Retreatment with Direct Active Antivirals of Genotype 1, 3 and 4 Chronic Hepatitis C Patients who Previously Failed an Anti-NS5A-Containing Regimen in Real World

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INTRODUCTION

Treatment with direct acting antivirals (DAAs) has shown high efficacy but a substantial proportion of patients (5%-15%) remains resistant to DAAs (1). As previously reported, treatment failure is generally associated with emergence of HCV resistance associated variants (RAVs) reducing susceptibility to DAA agents (1-5).

Recent guidelines recommend that patients who failed DAAs treatment with nonstructural protein 5A inhibitors (NS5A) should be retreated 24 weeks with Sofosbuvir (SOF) combined with either a protease inhibitor for those with NS5A RAVs, or with a NS5A inhibitor for those without NS5A RAVs (1, 6, 7). Little is known on real life retreatment of patients who had failed to achieve a sustained virological response (SVR) on previous NS5A-based therapy (1).

AIM

Our aim was to study retreatment according to baseline NS5A RAVs after first DAAs treatment failure.

PATIENTS & METHODS

Patients: From January 2014 to March 2016, 2955 HCV infected patients were treated with NS5A inhibitors in six French referent liver centers: 80 (2.7%) patients relapsed. This “real-world” study included 24 patients among these 80 patients who had failed to achieve SVR on previous NS5A-based therapy. These patients were retreated with different regimen combinations including SOF + Daclatasvir (DAC) ± Simeprevir (SM) (25%), SOF + Grazoprevir + Elbasvir (29%), SOF + Ledipasvir (8%), SOF + SM (17%), Ombitasvir (OBV) + Paritaprevir (PTV) + Ritonavir (RTV) + Dasabuvir (DS) ± SOF (21%), with or without RBV for all regimens. Antiviral efficacy was evaluated using the primary endpoints of SVR at weeks 4 and 12 post-treatment (SVR4, SVR12).

NS5A Sequencing: NS5A sequencing was performed using the DeepChek NS5A assay (ABL, SA, Luxembourg, Luxembourg). Prevalence of NS5A RAVs/polymorphisms was analyzed using Sanger sequencing, HCV subtype and drug-resistance interpretations were identified using DeepChek® software (ABL, SA, Luxembourg, Luxembourg). As recommended, the HCV resistance testing used in this study was based on population sequencing (reporting RAVs as “presumed RAV rate” with 10% cut-off).

RESULTS

Among the 24 retreated patients, 20 were males, median age was 54 years ([min-max 26-78], HCV genotype (GT) 1 in 17 cases (1a=10, 1b=7), GT3a in one case, GT4 in six cases. All 24 patients presented severe liver fibrosis (F3 to F4) among whom 16 had cirrhosis (F4) and two were HIV coinfected.

All patients achieved SVR with a HCV RNA below lower limit of quantification (<15 UI/mL) by the end of treatment.

Table 1: NS5A RAVs according to HCV genotype for first and second line of treatment

Among the 17 GT1 patients, 14 (82%) had at least one NS5A RAV at the time of failure, 18: SVR rates after retreatment of genotype 1 patients according to therapy regimen.

• Given the emergence and persistence of RAVs, retreatment of patients after a first failure to DAA therapy remains a challenge.

• The present study showed that, based on recommendations, retreatment of patients after a first NS5A-based regimen failure is effective (96% SVR).

• Table 2 reports findings of major real-world studies and clinical trials on retreatment of patients who failed a previous DAA-therapy. Our study included patients from our routine clinical practice presenting the advantage to study a more diverse population contrary to other clinical trials, which usually have restrictive inclusion criteria.

• This study on retreatment of patients after a first DAAs failure including a NS5A regimen is very encouraging.

• If guidelines are respected, the rate of success is high with the current available drugs. The upcoming regimens, either dual or triple therapy, may have similar results with shorter treatment duration.

• Baseline RAVs did not impact treatment outcome. However, despite the strong efficiency of this strategy of therapy, some very small limits can be observed in very few “difficult-to-cure” patients.

CONCLUSIONS

Table 1: Overview of the main real-world studies and clinical trials on retreatment of patients who failed a previous DAA-therapy

REFERENCES

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