ORIGINAL ARTICLE

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First-generation HCV protease inhibitors: A sustainable innovative technology?

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ABBREVIATIONS
CHC: chronic hepatitis C; G1: genotype 1; DT: dual therapy; PEG-IFN: pegylated interferon; RBV: ribavirin; PI: protease inhibitors; BOC: boceprevir; TVR: telaprevir; ICER: incremental cost effectiveness ratio; NR: null responder; PAR: partial responder; RR: relapser.

The estimated global prevalence of hepatitis C virus (HCV) is 2.2%, corresponding to approximately 130 million people HCV-positive throughout the world, most of which is chronically infected (1). A recent paper reviews the literature (2) reported that the estimated prevalence of HCV infection in Europe varies from 0.6% to 5.6%. This figure is substantial, since HCV is the leading cause of cirrhosis and hepatocellular carcinoma (HCC) in Western countries. The prevalence of HCV-related cirrhosis and its complications probably will continue to grow during the next decade, mainly in patients older than 60 years of age (3). Moreover, patients with genotype 1 chronic hepatits C (CHC) who fail to dual therapy (DT) with peginterferon (PEG-IFN) plus ribavirin (RBV) are about 50% of all treated subjects, and therefore represent a growing cohort of individuals at higher risk of liver related complications . Considering the high likelihood of disease progression of CHC patients failure to DT with PEG-IFN and RBV, and the burden of HCV-related cirrhosis and its complications, the achievement of a sustained virologic response (SVR) is a very important surrogate outcome in the management of these patients. In fact, the eradication of the virus prevents the development of cirrhosis (4) and its complications, such as occurrence of esophageal varices (5), liver failure and HCC (6) and leads to the decrease in liver-related mortality (7).
DT for 48 weeks in previously untreated patients with G1 CHC (the most common HCV genotype in Western countries) has reached an SVR rate of about 40-50% (8). Data derived from indirect comparison meta-analysis of about 30 published RCTs of PEGIFN alfa (2a or 2b) and RBV in the treatment of untreated G1 CHC patients showed no differences between the two PEG-IFNs used, with a mean rate of SVR of 45% . Recent data have demonstrated that the presence of a polymorphism favorable, IL28B, and / or the attainment of rapid virologic response (RVR) identifies patients with more likely to achieve an SVR (about 80%) after DT (9 , 10).
An even better response obtained with the inclusion of new agents in therapy could significantly reduce the impact of the disease in the coming years. Two large randomized controlled trials (RCT) (11,12) failed to show a benefit on progression of liver disease by long-term maintenance therapy with low dose PEG-IFN, in CHC patients failure to DT. Different RCTs (13,14), and a recent meta-analysis (15) underlined that retreatment of G1 nonresponders with DT favours SVR achievement in only 10-15% of patients. Guidelines of the European Association for the Study of Liver Disease (EASL) (16) and of the American Association for the Study of Liver Disease (AASLD) 2011 guidelines (17) recommended that patients infected with G1 HCV and who failed to eradicate HCV after prior DT should not be re-treated with the same drug regimen, suggesting to wait protease inhibitor (PI) based-therapies.

Two NS3-NS4 protease inhibitors (PI), telaprevir (TVR) and boceprevir (BOC), have recently been developed and are ready for use in clinical practice. Randomized controlled trials (RCT), ie SPRINT2 and ADVANCE (18,19), have shown that these drugs, in combination with the DT, reach the SVR in approximately 65-75% of patients with HCV of genotype 1 not yet treated. Although these results are very encouraging, the use of these new drugs in clinical practice should be carefully evaluated in light of factors such as tolerability profile, the issue

of drug-drug interaction, the induction of viral mutations of uncertain significance , and high costs.
RCTs, namely RESPOND-2 and REALIZE (20,21), showed that triple therapy (TT) with PEG-interereferon, ribavirin and PI, achieves SVR in about 30-75% of experienced G1 CHC patients, with SVR rate progressively decreasing from relapse (RR) to partial responders (PAR) (HCVRNA drop>2LOG at week 12, but never not detectable), and further to null responders (NR) (HCVRNA drop<2LOG at week 12).
Due to a lack of consensus about the use of this new class of drugs (17,22), we sought to determine the cost-effectiveness of the DT and the triple therapy (TT) with BOC or TVR in naïve and experienced patients with CHC G1.
Our analysis demonstrated that BOC and TVR improved survival of about 4 years and quality-adjusted survival of about 7 years in naïve patients with G1 CHC, by ncreasing the SVR rate of about 25%. This gain came at a relatively low cost, resulting in an ICER per QALY of less than -15.000, a cost lower than the generally accepted societal threshold for willingness to pay , and indicating that the cost-effectiveness of these PI is favorable. The robustness of these results was confirmed in all the sensitivity analyses, being the cost-effectiveness of first generation PI highly sensitive to BOC/TVR costs, RVR and SVR rates, and IL28B CC prevalence, and moderately sensitive to costs, discounting and transition from CHC to cirrhosis and from compensated to decompensated cirrhosis.

The 2011 update of the practice guidelines by the American Association of the study of liver disease on Hepatitis C (17) did not recommend any approach to allocate treatment with first generation PI. In contrast, Aronsohn and Jensen (22) recently proposed a needs-based allocation system in which priority would be given to the sickest patient first (patients with cirrhosis). Therefore, a debated issue is if all naïve patients should be treated with triple therapy, especially considering the increase in costs due to PI, in an era where resource scarcity will be a prominent issue. Our analysis provides further evidence that a cost/effectiveness-based allocation system, fulfilling the moral framework of distributive justice, could be a solution for this allocation dilemma. Therefore, the key issue is the identification of the best cost/effective strategy for PI use. Our analysis suggests to use BOC only in patients who did not achieve RVR after the 4 week PR lead-in period and to restrict TVR only to patients with a genotype of IL28B CT or TT.
It is noteworthy to underline that compared to an indiscriminate use of PI in all G1 CHC naïve patients, using lead-in and genotype-guided strategy we are able to avoid exposure to PI in about 20%-30% of patients, reducing costs, risks and improving overall efficacy. Although the proposed algorithms are useful tools for decision making, the treatment strategy should be carefully agreed with the individual patient, taking into account all the different factors that can interfere with treatment response. In particular the choice of treatment should be targeted to obtain the best possible treatment in the individual patient without any economic analysis affecting the clinical value and ethical impact of this decision. Therefore, efforts aimed to identify strong SVR predictors to optimize and personalize DT in naïve patients, could be also applied in the PI era, to identify patients at higher likelihood of responding to dual therapy, reserving triple therapy only to patients with a low probability of response to DT. Further stratification of patients according to other variables interfering with SVR achievement (viral load, steatosis, fibrosis, insulin-resistance, vitamin D, etc.), and the possibility to use also TVR after a lead-in phase in naïve patients, could improve the cost-effectiveness of our strategies.
Another relevant issue arising from our analysis is that LEAD-in and genotype-guided strategies are attractive, not only in terms of cost reduction but also in terms of safety, being TVR and BOC therapies associated with higher side-effects, lower tolerability, and induction of virological mutations. Side effects of triple therapy, leading to treatment discontinuation in 15-20% of patients included in RCTs, increase management costs, and are expected to be more frequent in real clinical practice. This issue could lead to a higher treatment discontinuation and inefficacy also in patients potentially sensible to DT , finally reducing the likelihood of SVR in the individual patient.
Triple therapy have been also associated with occurrence of virological mutations, that theoretically, could compromise in non-responders future treatment with PI of next generation. In this line, sparing the use of first generation PI, and test the sensitivity to dual terapy with a lead-in phase, could further strength the useful of our proposed strategies.
Regarding experienced patients, TT improved survival by about 4, 3 and 2 years, in G1 CHC RR, PAR and NR patients, by increasing the SVR rate compared to DT of 55%, 40% and 30%, respectively. This gain came at a relatively low cost, resulting in an ICER per QALY of less than -4,000 in RR, -7,000 in PAR, and -13,000 in NR, indicating that the cost-effectiveness of HCV PI is highly favorable, as also observed in previous untreated G1 CHC patients.
Among non responder G1 CHC patients, we considered separately PAR and NR subjects, due to the different SVR rates of these two groups of patients. In PAR patients, BOC and TVR-based strategies were cost-effective compared to DT, and sensitive to changes in SVR rates, even if overall they maintained their cost-effective profile.
In NR patients, due to the lack of inclusion of NR patients in RESPOND-2 study we only evaluated TVR-based strategy showing that they were cost-effective compared to DT.
Nevertheless the pattern of previous response to DT has a great impact on SVR rates in case of retreatment with TT, due to the low availability of these data in all patients in clinical practice, it should be very useful the use of on treatment predictors of response to DT. Data from REALIZE and RESPOND-2 RCTs considering together all previously treated G1 CHC patients, showed significantly lower SVR rates in patients with HCV RNA drop <1LOG after 4 weeks of DT, compared to those with a drop>1LOG.. According to these data we showed that BOC and TVR-based strategies for the treatment of good or poor DT sensitive patients, are cost-effective compared to retreatment with DT, with a better cost-effective profile for good compared to poor DT sensitive patients, similar to that observed in the analyses on RR and NR patients, respectively.
We showed overall that BOC and TVR-based strategies for the treatment of experienced patients, were more cost-effective compared to that observed in previously untreated patients. However among previously treated patients, we could observe

a rating of cost-effectiveness, with a profile progressively improving from NR (or poor DT sensitive), to PAR, and further to RR (or good DT sensitive) patients. This clinical picture is further enriched when we considered the sub-group of previously treated patients with severe fibrosis. We observed that the profile of cost-effective of patients with severe fibrosis is strongly better than those of patients without severe fibrosis, likewise maintaining an increasing rate of cost-effective from RR, to PAR and further to NR. However it is worth to underline that these results are limited by the low number of patients with severe fibrosis included in registrative trials, and especially in RESPOND-2 RCT.

Our analyses both of naïve as well as experienced patients have several caveats, the most important of which concerns that efficacy data arise from available manufacturer-sponsored trials of BOC and TVR. In fact data from RCTs are not directly transferable in clinical practice, due the fact that trial patients are healthier, more adherent, and more intensive monitored. All our analyses were performed using summary data and more detailed treatment comparisons between DT and TT and between BOV and TVR could be achieved analyses of individual patient data. Unfortunately it is very unlikely that pharmaceutical companies make available individual data for these analyses. Second, we used the utilities considered to be acceptable for an Italian population . However it is well known that utilities vary widely across different patients subgroups and depend critically on quality-of-life assumptions. Another important limitation regards the transition probabilities from CHC to cirrhosis and from compensated to decompensated cirrhosis, which were assumed to remain constant over time. Finally, the study's perspective was not Societal. Therefore, our analysis was limited to direct medical costs: indirect costs such as lost productivity and caregiver salaries were not included.

In conclusion, we showed that triple therapy including first generation PI is a strongly cost-effective treatment, both in naïve as well in experienced patients with G1 CHC. In naïve patients, allocation systems based on lead-in or genetic testing strategies are likely to be cost-effective compared to indiscriminate treatment of all patients with PI, also potentially reducing the risk of side-effects and viral resistances related to treatment. In experienced patients a careful balance between pros and contra of retreatment, together with the assessment of on treatment response after a lead-in period of 4 week of DT, should be performed to improve cost-effectiveness and safety. ■

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