Mortality associated with the treatment of HCV with direct-acting antivirals

We read with interest the study by Welzel *et al*[1] confirming the high efficacy of oral direct-acting antiviral agents (DAAs) for the treatment of chronic HCV infection.[2] Results about safety are less clear, since in these patients who have a high risk of hepatic decompensation or death within 12 months, the rate of death was 7.8% during treatment and the 12 weeks post-treatment. These deaths and most safety events were associated with advanced liver disease and not considered treatment related. The largest phase III studies (COSMOS, ION1 and ION3, SAPPHIRE) did not report any death during DAA treatment and severe adverse events occurring during therapy were considered to be unlikely related to DAAs.[3] In real-life clinical settings, mortality has been observed in around 0.5% (0.3% for the French ANRS CO22 HEPATHER cohort and 0.6% for the US TARGET cohort).

In our tertiary care centre (part of the CO22 HEPATHER cohort), we have treated 996 patients, including 400 (40%) with cirrhosis, with a DDA-based regimen and 91.5% of patients achieved a sustained virological response (SVR12).

Twelve deaths (1.2%) occurred during the treatment or the 12-week post-treatment period (table 1), a prevalence lower than the 2.2% mortality reported in the Cupic study targeting only a cirrhotic population treated by pegylated interferon, ribavirin and a first-generation protease inhibitor. The median age at death was 68 (IQR, 63–71) years; seven patients (58%) were males, eight (66%) had cirrhosis, including six with a Child-Pugh score B or C. Six deaths (50%) occurred under DAA treatment and six during the follow-up. Four patients (33%) died from a liver-related event (one with hepatocellular carcinoma (HCC) and three with end-stage liver disease (ESLD)). In one of them, with a Child-Pugh score B, ESLD and consequent death were assumed to be likely related to the 6 weeks of ombitasvir+ritonavir+paritaprevir+ribavirin. We now know that protease inhibitors are contraindicated in decompensated cirrhosis. In three patients (25%) death was related to sepsis and in two (17%) patients death was related to haemorrhagic stroke, the risk of which is 2.5-fold higher in HCV infection with significant liver fibrosis. Finally, three (25%) patients died of sudden death at weeks 5, 8 and 12 under sofosbuvir-based treatment: one had a Child-Pugh score A cirrhosis with unbalanced diabetes and active smoking; one was a kidney allograft recipient with fibrosis F3 who was treated by amiodarone and had a pacemaker; the third patient had a F2 fibrosis and had a prior history of ischaemic heart disease, atrial fibrillation and a pacemaker.

Our data suggest that DAA-associated mortality is higher in real-life clinical

settings than in phase III clinical trials, and can be observed with any available DAA combination. One-third of mortality cases were related to sudden deaths in patients with elevated cardiac risk, including one amiodarone-treated patient. We have previously reported the risk of cardiac arrythmia in patients treated by sofosbuvir, with causality suggested by the timing of occurrence, the relapse on reintroduction of sofosbuvir and the pacemaker data.[4] The preclinical toxicology studies described heart degeneration and inflammation with over dosage of the main metabolite of sofosbuvir (GS-331007), and another NS5B HCV nucleotide polymerase inhibitor, BMS-986094, has been withdrawn due to an association with cardiomyopathy. This risk is not only restricted to amiodarone-treated patients[4] and particular attention should be applied when extending DAAs to any infected patient, especially in those with cardiac risks.

Anne Laurain, Laura Kramer, Philippe Sultanik, Anaïs Vallet-Pichard, Philippe Sogni, Stanislas Pol

Université Paris Descartes; APHP, Unité d'Hépatologie, Hôpital Cochin; INSERM U1223 and USM20, Institut Pasteur, Paris, France

Correspondence to Dr Anne Laurain, Département d'Hépatologie, Hôpital Cochin, 27 rue du Faubourg Saint Jacques, 75679 Paris Cedex 14, France; anne.laurain@aphp.fr

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