DAA Treatment Failure in Chronic Hepatitis C - The Swiss Experience

1. Background

Hepatitis C virus (HCV) infection remains one of the most important causes of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC), affecting an estimated 70 million individuals worldwide and an estimated 40'000 chronically infected persons in Switzerland (1-2).

In the past years, major progress has achieved in the treatment of chronic hepatitis C, with the introduction of direct antiviral agents (DAA) (3). These do not only present excellent tolerance and relatively short treatment duration but also very high efficacy, yielding sustained virologic response (SVR) rates > 95% with the latest pangenotypic treatment regimens. A goal set by the WHO is now to achieve HCV elimination by 2030 (4).

On this background, we characterized in a first step all cases of DAA treatment failure observed in the Service of Gastroenterology and Hepatology of Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois, CHUV) between January 2015 and August 2018 in order to identify host and/or viral factors associated with lower rates of SVR. The results of this study were presented at the SGG-SGVC-SASL Annual Congress 2019 (Cottagnoud S *et al*.). Interestingly, patients infected with HCV genotype 4 fared worse than the others, especially those infected with subgenotype 4r found in sub-Saharan Africa (see also refs. 5-6). However, many of the patients included in this study had been treated with first-generation DAAs and a significant proportion had advanced liver disease. Additional interesting observations were the absence of non-virological treatment failures, failures to second-line DAA regimens in patients with active HCC and two cases of late relapses, i.e. occurring > 12 weeks after the end of treatment. Hence, it is important to extend this study to all centers in Switzerland and to include patients treated with second-generation DAAs.

2. Aim

The aim of this study is to extend our preliminary analysis to all Swiss tertiary centers involved in the treatment of chronic hepatitis C.

The primary endpoint is to define the evolution of SVR rates from 2015 to 2019. Second, we aim to identify risk factors associated with DAA failure, including viral resistance-associated substitutions (RAS). Third, we shall assess the response to second-line DAA treatment regimens.

For this purpose, we shall on the one hand analyze the clinical characteristics of patients with relapse as compared to SVR (sex, age, ethnicity, stage of liver fibrosis, liver function, history of previous anti-HCV treatment, HBV co-infection and presence or absence of HCC).

On the other hand, we shall characterize the viral determinants, including genotype as well as the presence or absence of RAS in the NS3-4A protease, the NS5A protein and the NS5B polymerase.

Patients who experienced DAA treatment failure shall be compared to patients who achieved SVR within the same time period.

3. Patients and methods

All patients treated with interferon-free DAA regimens between January 2015 and December 2019 shall be included in the analysis, with distinction between those who achieved SVR and those who experienced DAA failure. Pediatric patients (< 18 years old) as well as HIV-HCV co-infected patients shall be excluded from this analysis.

Data collection will be retrospectively pursued, including demographic aspects (age, sex, ethnicity), clinical characteristics (stage of liver fibrosis, liver function, history of previous anti-HCV treatment, HBV co-infection and presence or absence of HCC) as well as virologic data (genotype and presence or absence of RAS in the NS3-4A protease, the NS5A protein and the NS5B polymerase).

For those who did not have analyses performed yet but still have available samples, viral sequencing analyses by NGS will be performed at the CHUV, within the Laboratory of the Immunology and Allergology Department at viral relapse and at baseline.

All data will be reported in a codified form and collected in an Excel database. The code will be saved in a separate Word document. No patient name or birth date shall appear in the table. Each patient shall be assigned by an ID number that will be saved in a separate Word document. All data allowing identification (name, address, date of birth, patient number, etc.) will be kept separately from the actual study data in a locked drawer to which only the research team shall have access.

All centers will be individually contacted and invited to participate to the study. In case of positive response, they will be asked to transmit coded information to E. Moschouri and Dre Montserrat Fraga without having to provide patient names or birth date.

In Lausanne, Eleni Moschouri under the supervision of Dr. Montserrat Fraga will be responsible for the transfer of data from the patients' charts to a password-protected Excel database by coding them with a neutral study number.

Once the study is completed, the data will be kept for 10 years in the form of an Excel database and a separate Word file with the patient codes. The passwords will be kept and exclusively known to the research team.

The study protocol has already been approved by the Ethics Committee of the Canton de Vaud. An amendment will shortly be submitted to extend our work to all Swiss tertiary centers.

4. Budget and publication policy

We hope to include about 2500 DAA-treated patients for the planned study period. We are currently soliciting unrestricted research support from different sources for a part-time study nurse as well as the expenses for NGS analyses.

The analyses shall be performed by Eleni Moschouri as part of her MD thesis.

Two representatives from each participating center shall be offered coauthorship in an eventual publication resulting from this study.

5. Expected significance

This study will describe the current landscape of DAA treatment of chronic hepatitis C in Switzerland and contribute to the characterization of treatment failure. It shall increase awareness for special situations increasing the probability of DAA failure and may result in specific treatment recommendations for the remaining few difficult-to-treat patients, e.g. primary triple therapy in patients with HCV genotype 4r infection and specific baseline resistance-associated substitution profiles.

References

1. Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol 2017;2:161-176.
2. Zahnd C *et al.* Analyse de Situation des Hépatites B et C en Suisse. 23.03.2017. (www.bag.admin.ch)
3. Spearman CW *et al*. Lancet 2019;394:1451-1466.
4. Thomas DL. N Engl J Med 2019;380:2041-2050.
5. Fourati S *et al*. Hepatology 2019;69:513-523.
6. Childs K *et al*. J Hepatol, in press (epub Aug 7, 2019).