Reply to: "The "pegylated" story continues – Perhaps because both ends (α2a and α2b) are true?"

To the Editor:
We thank Professors Reiberger and Peck-Radosavljevic for their comment to our article [1], and generally agree with them that results coming from any post hoc analysis need to be interpreted with caution. With respect to our sub-analysis of the MIST study [2], the main concerns mostly rely on the lack of stratification for fibrosis stage in the randomization process, as well as the lack of data on the Interleukin 28B (*IL28B*) genotype. Indeed, at the time of preparation of the manuscript we had not run the *IL28B* test in the entire study cohort, but are now able to provide the complete results for the cohort of HCV-1 and 4 patients, a patient population where the *IL28B* genotype has been shown to be a strong predictor of treatment outcome [3–5]. The prevalence of the non-responsive T allele of the rs12979860 single nucleotide polymorphism did not differ between the two treatment regimens (α2a: 76% *vs.* α2b: 72%). The same was true even when patients were divided into those with a staging <3 (α2a: 81% *vs.* α2b: 66%), and those with a staging ⩾3 (α2a: 72% *vs.* α2b: 76%) (Table 1). When SVR rates were analyzed by combining the staging score and the *IL28B* genotype, they were consistently higher in patients receiving PegIFNα2a, reaching statistical significance in the T allele patients with advanced fibrosis (α2a: 34% *vs.* α2b: 8%; *p* = 0.003) (Table 1). This information further supports that, at least in our study, the PegIFNα2a regimen was generally more effective than the PegIFNα2b regimen in the most difficult-to-cure patients, such as those with advanced fibrosis and unfavorable *IL28B* genotype, while the two regimens were somewhat similar in terms of SVR rates in patients with baseline factors predictive of treatment success. We can reasonably exclude PegIFN/RBV dose reductions or treatment discontinuations to have played a role in our results, as they did not differ between the regimens even when analyzed on the basis of degree of fibrosis, as already discussed in detail in our paper. Indeed, the higher prevalence of treatment discontinuations in the PegIFNα2b arm was actually the consequence of more patients failing to respond on-treatment, and thus meeting the week 12 or 24 stopping rules, compared to the PegIFNα2a arm (α2a: 13% *vs.* α2b: 23%). In fact the discontinuation rates for non-virological reasons were similar between the two regimens (α2a: 8% *vs.* α2b: 10%).

In conclusion, although we do not have a clear-cut answer as to why the PegIFNα2b regimen was associated with hypo-responsiveness in patients with advanced fibrosis, and can only speculate that it might be for the different pharmacokinetic parameters of the two PegIFNs [6], we can certainly exclude skewed distribution of the *IL28B* genotype as well as reduced patients' compliance to be the culprits.

Conflict of interest

References

[1] Prati GM, Aghemo A, Rumi MG, D'Ambrosio R, De Nicola S, Donato MF, et al. Hyporesponsiveness to Pegifnα2b plus ribavirin in patients with hepatitis C-related advanced fibrosis. J Hepatol 2012;56:341–347.

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[3] Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance. Nature 2009;461:399–401.

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[5] De Nicola S, Aghemo A, Rumi MG, Galmozzi E, Valenti L, Soffredini R, et al. Interleukin 28B polymorphism predicts pegylated interferon plus ribavirin treatment outcome in chronic hepatitis C genotype 4. Hepatology 2012;55:336–342.

[6] Aghemo A, Rumi MG, Colombo M. Pegylated interferons alpha2a and alpha2b in the treatment of chronic hepatitis C. Nat Rev Gastroenterol Hepatol 2010;7:485–494.

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Table 1. Sustained virological response rates in HCV-1 and 4 patients.

	PegIFNα2a + RBV (n = 108°)	PegIFNα2b + RBV (n = 113)	*p**
Staging 0-2			
IL28B CC	7/8 (88%)	11/17 (64%)	0.3
IL28B CT/TT	13/35 (37%)	11/33 (33%)	1
Staging 3-6			
IL28B CC	16/18 (89%)	10/15 (67%)	0.2
IL28B CT/TT	16/47 (34%)	4/48 (8%)	0.003

°One patient could not be tested for *IL28B* rs12979860 genotype.
*Fisher exact probability test.