

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

2016-0738

[REDACTED]
[REDACTED] [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

 [REDACTED]

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): [NCT02278419 - A Phase 2a, Partly Randomized, Open-label Trial to Investigate the Efficacy and Safety of an 8 or 12-Week Treatment Regimen of Simeprevir in Combination With Sofosbuvir in Treatment-Naive and Experienced Subjects With Chronic Genotype 4 He](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Efficacy and safety of Sofosbuvir and Simeprevir for the Treatment of Chronic Hepatitis C genotype 4: a pooled

analysis of existing data

Narrative Summary:

Simeprevir has antiviral activity against genotype 1 and 4. Results from the RESTORE trial, evaluating Simeprevir in combination with Pegylated Interferon and ribavirin, has shown a high efficacy and a favorable tolerance profile in G4 infected patients.

Sofosbuvir is approved for the treatment of HCV, and has pangenotypic activity. The combination of Sofosbuvir and Simeprevir has been evaluated in phase 3 trials and in real-life in HCV patients infected by genotype 1.

The combination of Sofosbuvir and Simeprevir is approved in Europe for HCV-1 and -4 patients. However, efficacy data in HCV-4 patients are scarce. The aim is to pool existing data on this combination in HCV-4 patients.

Scientific Abstract:

Background: Data on efficacy and safety with Sofosbuvir + Simeprevir with or without ribavirin in HCV patients infected by genotype 4 are scarce (HCV-4)

Objective: To pool existing data from existing real-life existing cohorts and clinical trial (Osiris study)

Study design: analysis of data in HCV-4 patients coming from real life existing cohorts (Belgium, France, Saudi Arabia, Italy, Qatar, Germany) and Osiris trial, with the aim to study the impact of fibrosis stage, use of ribavirin and other predictive factors on SVR and safety

Participants: HCV-4 patients from real-life cohorts treated with Sofosbuvir + Simeprevir +/- ribavirin (85 GT4 patients from Belgium, 30 GT4 patients included in APROVVIE cohort, 12 ADVLIB cohort and REAL SIM SOF cohort from France, Abu Dhabi cohort, cohort from Dr Mangia in Italy, GT4 from Qatar HCV registry, GT4 patients included in SOF GER cohort from Germany) and Osiris trial (patients treated with 12 weeks). In those real-life cohorts, baseline demographics including patients demographics, disease severity data, fibrosis stage, treatment characteristics (use of ribavirin and dose, duration of therapy) and viral characteristics (sub genotype, viral load), SVR 12 data and occurrence of SAEs are available

Main outcome measures: SVR 12, occurrence of SAEs

Statistical analysis: To compare SVR 12 between patients receiving or not ribavirin, between F4 Fibrosis stage and non-F4 Fibrosis stage patients, and to identify other predictive factors of SVR12 by logistic regression such as ethnicity, GT4 subgenotype, disease severity parameters

Brief Project Background and Statement of Project Significance:

Chronic hepatitis C virus infection affects over 180 million individuals worldwide. The risk of developing cirrhosis and hepatocellular carcinoma as well as progression to liver failure remains a large global health burden. HCV exhibits great genetic diversity particularly among genotype 4, which accounts for 20% of all HCV cases worldwide. HCV genotype 4 infection is most prevalent in the Middle East and sub-Saharan Africa, accounting for over half of all cases reported in Saudi Arabia and Syria as well as 90% of HCV infections in Egypt. Though this genotype was once largely isolated to these regions, with global migration it is now increasingly seen in parts of Europe. The marked genetic variability of HCV genotype 4 infection includes 17 confirmed subtypes, with subtype 4a predominately seen in Egypt, while Saudi Arabia and parts of Europe have high rates of subtypes 4a, 4c, and 4d. In the era of potent and well tolerated direct-acting antiviral agents, current treatment guidelines for HCV genotype 4 infection from the European Association for the Study of the Liver include several different direct-acting antiviral combinations, with or without ribavirin, for either 12 or 24 weeks. Though these available treatments provide high efficacy and improved safety over pegylated interferon/ribavirin, their use is based on a limited number of clinical trials with small sample sizes, particularly small numbers of patients with cirrhosis.

Simeprevir is a second generation DAA (NS3/4a inhibitor), with potent antiviral activity against genotype 1 and 4. Results from the RESTORE trial, evaluating Simeprevir in combination with Pegylated Interferon and ribavirin, has shown a high efficacy and a favorable tolerance profile in HCV-4 patients. Those results are comparable to those reported for genotype 1.

Sofosbuvir is a nucleotide polymerase inhibitor approved for the treatment of HCV, with a pangenotypic activity. The combination of Sofosbuvir and Simeprevir has been evaluated in phase 3 trials and in real-life in HCV patients infected by genotype 1.

The combination of Sofosbuvir and Simeprevir is approved in Europe for HCV-1 and HCV-4 patients. However, efficacy data in HCV-4 patients are scarce and no phase 3 clinical trial supporting this recommendation has been performed.

Specific Aims of the Project:

The aim of the present project is to pool data from Osiris study and existing real-life HCV-4 cohorts in order to study efficacy and safety of Sofosbuvir + Simeprevir +/- ribavirin in a large sample size of patients, with different fibrosis stages, ethnicity, subgenotypes...

The study will study the effect of fibrosis stage and ribavirin use on SVR12, and will study predictive factors of SVR12 in HCV-4 patients.

What is the purpose of the analysis being proposed? Please select all that apply. Participant-level data meta-analysis

Participant-level data meta-analysis will pool data from YODA Project with other additional data sources

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

HCV-4 patients from real-life cohorts treated with Sofosbuvir + Simeprevir +/- ribavirine (85 GT4 patients from Belgium, 30 GT4 patients included in APROVVIE cohort, 12 from ADVLIB cohort and 44 from REAL SIM SOF cohort from France, 20 from Abu Dhabi cohort, 9 from cohort from Dr Mangia in Italy, 30 GT4 from Qatar HCV registry, 8 GT4 patients included in SOF GER cohort from Germany) and Osiris trial (patients treated with 12 weeks). Inclusion of patients included in Osiris trial will allow us to increase the sample size and to add an ethnicity to our analysis (Egyptian). The aim is also to include all existing data from GT4 patients treated by Sofosbuvir + Simeprevir +/-ribavirine.

Inclusion criteria:

chronic HCV-4 patients treated with SOF-SMV +/- RBV for 12 weeks or more

Exclusion criteria:

post-Liver transplant patients

HCV-4 patients co-infected by other HCV genotypes

Data source:

Information on fibrosis stage, treatment history, liver function, use of ribavirin, treatment duration, demographics will be collected

Main Outcome Measure and how it will be categorized/defined for your study:

Primary outcome: SVR12, defined by HCV RNA < LLQ 12 weeks after the end of treatment. This study will only include treated patients. No untreated group will be included. The rationale is the lack of SVR12 data on a large cohort of GT4 HCV patients treated with Sofosbuvir and Simeprevir with or without ribavirine.

Secondary outcomes: Serious adverse events, evolution of liver function at the end and 12 weeks after therapy

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The following variables as predictor of SVR12 will be studied:

ribavirin use or not

presence of Cirrhosis or not

treatment duration: 12 vs 24 weeks

Demographics: BMI, ethnicity, subgenotype (4a or not), baseline liver function (platelet count, albumin level, bilirubin level, MELD score, Child-Pugh score)

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

HCV RNA at week 4 (when available) and treatment duration (12 vs 24 weeks) as predictor of SVR 12

Statistical Analysis Plan:

Descriptive analysis of the pooled cohorts

We will compare SVR 12 between patients receiving or not ribavirin, between F4 Fibrosis stage and non-F4 Fibrosis stage patients, and to identify other predictive factors of SVR12 by logistic regression such as ethnicity, GT4 subgenotype, disease severity parameters, treatment duration

Project Timeline:

Project start date: data collection will start on March 1, 2016

Analysis completion date: june 2016

An abstract will be submitted at AASLD 2016, submission around june 2016

First manuscript draft for publication: november 2016

Dissemination Plan:

international journal in Hepatology: Liver international as a target

Bibliography:

Lavanchy D. Global surveillance and control of hepatitis C: report of a WHO consultation. *J Viral Hepat* 1999;6(1):35-47.

Moreno C, Hezode C, Marcellin P, Bourgeois S, et al. Once-daily siméprévyr (TMC435) with peginterferon/ribavirin in treatment-naïve or treatment-experienced chronic HCV genotype-4 infected patients:SVR12 results of a phase III trial. *Journal of Hepatology* 2015

Sulkowski MS, Vargas HE, Di Bisceglie AM, Kuo PA, et al. Effectiveness of simeprevir plus sofosbuvir, with or without ribavirin, in real-world patients with HCV genotype 1 infection. *Gastroenterology* 2015 Oct 21 (Epub ahead of print)