Scientific context.

Since 2017, treatment with direct-acting antivirals (DAA) is recommended in all patients with chronic Hepatitis C Virus (HCV) infection in France, with the target objective to eradicate HCV by 2025. Using DAA, a sustained virological response - i.e. an absence of detectable HCV RNA in the serum 3 to 6 months, is obtained in more than 95% of patients 1.

In observational studies, these virological responses are strongly associated with histologic improvements (regression of liver fibrosis and inflammatory activity) and with decreased risks of liver related complications including decompensation, hepatocellular carcinoma and liver related deaths 2,3, thereby suggesting a “benefit” of antivirals. Recent studies also highlighted a potential decrease of non-liver related cancers (including non-Hodgkin lymphoma) 4 or metabolic complications such as dyslipidemias, diabetes, chronic kidney disease, and cardiovascular events 5 in relation with a virological response to chronic HCV infection 6.

In order to correctly estimate the public health impact of antiviral therapy in chronic hepatitis C, (at least) two challenging issues must be addressed:

1) Most of the available information on antiviral “benefits” comes from observational studies comparing treated patients who did, or did not, develop virological responses. Since all participants in these studies received treatment, it is likely that a part of the differences in clinical outcomes are due to inherent differences in patients who respond or do not respond to treatment 7. Such a phenomenon, i.e., confounding by prognosis factors, hampers an accurate quantification of the clinical benefits associated with antivirals. Actually, the relevant analysis for evaluating and comparing the clinical impact of antivirals should be a comparison of treated versus untreated patients, irrespective of the virological response, as would be done in a randomized trial. To the best of our knowledge, very few studies have performed a comparison of treated versus untreated patients focusing on liver related outcomes 8,9, and none has been performed on non-liver related outcomes.

2) In longitudinal studies, the strength of association between exposure to antiviral therapy and a clinical outcome is usually presented as a fixed-time Hazard-Ratio (HR) estimate, that is, a hazard in the treated group divided by a hazard in the untreated group. However, for some outcomes (e.g. liver cancer), it is clearly obvious that the HR will change over time 10: the risk of liver cancer is strongly associated with the severity of liver fibrosis and the action of treatment will take several years for a complete reversion of fibrosis. Even if we assume a constant hazard in the untreated group, the HR of treated vs untreated patients will obviously decrease with time since treatment, all other things being equaled 11.
The general thesis objective will be to estimate the public health impact of universal HCV treatment in France. We will combine estimates from past analyses (liver-related outcomes in the short term\textsuperscript{4}), and future analyses (non-liver-related outcomes) based on two sources of data with individual linkage: the ANRS CO22 HEPATHER cohort and the Système National des Données de Santé (SNDS).

Questions:
The thesis will address the following questions:
- what is the expected clinical impact on non-liver related outcomes over time of HCV antivirals according to age, sex, severity of the disease at treatment initiation?
- at a nationwide level, what is the public health impact of universal HCV treatment?

Data:
The thesis will use data from
- the ANRS CO22 HEPATHER cohort leads by our team - this cohort is funded by ANRS, "Investissements d'Avenir-Equipex", and 5 pharmaceutical companies. In the cohort, 11 630 patients with chronic HCV infection (≈ 10,000 have been treated with direct acting antivirals) followed-up from 2013. By March 2019, 755 deaths, 782 liver cancers and 2,793 other serious adverse events (including non-liver related cancers and cardiovascular events) have been reported in the cohort. Quality of Life (through EQ5D, SF12, and a "home-made ProQoL" questionnaires) are collected at entry, at treatment start and every two years, in all patients. These data will be used to quantify the time-varying impact of antiviral treatment on non-liver related outcomes according to age, sex and severity of fibrosis
- The Système National des Données de Santé (SNDS), the nationwide database including health insurance claims, hospitalization, and causes of deaths. As part of the scientific animation around our cohort, a collaborative group involving Santé Publique France, Haute Autorité de Santé and Agence Nationale de Sécurité du medicament, has been set up in 2018 to work on identification algorithm of people with chronic HCV infection in the SNDS (this specific work in not part of the thesis). SNDS will be used to quantify the public health impact of universal HCV treatment in France. In a preliminary (confidential) SNDS analysis, > 60,000 patients have been identified to have received direct-acting antivirals between 2015-2018. Importantly, we have been authorized by CNIL (in August 2018) to perform individual linkage of the HEPATHER cohort with the SNDS (linkage will be effective in June 2019): the HEPATHER cohort will be used to validate identification algorithm of people with chronic HCV infection and could help to impute missing clinical information in the SNDS.

Methods:
Our team has adapted a statistical framework to estimate time-varying hazard ratios in presence of time-dependent confounding\textsuperscript{11,12}. This framework will be used to quantify the time-varying impact of antivirals on different outcomes, namely: death, liver cancer, liver decompensation, non-liver related cancers, cardiovascular events, QoL. The PhD Student will specifically perform the analysis on non-liver related events.

It is expected that a first paper (paper I) on “Time-varying effect of HCV treatment on non-liver related clinical outcomes” will be submitted in a general medical journal or in a journal specialized in hepatology.

Using data from SNDS, it is expected that a second paper (paper II) on “Appraisal of universal HCV therapy: the French experience” will be submitted in a public health journal. This work will be based on an analysis of SNDS data, and will estimate the impact of universal treatment (years of life saved, QALYs) as well as its economic burden. Even if the cost-effectiveness of universal DAA is no longer a strategic issue (and a CE analysis is already ongoing using the Hepather cohort data), an accurate evaluation of health benefits and costs could be helpful to justify (or not) universal HCV treatment in countries where it is not yet implemented.

Of note, the PhD student will collaborate to analyzing the clinical effectiveness and safety of antiviral treatment in the ANRS CO22 HEPATHER cohort and will be associated with other papers published on these topics.

Schedule
October 2019-March 2020: bibliography on non-liver related events related to HCV and antiviral treatment impact.
Training in SNDS analysis. Identification and validation of non-liver related events in the cohort and using individual linked data from SNDS. First developments of statistical analysis.

April 2020- September 2020: Finalization and submission of paper I.
October 2020-March 2021: Analyses of nationwide SNDS data. Initial version of paper II. (Publication of paper I)
April 2020-September 2020: Finalization and submission of paper II
October 2020-March 2021: Elaboration of the thesis manuscript summary, 2nd paper to be published
April 2021-September 2021: Final version of the thesis manuscript and PhD Defense

Bibliography

**PRÉREQUIS, FORMATION:**
*MASTERS DEGREE IN EPIDEMIOLOGY/BIOSTATISTICS/PUBLIC HEALTH*

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**SPECIALITE DE LA THESE**

**EPIDEMIOLOGIE (AVEC EVENTUELLEMENT MENTION CLINIQUE OU SOCIALE OU GENETIQUE)**
**BIOSTATISTIQUE/BIOMATHÉMATIQUES**
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