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Editorial

Micro-elimination of hepatitis C virus infection in β-Thalassaemia major patients: Positively moving towards the World Health Organisation 2030 eradication goal

Treatment of chronic hepatitis C virus (HCV) infection has been completely revolutionised by the advent of direct acting antivirals (DAAs), making universal therapy-induced viral clearance possible and independently of previous negative predictive factors for treatment response such as viral (genotype and load) and host (genetic predisposition, liver disease stage, presence of comorbidities, previous treatment failures) characteristics [1]. These dramatically positive results have enabled clinicians – at various levels – to observe regression of liver fibrosis, to record clinically meaningful reductions in portal hypertension, and to delist patients from liver transplantation waiting list [2–4]. Moreover, despite earlier contrasting results, more recent comprehensive evaluations have clearly demonstrated that successful viral clearance is also associated with a decrease in the rate of hepatocellular carcinoma development and recurrence [5,6].

In Italy, at the time of writing, more than 160,000 patients with HCV have been treated with DAAs since the advent of this therapy, and the current treatment rate is almost 60,000 patients *per* year [7]. Given a country prevalence of HCV infection of approximately 1.7%, according to latest published estimates, Italy should theoretically be able to reach the World Health Organisation goal of HCV infection confinement, or elimination, by the 2030 deadline [7,8]. However, confinement of HCV does not only go through treatment of patients with known infection, and identification and linkage to care of subjects who were previously unaware of being infected, but also through the a process of micro-elimination, that is targeting discrete populations such as people who inject drugs, prisoners, physicians and nurses, patients on renal replacement therapy, where eradication of infection can actually be obtained within a reasonable short period of time, and where the positive message of HCV elimination may foster activity at the population level [9,10].

In this issue of *Digestive and Liver Disease*, Ponti et al. report the results of their effort following the micro-elimination policy, as they managed to eliminate HCV infection in one of the largest community of patients with β-thalassaemia major in Europe [11]. Indeed, β-thalassaemia major patients do represent a population with a well-defined source and period of infection, with a negligible risk of re-infection, where there are several comorbidities – such as iron overload and diabetes – that may accelerate liver fibrosis progression and that were relevant negative factors for interferon and ribavirin treatment, thus leaving a large proportion of the thalassaemic community still viraemic due to inadequate response to previous antiviral therapies [13]. Moreover, β-thalassaemia major patients may have a greater than standard risk of developing hepatocellular carcinoma due to transfusion-related iron overload and hepatitis viruses co-infection, and might have competing causes for death besides liver disease [12]. Overall, the results of the Ponti et al. study showed that DAA treatment was able to cure HCV infection in 96.9% of β-thalassaemic patients who completed the first course of treatment, and that the only 3 patients who showed viral relapse were successfully re-treated, thus reaching a 100% Per-Protocol sustained virological response rate [11]. Noteworthy, besides obtaining likely universal aminotransferases normalisation, after a mean follow-up of almost 2 years, none of the patients developed hepatocellular carcinoma, and despite only a minority of patients had symptomatic cryoglobulinaemia, after successful treatment cryoglobulins disappeared in 69% of patients, a finding that may be related to the presence of a more subtle and heterogeneous genetic and/or immunological background [11,14,15]. Most importantly, the authors demonstrated that DAAs treatment is safe also in this peculiar population where the presence of comorbidities and polypharmacy may be associated with a greater likelihood of potential side effects or drug-drug interactions. In particular, the authors found no interactions between DAAs and iron-chelating agents, and no increase in the need for blood transfusions was observed during treatment. These positive aspects notwithstanding, two patients – both cirrhotics – died despite HCV RNA negativity, a further reminder that in some patients viral clearance is not able to modify the natural history of disease: despite these small numbers, the authors unfortunately do not report further information regarding these patients, such as the Model for End-stage Liver Disease score, thus not allowing the reader to evaluate whether these patients might have been beyond the "point-of-no-return" [16–18].

What are the main messages delivered by this study? Overall, the study results — obtained in the largest single-centre population of HCV positive β-thalassemia patients treated with DAAs, clearly show that micro-elimination of HCV infection is feasible and gen-

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erally safe even in difficult-to-treat patients. Moreover, they do confirm previous efficacy results obtained in multi-centre studies that included patients with less advanced liver disease, without identifying any signal of potential increase in liver carcinogenesis even in a population where cirrhosis was present in one out of four treated patients [11,19].

To conclude, we feel that Ponti et al. should be commended for their clinical and scientific effort, as their activity is the best demonstration that micro-elimination of HCV is obtainable and may enhance the efforts put in place by the stakeholders and physicians so as to reach the World Health Organisation goal of HCV elimination by 2030. For patients with β-thalassaemia, further follow-up is needed to assess whether HCV eradication in this fragile population may also be associated not only with a consistent reduction in hepatocellular carcinoma development but also with a decline in liver-related mortality and other, solid end-points such as decrease in all-cause mortality.

Conflict of interest

Edoardo G. Giannini, no conflict of interest to declare.

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