

APCs are good targets for development of vaccine adjuvants or immunotherapy.

Conflict of interest

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Renal impairment and anemia during triple therapy

To the Editor:

We read with great interest the recently published review by Romero-Gómez and colleagues concerning the management of anemia induced by triple therapy in patients with chronic hepatitis C [1]. In their work, authors thoroughly discuss about pathophysiological mechanisms responsible for the anemia observed during triple therapy with telaprevir or boceprevir, remark baseline and on-treatment factors predictive of more severe anemia, and propose a sequential strategy to manage anemia based first on ribavirin dose reduction and then on epoetin administration. We strongly agree with the authors that anticipation of anemia, which is based mainly on the knowledge of predictive factors, is among the essential requisites for a tailored approach to patient monitoring and management. In this regard, we consider that the issue of a possible renal impairment during triple therapy with telaprevir or boceprevir, which is associated with a more severe degree of anemia, deserved to be mentioned in an updated review on this item. Indeed, simultaneously or right after the publication of the work by Romero-Gómez *et al.*, several papers have been published concerning a possible renal impairment during triple therapy with telaprevir or boceprevir

[2–5]. While a decline of renal function was not reported as a safety issue in clinical trials with any of the two drugs [6–9], cases of renal failure were firstly signaled in the French early access program [10]. More recently, in a large cohort of patients undergoing triple therapy, Mauss *et al.* reported a week 12 incidence of renal insufficiency stage 3, i.e., estimated glomerular filtration rate (eGFR) <60 ml/min, of 6.6% in patients treated with telaprevir and of 4.7% in patients treated with boceprevir [2]. Patients with a drop of eGFR <60 ml/min had a higher absolute decrease in hemoglobin and a lower week 12 hemoglobin level [2]. Independently from the development of overt renal failure, Kapeluszniak *et al.* reported a mean maximal change of eGFR of –22 ml/min with respect to baseline in a group of 72 patients analyzed at different time points during triple therapy with boceprevir [3], Fukuda *et al.* observed a rapid decline of eGFR in 25 patients in triple therapy with telaprevir [baseline: 84.8, week 1: 69.9 ml/min, *p* <0.001] [4], and Karino *et al.* reported an almost identical mean drop of eGFR at week 1, which was substantially stable at the subsequent time points, in 68 patients in triple therapy with telaprevir [baseline: 85.8, week 1: 69.6, week 4: 69.2, week 12: 72.5 ml/min] [5]. In the latter study, at week 1,

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there was a significant positive correlation between delta eGFR and ribavirin serum concentration, and the ribavirin serum concentration at week 1 was negatively correlated with the Hb levels from week 2 to week 8 [5]. Although the exact mechanisms are still not completely understood, all together, these data suggest that telaprevir and boceprevir can impair renal function early in the course of triple therapy for hepatitis C infection, and that this impairment can lead to ribavirin accumulation and can explain, at least in part, the higher rates of anemia observed in triple vs. double therapy. On the base of these evidences, we think that renal function should be assessed not only before, as already recommended, but also early after the beginning of triple therapy (1–2 weeks), that those patients experiencing a decline of eGFR should be strictly monitored, and that an early reduction of ribavirin dose should be strongly considered at least in patients experiencing a reduction of eGFR to <60 ml/min.

Conflict of interest

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Reply to: “Renal impairment and anemia during triple therapy”

To the Editor:

We appreciate the comment by Vespasiani-Gentilucci *et al.* about renal impairment and anemia during hepatitis C treatment with protease inhibitors. We agree with the authors that renal impairment is a growing concern in these patients, although the prevalence of estimated glomerular filtration rate (eGFR) <60 ml/min does not seem to be significantly high with these drugs (6.6% with boceprevir and 4.7% with telaprevir [1]). Additionally to protease inhibitors, older age, arterial hypertension, high baseline serum creatinine as well as type 2 diabetes mellitus were found to be associated with anemia [2]. Probably, the link between these factors and anemia is the appearance of renal impairment [3]. Indeed, the mechanisms involved in renal impairment with protease inhibitors remain poorly understood. Significant inhibition of some human renal drug transporters that could influence ribavirin serum concentration has been described with telaprevir [4]. This has been correlated with delta eGFR [5]. Telaprevir though has shown an acceptable tolerability in haemodialyzed patients who were listed for kidney transplantation, managing successfully anemia with erythropoietin and ribavirin dose reductions [6]. On the other hand, mean boceprevir concentration

was comparable in patients with end-stage renal disease and in healthy subjects [7]. In conclusion, there is a mild risk of renal insufficiency stage 3 with protease inhibitors that could be responsible, at least in part, of the anemia that develops during triple therapy. Thus, renal function should be closely monitored to anticipate the appearance of anemia.

Conflict of interest

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