Italian Platform for the Study of Viral Hepatitis Therapies (PITER): a useful real life framework to evaluate DAAs cost-effectiveness and guide evidence-based health policy

Kondili Loreta[1], Brunetto Maurizia[2], Zignego Anna Linda[3], Rizzetto Mario[4], Di Leo Alfredo[5], Raimondo Giovanni[6], Orlandini Alessandra[7], Craxi Antonio[8] and Vella Stefano[1] on the behalf of PITER collaborating group[9]

[1] Istituto Superiore di Sanita; [2]Azienda Ospedaliera Pisana; [3]Università di Firenze; [4]Università di Torino; [5]Università di Bari; [6]Università di Messina; [7]Azienda Ospedaliero Universitario Di Parma; [8]Università di Palermo [9]Piter Collaborating Group avallale in www.iss.it/piter

Background:

Chronic HCV infection affects an estimated 170-200 million people worldwide (about 3% of the world's population) and Italy has one of the highest prevalence rates of HCV infection in Europe. In Italy HCV infection is the leading cause of cirrhosis, HCC, and liver-related death. The potential overall impact of the wide-scale use of direct-acting antiviral agents (DAA) for hepatitis C, would be enormous, in terms of reducing both morbidity and mortality, as well as the direct and indirect costs associated with them however, the cost of these drugs is exorbitant, and their sustained use is not feasible for Sanitary Health Systems. It is imperative, that considering patients' characteristics, to determine what the best timing of treatment would be, with cost-effectiveness being a fundamental part of this decision. Reaching this goal would require data on the long-term effects of DAA therapy in different disease stages. To this end, a prospective HCV cohort study, known as "PITER" has been conducted.

The specific expected outcomes of PITER cohort study are:
1) production of a continuously updated national picture of the epidemiology of HCV chronic liver disease through an updated picture of patients in care;
2) evaluation of the real-life long-term impact of new DAA therapies on the outcomes of chronic HCV infection in terms of morbidity and mortality in patients at different stages of disease;
3) 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.
4) development of appropriate algorithms for care and therapy for special, difficult-to-treat and difficult-to-reach populations,
5) evaluation of the economic impact of the progressive introduction of DAAs and their cost-effectiveness through the construction of a continuously updated cost-effectiveness framework.

Aims

We assessed the impact of The European Association for the Study of the Liver (EASL) indications for treatment of chronic Hepatitis C in 2015 on this large real-life cohort of 6831 consecutive patients enrolled in PITER for whom the data entry was completed at the time of analysis.

Patients and Methods

The cohort is under construction and to date consists of a representative sample of approximately 7500 consecutive patients with chronic HCV liver disease who are undergoing clinical care in more than 80 clinical centers in various regions of Italy (Figure1). The follow-up of these patients is expected to last at least 10 years. The bespoke electronic data-collection system, is being used to collect data from the enrolled patients and covers all clinical and therapeutic aspects of chronic HCV infection enabling interoperability, sharing of information and development of specific studies (Figure2). A close interaction between the coordinating centre located in *Istituto Superiore di Sanita'* and the participating clinical centres ensures the quality of follow-up data. The first round of enrolment began in May 2014. Further enrolment periods 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 epidemiological situation and with the introduction of new DAAs and new combinations.

Figure 1 Enrolment rate of patients in PITER platform

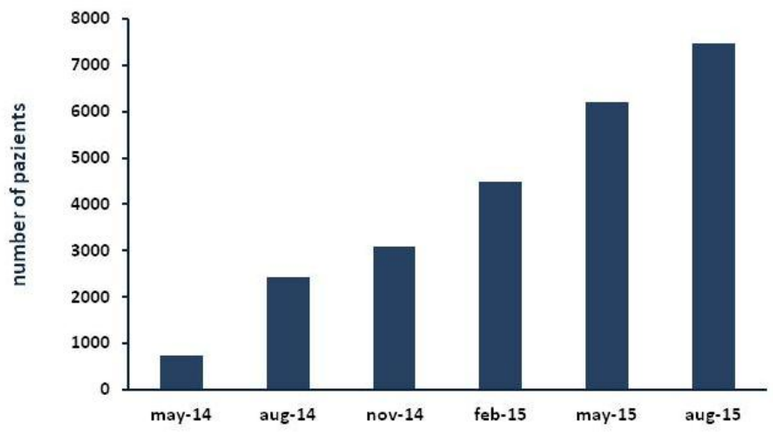
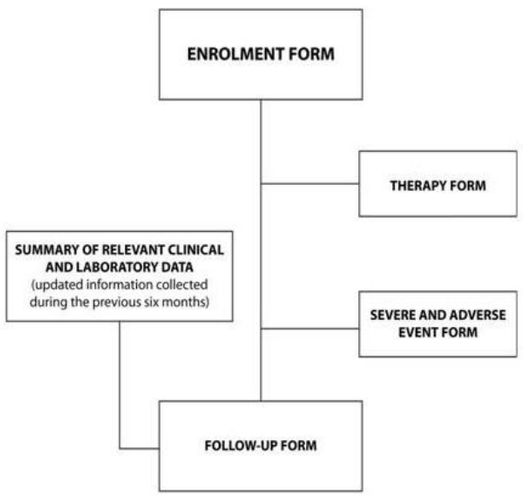


Figure 2 Work flow of data collection in PITER platform



Results

We apply of EASL indications in 6831 patients enrolled in PITER with completed "data entry " and the treatment allocation according to the reported characteristic is reported in Table 1. Finally we applied a model excluding from these priorities patients with severe comorbidities **and** age older than 75 years classifying them in this model as " low life expectancy" thus as treatment *not reccomended.*

Factors analysed	ND N (%)	F0-F1 N (%)	F2 N(%)	F3 N(%)	F4/cirrosi N(%)	Child B/C or HCC N (%)	Total 6831 (%)
Age younger than 60 years	143 (4)	1354 (40) ¥	478(14) §	319(9)*	798 (24)*	279(8)*	3371 (49)
Age > 61 years	186 (5)	994 (29) ¥	366 (11) §	420(12) *	1048 (30)*	444(13)*	3459 (51)
Women <40 years	11 (6)*	125 (72)*	21 (12)*	12 (7)*	4(2)*	1(0)*	173 (3)
Current Drug use	2(1)*	15 (5)*	4(1)*	2(1)*	2(1)*	3(1)*	280 (0.4)
HBsAg/HIV	23(6)*	141(36)*	45(11)*	38(10)*	98(25)*	52(13)*	397 (6)
Symptomatic crioglobulinemia and or lymphoma	5(1)*	172 (29)*	49(8)*	64(11)*	254(43)*	43(7)*	587 (9)
Hemodyalisis	0*	13 (57)*	5 (22)*	1(4)*	3(13)*	1(4)*	23 (0.3)
Liver Transplant list (OLT)	0*	0*	0*	2(4)*	10(19)*	40(77)*	52 (0.8)
Recurrent HCV post OLT	2 (2)*	26(31)*	4(5)*	19(23)*	22(26)*	11(13)*	84 (1.2)
Overall	**treatment**	**allocation**	**applying**	**the**	**exclusion**	**criteria**	
Prioritized *	**38 (1)**	**436 (13)**	**116 (3)**	**553(16)**	**1675 (49)**	**599 (18)**	**3417 (50)***
Justified §		**0**	**440 (100)**	**0**			**440 (6)§**
Deferred ¥		**661 (100)**	**0**	**0**			**661 (10)¥**
Not recommended	**291 (13)**	**1547 (67)**	**76 (3)**	**104 (4)**	**171(7)**	**124 (5)**	**2313 (34)**

Hence applying this model, treatment should overall be prioritized in 3417 (50%) patients, the prioritization algorithm endorsed by AIFA, mostly based on fibrosis alone, would allow treatment of only 2827 (41%) of them. However, this is only a model and considering that the age is not an ethic limitation for HCV treatment access, further models that better define the "short life expectancy" in the real clinical practice should evaluated.

Conclusions: PITER is a useful framework for a validated cost-effectiveness predictive model in order to assess the impact of delaying treatment or not treating patients with different clinical and virological characteristics. It could be the backbone for pharmaco-economic models of the direct and indirect costs of morbidity due to chronic HCV infection versus the cost of the new treatments. PITER 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 the access to HCV antiviral treatment..