Special Article

Ethical assessment of hepatitis C virus treatment: The lesson from first generation protease inhibitors

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A R T I C L E   I N F O

Article history:
Received 5 March 2014
Accepted 15 November 2014
Available online 24 November 2014

Keywords:
Direct-acting antivirals
Ethics
Health technology assessment
Hepatitis C virus

A B S T R A C T

Since chronic hepatitis C has mostly become curable, issues concerning choice and allocation of treatment are of major concern. We assessed the foremost ethical issues in hepatitis C virus therapy with 1st generation protease inhibitors using the personalist ethical framework within the health technology assessment methodology. Our aim was to identify values at stake/in conflict and to support both the physicians’ choices in hepatitis C therapy and social (macro-) allocation decision-making.

The ethical assessment indicates that: (1) safety/effectiveness profile of treatment is guaranteed if its use is restricted to the patients subgroups who may benefit from it; (2) patients should be carefully informed, particularly on treatment deferral, and widespread information on these therapies should be implemented; (3) since treatment was proven to be cost-effective, its use is acceptable respecting resource macro-allocation. Concerning individual (micro-) location criteria: (a) criteria for eligibility to treatment should be clearly identified and updated periodically; (b) information on criteria for eligibility/deferral to treatment for specific patients’ subgroups should be made widely known.

Interferon-based regimens will disappear from use within the next year, with the introduction of highly effective/tolerable combination regimens of direct-acting antivirals, thus profoundly changing social choices. Nonetheless, our model could support future ethical assessment since the evaluation pertaining ethical domains remains generally applicable.

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1. Introduction

Hepatitis C virus (HCV) infection is a major health issue worldwide \cite{1,2}. The actual burden of HCV infection and disease may be underestimated because of biases caused by the changing epidemiology of HCV worldwide, by the ageing general population, and by the incompleteness of the cohorts studied \cite{3}. HCV infection stands as a major global issue for several reasons: one is the high percentage of undiagnosed infected subjects, often with latent but significant disease, who may act as reservoirs for infection. Moreover, HCV infection is the main cause of cirrhosis, hepatocellular carcinoma (HCC), and liver transplantation in Western countries \cite{4}. Data on the burden of HCV-related disease for the United States and Europe confirm hepatitis C as a major health problem, with a mortality rate exceeding that of immunodeficiency virus infection (HIV), and highlight the importance of timely antiviral treatment. Other elements are the significant social impact of the infection caused by undeniable psychological and relational damages (fear of contagion, fear for own life and for relationships) and, last but not least, the significant economic burden of chronic hepatitis C (CHC). Both direct costs (linked to treatment) and indirect costs (connected to the loss of productivity and early deaths) gradually increase proportionally to the disease progression.
Starting from the early 2000s, pegylated interferon alpha plus ribavirin (P/R) therapy has made CHC a curable condition for a considerable proportion of patients. A further advance since 2011 has been the addition to P/R of direct antiviral agents (DAAs) as triple therapy (TT); further relevant improvements are expected by the introduction of interferon (IFN) and ribavirin-free regimens.

The standard of care (SOC), which specifies the most appropriate treatment for each patient, is continuously evolving and its definition is influenced not only by changes in the availability of effective drugs but also by the changing pattern of a specific illness. Concerning HCV genotype 1, the SOC has evolved over the last three years from P/R to TT with DAAs, and more recently to IFN-free regimens. The latter are used as SOC in the US and many European countries, while in other countries IFN-based regimens are still widely used as SOC for the “easy-to-cure” IFN-sensitive patients.

Assessment of host and viral factors allows optimizing the approach to individual patients by stratifying them according to the likelihood of disease progression and the potential response to P/R or TT. The current scenario encompasses six different clinical situations: (a) patients who can be easily cured by P/R; (b) patients who can obtain a significant advantage with the use of TT with P/R and first/second generation DAAs [5](naive subjects with unfavourable predictors of response and treatment-experienced subjects who failed to clear HCV on P/R with a profile of partial response); (c) subjects who are unlikely to respond to TT (null responders to previous P/R); (d) patients unfit for any type of IFN-based regimens, who should wait for IFN-free therapies even in the presence of progressive disease; (e) subjects who have slow or non-progressive disease and can thus wait for newer, better therapies (“too mild to treat”); (f) subjects who should not be treated at all, due to advanced age or relevant comorbid conditions that shorten life expectancy (“too sick to treat”).

Further therapeutic options will be soon available worldwide. Three new DAAs, the nucleotide polymerase inhibitors sofosbuvir, the second-generation protease inhibitor (PI) simprevir, and the NS5A inhibitor daclatasvir, are now authorized by the regulatory agencies in the US and the EU and are already available for use. Conceivably other IFN-free combinations will receive regulatory approval within 2015.

We here assessed the ethical issues raised by the use of the first-generation HCV PIs and by the selection of patients for the most appropriate IFN-containing regimen within a Health Technology Assessment (HTA) process. Our aim is to support decision-making not only by giving a proper ethical assessment in an HTA framework for PIs that could be used for restricted patients subgroups, but also by presenting a model that could fit for new upcoming protocols.

2. Methodology and toolbox

The present ethical assessment was conducted as an integrated part of two HTA processes of the Italian Workshop on Pharamacoconomics (Workshop Nazionale di Economia e Farmaci in Epatologia – WEF-E). The topic was the use of the first-generation anti-HCV PIs.

The WEF-E was set up by the Technology Assessment Unit (Unità di Valutazione delle Tecnologie (UVT)) and the Department of Internal Medicine and Gastroenterology of Policlinico Gemelli Hospital of the Università Cattolica del Sacro Cuore (UCSC) of Rome (Italy).

The workshops involved a panel of experts from several fields and were held in Rome in June 2011 and April 2012 (WEF-E 2011, WEF-E 2012).

HTA can be a convenient method for supporting effective and sustainable healthcare decision-making activities. It represents a systematic assessment of the properties and effects of a health technology in a defined context. HTA extends beyond safety, effectiveness, and costs in order to consider the social, organizational, legal, and ethical consequences of the use of a health technology. Considering that technologies are always introduced into a society or organization together with a set of values, and that their implementation can raise moral consequences, the ethical domain has been identified as a key element of HTA since its inception in the 1970s, with the aim to identify and analyse the ethical questions raised by the use of a certain technology.

A considerable number of validated models and frameworks can be successfully used to address ethical issues in HTA [6–10]. However, since different methods stem from different ethical models, the outcome of the analyses could be slightly different, while the main ethical aspects to be examined remain the same.

Among several options, the personalist approach (“triangular model”) was chosen [10]. In short, this approach is established on the human person as reference-value. The person is conceived as a complexity of body-mind into which all ethical judgments, also from the social point of view, should be steered.

Omitting a full explanation of its theoretical aspects, this method practically performs ethical evaluations through three fundamental steps: (1) data collection (data level); (2) ethical analysis (anthropological level); (3) ethical evaluation (assessment level).

The first step (the point “A”) is an in-depth study of all empirical data (clinical, economical, etc.) concerning the technology in question. Regarding the present assessment, this level is represented by the work carried out during the WEF-E 2011 and WEF-E 2012 on first generation PIs.

The second step (point “B”) is the ethical analysis of possible values at stake or in conflict, in light of the human person-centered perspective about the technology in object. This step is conducted through a comparison with the following operating criteria/principles: (a) the defence of human physical life as a whole, and its integrity and quality; (b) the therapeutic principle, according to which the ethical acceptability of a treatment requires that the following conditions should be met: the intervention in question is on a sick part of the body in order to save/cure the patient; invasive interventions are justified when less invasive alternatives are not available; a proportionate clinical outcome; patient’s informed consent; (c) the principles of freedom and responsibility, according to which the patient is required to give free and informed consent to a treatment, but also to consider all possible consequences related to it, including the ethical issues; (d) the principles of sociality and subsidiarity. According to the principle of sociality, in promoting life and health all citizens work toward respecting their own lives and the lives of others as a good; according to the principle of subsidiarity, the community must, on the one hand, help more where the need is greater and, on the other hand, must not supplant/replace free initiatives of individuals and groups.

The third step (point “C”) consists of the ethical assessment that could support practical choices. The assessment should show key-points on ethical concerns in order to support decision-making activities.

3. Ethical evaluation

3.1. Defence of human physical life/therapeutic principle

The first requirement needed to evaluate whether the use of any treatment is ethically acceptable, is to assess the balance between benefits and risks/adverse effects for patients, assuring firstly the defence of human physical life and, consequently, the quality of life.

Sustained virological response (SVR) is considered as a good surrogate end-point of antiviral therapy in patients with CHC or cirrhosis [5], being a prerequisite to obtain the ultimate end-points
of prevention of liver-related complications and improvement of survival.

Regarding the first generation TT, restricted to patients with HCV genotype 1, current data show that [5]: (1) the SVR rate is generally higher than with P/R in naïve subjects; (2) some naïve subjects respond equally well to P/R and TT; (3) subjects who have failed previous P/R are most likely to obtain SVR on TT if they had a previous partial response to P/R, but much less so if they are IFN-insensitive, i.e. previous “null responders”; (4) duration of TT may be shorter than that of P/R in selected patients, if a response-guided approach is used; (5) the SVR rate may be modest in the presence of advanced fibrosis or cirrhosis, i.e. subjects who are in greater need of treatment. Moreover, treatment with IFN-containing regimens in patients with cirrhosis is associated with increased toxic effects; (6) special patient groups (patients with organ transplants, or subjects with HIV/HCV co-infection) may respond less and have specific adverse events.

Nevertheless, safety/effectiveness data show the following critical points: (1) phase 3 studies do not consider some safety issues related to populations with specific comorbidities, in which renal damage [11], unforeseen drug–drug interactions [12], or resistance-associated viral variants due to inappropriate drug use could occur; (2) effectiveness data on TT (phase 4, post-marketing surveillance) are vastly incomplete since the groups that form the bulk of everyday practice are poorly represented; (3) studies do not consider issues related to genetics, epigenetics, and environment; (4) no large prospective assessment of on-treatment and post-treatment quality of life (QoL) of patients receiving TT has yet been made available.

TT with boceprevir or telaprevir yields better results than P/R in terms of viral eradication, however more adverse events occur in real-life, especially in patients with advanced disease [5,21]. The safety/effectiveness profile of these PIs is acceptable if they are used in specific classes of patients: i.e. patients with HCV genotype 1 and patients for whom the SOC is ineffective. Another possible benefit of their use is preventing the development of drug resistance to PIs.

Therefore, the use of first-generation HCV PIs seems to fulfill the defence of human physical life and the therapeutic principle.

3.2. Freedom and responsibility

Another ethical prerequisite to use any treatment is the patient’s free and responsible choice. This aspect is associated to the issue of informed consent. Informed consent is generally a process by which the health care provider discloses appropriate information to a competent patient, so that the patient may make a voluntary choice to accept or refuse treatment. In this sense, informed consent is linked to the principles of freedom and responsibility.

An ethically relevant issue in HCV treatment is the “treatment deferral”, which raises specific concerns [13]: if an effective/safe therapy is available, the patient’s choice to defer could have implications for his/her health, as much as the choice of initiating, withholding, or withdrawing therapy. Consequently, physicians need to provide the patient with accurate, understandable information about risks/benefits of deferral.

Arohnson and Jensen [13] argue that key-points of disclosure about deferral include the following: there are limitations both in the staging of liver disease through biopsy and in predicting the progression of fibrosis; the timing and availability on the market of new, more effective, and safer agents in the pipeline is not always exactly foreseeable; in countries where patients’ insurance status is relevant, it might change over time and, consequently, someone may be excluded from a future treatment regimen; deferred initiation of therapy could be more complicated due to both progression of liver disease and new health comorbidities; for high-risk behaviour patients, deferral could put other subjects at risk of HCV infection. Thus, the conclusions of the authors, which can be shared, are: “Although waiting for new therapy is justifiable and appropriate for many patients, this decision should not be viewed as a mere default. With safe and effective therapy available, treatment deferral is no longer a passive decision, but rather an action in itself that requires its own unique consent process: an informed deferral” [13].

Moreover, freedom/responsibility of the other stakeholders (health professionals, public opinion, patient organizations, industries, healthcare organizations/services) raise a further ethically relevant issue: the need for a suitable social information strategy. Social information should be focused on safety, effectiveness, and high costs of new anti-HCV drugs.

In conclusion, suitable information to patients, especially in case of treatment deferral, has to be assured and justified for clinical reasons; at the same time, accurate social information should be provided.

3.3. Sociality and subsidiarity

A third ethical issue required to evaluate the assignment of a treatment to an individual patient is the fulfillment of a fair allocation of resources.

Available cost-effectiveness analyses [14–17] and a pharmacoeconomic simulation carried out within the WEF-E 2012 [18] showed that PIs are cost-effective in the long term, despite requiring important additional investment in the short time (about 300 million Euros during the first year). This is counterbalanced by the expected reduction in liver morbidity and liver deaths and by the ensuring direct and indirect costs obtained by the increase in SVRs [14–19].

Further assessments should be made on: (1) economical, financial, and organizational sustainability for the National Healthcare Service (SSN)/Regional Healthcare Service (SSR); (2) fair access to health services for all citizens with similar clinical needs in different regions. In particular, it should be assessed if the SSNs/SSRs are able to provide the drug, after its authorization, throughout the whole country, also through a sustainable regional network of prescribing centres and “on-line” prescription registries, according to predefined eligibility, management, and stopping rules; (3) reimbursement of the TT regimen (by the healthcare system and/or other third-party payers). An important requirement is to review the costs periodically. Furthermore, a specific assessment about savings could be made for patients eligible for treatment with P/R alone, and patients who do not need immediate treatment with TT or P/R.

A final point deals with micro-allocative criteria of treatment, considering the imbalance between patients’ demand and DAAs/PIs supply. Both the high cost of the treatment and the high number of potential patients make DAA supply a huge economic burden for the SSN/SSR. The most debated criteria [20] are the “first-come, first-served” approach, whereby all patients are eligible for treatment, and the “needs-based” approach, which favours those who bear a higher burden of disease. Both criteria have “pros” and “cons” and the choice is not easy. In fact, all IFN-based regimens, either P/R or TT, are markedly less effective in patients with advanced fibrosis or cirrhosis [5]. However, these patients are those in whom the benefit of viral eradication is evident in terms of reduced hepatic and extra-hepatic mortality [16]. Thus, if those with early, mild disease are preferred for TT, the number of treatments will be high but the clinical benefit modest and distant in time. Conversely, if only those with severe fibrosis are considered for TT, less viral eradication but a more evident personal benefit in the cured patients will be likely.

From an ethical point view, the important points to be considered before selecting an approach are: (1) identifying, and
periodically updating, the categories of eligible patients for a particular therapy; (2) providing social information on the clinical reasons for which only certain subpopulations of patients can obtain PI therapy.

4. Conclusions

The rapidly evolving scenario of new treatments and the changing pattern of HCV disease require a continuous re-tuning on this subject.

Ethical assessment of a health technology is a multifactorial process, which has to take into account issues related both to patient needs/values and elements such as availability, ease of access, and pricing. In US and most Western countries, the on-going evolution of the therapeutic approach has already excluded boceprevir and telaprevir as components of IFN-based therapy. The latest release of the Recommendations for Hepatitis C Treatment from the American Association for the Study of Liver Disease [21] defines P/R and first generation TT as “not advisable” for any group of patients. At the same time, most European and Eastern countries will still be bound to the use of IFN-based regimens for an unforeseeable period of time due to registration and reimbursement issues [5]. In general, IFN-containing regimens will most likely disappear from use within the next year, with the introduction of IFN-free combination regimens, which reduce treatment duration to twelve weeks or less, and obtain viral eradication in more than 90% of patients at any stage of disease. This approach will clearly affect the social ethical issues, since problems related to ease of access and cost in the population—which is potentially much larger than that reached by boceprevir or telaprevir–containing regimens—will need rethinking of the “restrictive” attitudes. However, the reasoning on the current regimens remains important since: (a) these protocols will remain in use for a longer period in some countries; (b) pricing issues will probably create a niche for survival of these regimens in some patient groups [22,23]; (c) issues regarding clinical ethics remain overall applicable.

Moreover, from a pharmaco-economical point of view, we still need complete data about the pattern of use of forthcoming IFN-free regimens to allow a comprehensive and punctual ethical assessment.

Our ethical analysis (Table 1) within an HTA process could be henceforth a useful support to explore future ethical choices, since the problems on appropriateness assessment and how to equitably regulate the access to treatment will remain paramount over the coming years.

Table 1
Emerging outcomes from 1st generation hepatitis C virus protease inhibitors ethical assessment.

| The ethical assessment of the first-generation hepatitis C virus (HCV) protease inhibitors (PIs) has shown that: |
| 1. The use of PIs in HCV treatment fulfills the defence of physical human life and the therapeutic principle, if its use is restricted to specific classes of patients. |
| 2. The principle of freedom/responsibility is fulfilled if patients are carefully informed, particularly in the case of “treatment deferral”. Moreover, social information on these therapies should be implemented. |
| 3. Since PIs proved to be cost-effective, according to the principle of sociality/subsidiarity, their use is acceptable respecting the macro-allocation of resources. Regardless of micro-allocation criteria, key points include: |
| (a) to identify and periodically update the categories of eligible patients |
| (b) to provide widespread information on criteria for eligibility to treatment or its deferral for specific patient subgroups. |

Conflict of interest
None declared.

Acknowledgement
The authors thank all other participants of the WEFs held on 2011 and 2012, which they represent in this article.


References
