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Ongoing Clinical Trials

PITER: An ongoing nationwide study on the real-life impact of direct acting antiviral based treatment for chronic hepatitis C in Italy

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1. Rationale and aims

The recent development of direct-acting antiviral agents (DAAs) that specifically target the hepatitis C virus (HCV) represents a historical breakthrough, in that the second generation DAAs are capable of eradicating HCV and preventing chronic liver disease from developing into cirrhosis and hepatocellular carcinoma (HCC) [1–3]. There is great potential for overall harm reduction through effective therapy; however, many challenges remain, beyond that of the exorbitant cost of these drugs [4–6]. In particular, the actual clinical impact of DAAs on long-term morbidity and mortality and in relation to the clinical profiles of chronic liver disease and co-factors of disease progression (i.e., co-infections and comorbidities) is still unknown.

Italy has one of the highest prevalence rates of HCV infection in Europe, and HCV infection is the leading cause of cirrhosis, HCC, and liver-related death [7–9]. DAAs would clearly have a huge public health impact in Italy, yet determining exactly what this impact would be, requires evaluating whom to treat based on the balance between the benefits of therapy and its affordability. In other words, reaching the objectives promised by the use of these drugs is linked not only to their quality, safety and effectiveness but also to the development of suitable research for evaluating their impact in a real-life setting. In fact, it is necessary to mount holding strategies, to move from the urgent need for treatment in selected patients to evidence-based escalation strategies in other patients according to their disease profile and overall benefit from treatment. In this regard, much could be learned from the experience with HIV infection. In about thirty years, thank of antiviral therapy, HIV become a chronic disease, though the combined antiretroviral treatment can have different results depending on the disease stage during which it is administered. Moreover, it now appears clear that antiretroviral therapy not only provides clinical benefit to the individual (in terms of risk-benefit ratio and public health policy) but has also the potential of decreasing the incidence of new infections at a population level [10–12]. In the case of HCV infection patients can be cured with DAAs, however the cost of providing early treatment to all patients would be prohibitive. It is thus imperative, considering patients' characteristics and comorbidities, to determine the best timing for treatment, with cost-effectiveness being a fundamental part of this decision. Reaching this goal would require accurate data on the long-term effects of DAA therapy for individuals in different disease stages.

To this end, a longitudinal prospective HCV cohort study known as "PITER" (Italian Platform for the Study of Viral Hepatitis Therapies) has been conducted. PITER is a structured network that benefits from an integrated collaboration involving Italy's National Institute of Public Health (Istituto Superiore di Sanità), the Italian Society for the Study of the Liver (AISF), the Italian Society for Infectious Diseases (SIMIT) and their affiliated clinical centres.

The main goal of PITER is to evaluate the expected impact of DAAs on the natural course of infection and on long-term morbidity and mortality in a real-life setting. The study will address such unresolved questions as: Will early treatment be able to modify long-term outcome of progression of liver disease? Will alternative approaches be needed in patients with coexisting conditions such as kidney failure, hepatic decompensation, or liver transplant, as well as those with previous failure of a DAA combination? Will antiviral treatment have an impact on extra hepatic HCV-related diseases or the natural history of other viral co-infections?

The specific expected outcomes include: obtaining a continuous update of the epidemiology of HCV chronic liver disease through data from patients in care; evaluation of the real-life long-term impact of new DAA therapies on the outcomes of chronic HCV infection; monitoring of the use of the different options for DAA combinations in a real-life setting, their possible pharmacological interactions and the long-term safety; development of appropriate algorithms for care and therapy for special, difficult-to-treat and difficult-to-reach populations, as well as for specific populations such as the elderly, women, non-responders to standard treatment protocols, patients awaiting liver transplantation, and liver transplanted patients; evaluation of the economic impact of the progressive introduction of DAAs and their cost-effectiveness through

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the construction of a continuously updated cost-effectiveness framework.

2. Study design

2.1. Study population

The cohort will consist of a representative sample of approximately 10,000 consecutive patients with chronic hepatitis C (CHC) receiving care in over 100 public general hospitals and university medical centres in Italy. The follow-up of enrolled patients is expected to last at least 10 years. The geographic distribution of the participating centres is available at: www.iss.it/piter

Inclusion criteria: all HCV-infected patients (any stage, any genotype, including HBV, HDV, or HIV co-infected) at least 18 years of age consecutively referred to the outpatient clinics of the participating clinical centres during enrolment phases (approximately 6 months), who are untreated at the time of enrolment. Eligible patients are those who will receive DAAs as first therapy, or who have failed a prior peginterferon/ribavirin-based therapy; the study will also follow patients eligible for treatment who cannot be prescribed DAAs (i.e. for non-advanced stages of fibrosis), and are warehoused.

2.2. Study procedures

An *ad-hoc* web-based platform, certified to international standards, is used to collect data on enrolled patients, enabling interoperability, sharing of information and development of specific studies (Supplementary Figure S1). The electronic data-collection system covers all clinical and therapeutic aspects of CHC of the PITER study; however, this system will also be used for all spin-off studies and other future research related to PITER. The quality of data is checked using queries specifically designed to control for incorrect data entry and clinical congruencies. A close interaction between the coordinating centre and the participating clinical centres will ensure the quality of follow-up data.

2.3. Main study endpoints and statistical analysis

Through a cross sectional analysis of enrolled patients, the following endpoints will be evaluated:

(a) Prevalence of the main clinical characteristics of CHC: fibrosis stage; complications of cirrhosis such as portal hypertension, liver cancer and end-stage liver failure requiring liver transplantation.
(b) Prevalence of extra hepatic HCV-related disorders, specifically, cryoglobulinemia and lymphoproliferative disorders (at baseline and during anti-HCV antiviral therapy).
(c) Virological characterisation of HBV, HDV and HIV co-infections (baseline and during anti-HCV and other antiviral therapies).
(d) Prevalence of liver and extrahepatic co-morbidities.
(e) Prescription of types of anti-HCV treatment regimens, their treatment efficacy based on rates and speed of sustained virological response (SVR), and adverse effects in different subgroups of patients.

The longitudinal prospective analysis will evaluate morbidity and mortality outcomes in treated and non-treated patients. The progression of liver disease will be determined by evaluating: changes in fibrosis stage; development of portal hypertension, decompensated liver disease, and HCC; the need for liver and/or other organ transplantation; the outcome of extra hepatic HCV-related disorders and co-morbidities; hospitalizations and overall mortality in association with clinical profiles of liver disease and comorbidities at enrolment. The efficacy of treatment will be determined based on long-term effectiveness; this evaluation will focus on assessing the residual risk (after SVR is achieved) of life-threatening complications such as liver failure, portal hypertension, HCC and the need for liver transplantation. Pharmaco-economic models of the direct and indirect costs of morbidity due to chronic HCV infection versus the cost of the new treatments will be developed.

2.4. Ethical considerations

The main protocol of the study has been approved by the central ethics committee and the ethics committee of each clinical centre. Clinical centres are involved in the study on a voluntary basis. The study start-up was supported by "Research Project PITER 2010" RF-2010-2315839, National Institute of Public Health funds for start-up studies and by un-conditioned partial support from Bristol-Myers Squibb, Roche and Merck (MSD Italia). Each private financial support has been evaluated by the Ethics Committee of the National Institute of Public Health according to strict conflict of interest policies, to ensure impartiality and integrity. Future public and/or private funds will be required for the coordination and conduction of the study.

2.5. Current enrolment status

The first round of enrolment began in May 2014 and lasted for 6 months. Enrolment will be re-opened regularly for three-month periods during the spring and fall of subsequent years in order to keep up with the changing of the epidemiological situation and with the introduction of new DAAs and new combinations in the real life. To date, 80% of participating clinical centres have begun enrolment, and they have already enrolled approximately 6000 patients; the remaining centres are preparing for enrolment (Supplementary Figure S2). The PITER Study will be the backbone for further specific research studies and is expected to provide much needed guidance in evidence-based health policy for the better management of chronic HCV infection and for prudent resource allocation in order to guarantee equity in access to treatment.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2015.05.022

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