinical benefit of \textit{IFNL4} in the prediction of a response to PEG/ RBV in Caucasian patients.

Recently, the finding that recombinant \textit{IFNL4} protein exerts a potent antiviral activity against both HCV and human coronaviruses\cite{1} works against the assumption that the same protein does inhibit clearance of HCV, i.e. negatively interfering with HCV infection, while being endowed with a strong anti-HCV activity. This suggests the existence of a complex relationship between \textit{IFNL4} and HCV in humans, similar to that recently described for IFN-1 and lymphocytic choriomeningitis virus in mice,\cite{2} where chronic IFN-I signalling due to persistent infection drives immunosuppression and disease progression.

Although validation studies in large cohorts of patients, like the one investigated by Stättermayer \textit{et al.},\cite{1} may help understand the clinical utility of \textit{IFNL4}, these studies have so far failed to demonstrate any causal relationship between \textit{IFNL4} protein and nonresponse to interferon therapy in chronic HCV patients. Among other approaches, the assessment of the missense variants previously described in the \textit{IFNL4} coding region,\cite{2} may help unravel this issue.

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**Letter: does the \textit{IFNL4} gene discovery really provide a causal role for the \textit{IL28B} haplotype blocks? Authors’ reply**

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Sirs, We thank Dr Galmozzi and Dr Lampertico for their comment on our recently published paper on the effect of the dinucleotide frameshift variant in ss469415590 in the interferon (IFN)-\textit{\lambda} gene on interferon/ribavirin treatment and its relationship with the two commonly used single nucleotide polymorphisms (SNP) in \textit{IL28B} (rs12979860, rs8099917).\cite{1,2}

We agree that our study does not provide insights on the causal relationship between \textit{IFNL4} and treatment response in patients with chronic hepatitis C virus (HCV) infection. Nevertheless, our study was designed to investigate the clinical usefulness of the different SNPs in \textit{IL28B} and \textit{IFNL4} in a large cohort of Caucasian patients infected with chronic HCV.

Hamming \textit{et al.} demonstrated that \textit{IFNL4} encodes an active type III interferon with potent anti-viral activity against both HCV and coronaviruses.\cite{3} Galmozzi and Lampertico therefore conclude that this strong anti-viral activity works against the assumption of an inhibition of the \textit{IFNL4} protein of treatment-induced HCV clearance. We would like to remind them that up-regulation of intrahepatic interferon-stimulated genes (ISG) is associated with treatment failure in patients with chronic HCV, and levels of ISG are differentially distributed according to different \textit{IL28B} genotypes.\cite{4} Furthermore, Prokunina-Olsson and her collaborators demonstrated that \textit{IFNL4} induces ISG expression in HepG2 hepatoma cells.\cite{5} Thus, high baseline ISG levels might be associated with poor response to exogenous IFN, by exhausting the IFN response pathways.\cite{6}
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Finally, we agree that the causal role of IFNL4 genotypes for viral clearance is conflicting, and further studies need to be performed to elucidate the molecular mechanistic relationship.

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Letter: the irony of oral iron – not an underdog for post-gastrointestinal bleeding anaemia

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Sirs, Bager et al.1 reported a randomised controlled trial comparing oral (100 mg twice daily ferrous sulphate for 3 months) or intravenous (1000 mg ferric carboxymaltose, single-dose infusion) iron supplementation and placebo for anaemia after nonvariceal upper gastrointestinal (GI) bleeding. Peptic ulcers were the most common sources of bleeding (70%).

Patients in the placebo group prematurely discontinued the study medication because 25% of patients were still anaemic at the end of the 13-week follow-up period and, therefore, required rescue therapy. The study shows that either oral or intravenous were significantly more effective than placebo to overcome anaemia, and iron stores were more effectively replenished with intravenous iron when compared with oral.

On reading the abstract, one may tend to think the results were foreseeable, but this study deserves a higher consideration. The first important conclusion we can draw is that no patient should be discharged after upper GI bleeding without iron supplementation whenever anaemia is present. Although logical, this protocol is not applied in routine daily practice, and had been seldom addressed in the literature.

Intravenous iron did not lead to better results at week 1, 4 or 13 when compared with oral supplementation, even though only 56% had complete adherence to oral therapy. At the very least, these findings seem counterintuitive. Whether the efficacy of oral iron was related to higher intestinal absorption because of few patients on proton pump inhibitor therapy (17%), even though peptic ulcer was the most common cause of GI bleeding, remains unknown. In addition, oral iron is notably cheaper.

This study highlights the importance of iron supplementation after post-bleeding anaemia, with a clear cost-effective advantage for oral administration, but with similar results for the intravenous route in case of oral iron intolerance. The results are especially relevant given that restrictive transfusion strategies for upper GI bleeding (transfusion when haemoglobin level <7 g/dL) have been associated with better outcomes for nonvariceal upper GI bleeding.2 In this context, most patients will be expected to be anaemic at discharge, and this study sheds light on the optimal short-term clinical management regarding iron supplementation.

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