patients relapsed (Hezode *et al.*, 2016). Presence of simeprevir resistance associated variant polymorphisms (R155K or Q80K) at baseline did not predict retreatment failure.

The SLAM C randomized open-label study compared sofosbuvir plus ledipasvir with sofosbuvir plus simeprevir in acute hepatitis C virus infection (Basu *et al.*, 2015). Of the 15 patients treated with sofosbuvir plus simeprevir for 8 weeks, 93% achieved an SVR, but 100% of those given sofosbuvir plus ledipasvir for 4 weeks achieved SVR.

Cohort studies

In the TRIO cohort, 317 genotype 1 patients were treated with sofosbuvir plus simeprevir with or without ribavirin for 12 weeks (Dieterich *et al.*, 2015). Overall, 10 patients (3.2%) discontinued treatment; 4 of whom experienced adverse events. In a per protocol analysis overall SVR rates were 90% (263/292), 93% in treatment-naive patients, 87% in treatment-experienced patients, and 83% in cirrhotic patients. There were some slight nonsignificant differences between subtypes 1a and 1b, with SVR rates of 92% and 98% in treatment-naive, 88% and 84% in treatment-experienced, and 81% and 84% in cirrhotic patients, respectively.

In the TARGET cohort, 836 genotype 1 patients were treated with sofosbuvir plus simeprevir with ribavirin (169) or without ribavirin (667) (Sulkowski *et al.*, 2016). The overall SVR rate was 84% (83% in genotype 1a and 89% in genotype 1b). Subjects with cirrhosis, those with prior decompensation, or those with previous failure of protease inhibitor treatment were less likely to achieve an SVR: Model-adjusted SRV estimates for patients with cirrhosis were 80.5%; those for prior decompensation and previous protease inhibitors treatment were74%. The addition of ribavirin had no detectable effect on SVR. Serious adverse events and treatment discontinuation occurred in only 5% and 3% of participants, respectively.

In the French HEPATHER cohort, 551 patients (148 genotype 1a, 266 genotype 1b, and 119 genotype 4) were treated with sofosbuvir plus simeprevir with (11%) or without ribavirin for 12 (86%) or 24 (14%) weeks (ANRS/AFEF *et al.*, 2015). Most patients were cirrhotic (56%). SVR rates were somewhat disappointing: 83% in genotype 1a, 87% in genotype 1b, and 86% in genotype 4. There were no significant differences in SVR between those treated with ribavirin (92%) or without ribavirin (86%) and those treated for 12 weeks (85%) or 24 weeks (93%). Overall SVR rates were between 80% and 90%. Neither treatment extension nor addition of ribavirin seems to significantly increase the efficacy of the regimen, which had fair tolerability, with 6% of subjects having serious adverse events.

The same results were obtained in the French Real-life SimSof study conducted in academic, community, and private practice centers. A total of 203 genotype 1 and 4 patients were treated with the same basic regimen for 12 weeks (97%) (Nguyen-Khac *et al.*, 2015). Overall 92% of the patients achieves an SVR, 89% in cirrhotic and 96% in noncirrhotic patients.

Considering all the data, the combination of sofosbuvir plus simeprevir for 12 weeks for treatment of patients with genotype 1 and 4 appears, in both clinical trial and real life, to provide slightly suboptimal SVR results, with ~ 6% with adverse reactions in genotype 1 and 4 patients.

5. SOFOSBUVIR AND NS5A INHIBITORS

The combination of sofosbuvir with NS5A inhibitors is a very attractive combination due to the potency and the pangenotypic activity of both molecules and the high barrier to resistance of sofosbuvir. To date, sofosbuvir has been associated with 3 NS5A inhibitors (daclatasvir, velpatasvir, and odalasvir), all of which were active in all HCV genotypes (pan-genotypic), and one multi-genotypic inhibitor (ledipasvir) active against genotypes 1, 4, 5, and 6, but not 3.

5a. Sofosbuvir and daclatasvir

GENOTYPE 1

Pivotal studies

Sofosbuvir was initially evaluated in combination with daclatasvir (60 mg daily) with or without ribavirin for 12 or 24 weeks in 126 treatment-naive genotype 1 patients with mainly mild fibrosis in a phase II study (Sulkowski *et al.*, 2014a; Table 262.4). All patients treated for 24 weeks achieved SVR. Among those treated for only12 weeks, the SVR was 100% without ribavirin and 95% with ribavirin, with no on-treatment breakthrough. This combination for 24 weeks was also evaluated in 41 patients with mild to moderate fibrosis who had failed prior triple therapy with first-generation protease inhibitors (either boceprevir or telaprevir). All patients achieved SVR.

In a phase III open-label study, 60 patients with advanced cirrhosis and 53 patients with liver transplants who had a recurrence of HCV infection were treated for 12 weeks with sofosbuvir plus daclatasvir and ribavirin (Poordad *et al.*, 2016); 76% of the patients were genotype 1. Among the patients with advanced cirrhosis, SVR was achieved in 82% of the patients; by genotype; 82%, 80%, 83%, and 100% achieved SVR in genotypes 1, 2, 3, and 4, respectively. By Child-Pugh scores of A, B, and C, SVR was achieved in 92%, 94%, and 56% of patients, respectively. Among the liver transplant patients, SVR was achieved in 93% of the patients; in genotypes 1 and 3, SVR results were 95% and 91% (Poordad *et al.*, 2016).

Similar results were obtained in the ALLY-2 phase III study conducted in 151 HIV–HCV co-infected patients who were mostly genotype 1 (82%). These subjects were treated with sofosbuvir and daclatasvir for 8 or 12 weeks (Wyles *et al.*, 2015). Overall and genotype 1 SVR rates were 97% and 96.4% for those treated for 12 weeks and 76% and 75.6% for those treated 8 weeks. Among the 52 treatment-experienced, co-infected patients treated with the same combination for