Letter

Physician do no harm

Stephen Cameron1*

1International Medical Press, London, UK

*Corresponding author e-mail: stephen.cameron@intmedpress.com

Before the advent of direct-acting antivirals (DAAs), the sustained virological response (SVR) rate achieved with pegylated interferon-α (PEG-IFN) and ribavirin (RBV) in previously treatment-naive, genotype 1 HCV-infected patients was typically around 40–54% [1]. Recently, a number of studies evaluating combinations of DAAs for the treatment of genotype 1 chronic HCV infection have shown significantly improved efficacy compared with PEG-IFN/RBV. In the ELECTRON study, evaluating the combination of the nucleotide analogue GS-7977 and RBV, 100% of treatment-naive patients cleared the virus after only 12 weeks of treatment and 88% maintained this response 4 weeks later. In contrast, in patients classified as null-responders to previous PEG-IFN/RBV therapy (<2 log10 IU/ml decline in HCV RNA after 12 weeks of treatment), although the end-of-treatment response was still 100%, only 11% were able to maintain this response 4 weeks after the end of treatment [2]. This reduced response to DAA combinations in patients previously treated with PEG-IFN/RBV was also seen with the combination of ABT-450/ritonavir plus ABT-333; sustained virological response 12 weeks after cessation of treatment (SVR12) was achieved in more than 90% of treatment-naive patients but in only 47% of prior partial or null-responders to previous PEG-IFN/RBV therapy [3].

Why should this be? If it was because of a poor or altered endogenous interferon response in some patients and this was somehow critical to achieving an SVR then this would also be evidenced in a proportion of those treatment-naive patients treated by DAAs and 100% SVR would be impossible to achieve. As this is not the case, is it possible that treatment with PEG-IFN/RBV is somehow affecting either host or viral factors that subsequently reduce the response to therapy? For example, is it possible that PEG-IFN and/or RBV somehow impair the immune system, or could they affect the virus so that it is more refractory to clearance? This latter possibility would seem less likely since such a change in viral characteristics would be apparent over time, and none has been seen to date.

Another clue to what is happening is perhaps evidenced by the results from the registration trials for telaprevir. One arm of the Phase III REALIZE trial had a 4-week lead-in with PEG-IFN/RBV before the addition of telaprevir, whereas patients in other study arms commenced treatment with the triple combination. Those patients who had the lead-in strategy were found to have a slightly worse SVR compared with those who had triple therapy from the start [4].

It would seem possible therefore that, in a proportion of patients with HCV infection, treatment with PEG-IFN/RBV somehow impairs the immune system and, as a result, they will subsequently respond less well to DAA combinations.

Disclosure statement

The author declares no competing interests.

References