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Prioritization of high-cost new drugs for HCV: making sustainability ethical

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Abstract. – Hepatitis C virus (HCV) infection is a major health problem worldwide. Chronic HCV infection may in the long run cause cirrhosis, hepatic decompensation and hepatocellular carcinoma, with an ultimate disease burden of at least 350,000 deaths per year worldwide. The new generation of highly effective direct acting antivirals (DAA) to treat HCV infection brings major promises to infected patients in terms of exceedingly high rates of sustained virological response (SVR) but also of tolerability, allowing even the sickest patients to be treated. Even in the face of the excellent safety and efficacy and wide theoretical applicability of these regimens, their introduction is currently facing cost and access issues denying their use to many patients in need. Health systems in all countries are facing a huge problem of distributive justice, since while they should guarantee individual rights, among which the right to health in its broader sense, therefore not limited to healing, but extending to quality of life, they must also grant equal access to the healthcare resources and keep the distribution system sustainable. In the face of a disease with a relatively unpredictable course, where many but not of all chronically infected will eventually die of liver disease, selective allocation of this costly resource is debatable. In most countries the favorite solution has been a stratification of patients for prioritization of treatment, which means allowing Interferon-free DAA treatment only in patients with advanced fibrosis or cirrhosis, while keeping on hold persons with lesser stages of liver disease.

In this report, we will perform an ethical assessment addressing the issues linked to access to new therapies, prioritization and eligibility criteria, analyzing the meaning of the term "distributive justice" and the different approaches that can guide us (individualistic libertarianism, social utilitarianism and egalitarianism) on this specific matter. Even if over time the price of new DAA will be reduced through competition and eventual patent expiration, the phenomenon of high drug costs will go on in the next decades and we need adequate tools to face the problems of distributive justice that come with it.

Key Words:
Hepatitis C, Cirrhosis, Hepatocellular carcinoma, Direct acting antivirals, Distributive justice, Access to care, Prioritization, Ethics.

Introduction

Hepatitis C virus (HCV) infection is a major health problem worldwide. HCV infection causes chronic hepatitis, potentially leading to cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma (HCC), with an ultimate disease burden of at least 350,000 deaths per year worldwide[1]. The onset and accumulation of hepatic fibrosis is clinically silent in the early stages of disease, and identification of disease progression is, therefore, difficult and intrinsically scarcely predictable[2]. The yearly incidence of progression of hepatic fibrosis from minimal disease to cirrhosis has been modeled and estimated. The prevalence of biopsy-proven cirrhosis after 20 years of infection

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has varied between 7% (in retrospective studies) and 18% (in clinical referred settings)[3]. The risk of cirrhosis is increased in individuals abusing alcohol, in those who acquire the disease at an older age, in those with concomitant obesity, in men, in immunosuppressed HIV-positive patients, and in those with recurrent HCV after liver transplantation[4]. Patients with minimal fibrosis have a low risk of development of complications of liver disease during the subsequent two decades; conversely, patients with bridging fibrosis or cirrhosis have a higher risk. Serial assessment of fibrosis over time by liver biopsy or non-invasive imaging techniques such as fibroelastometry or acoustic resonance imaging samples[5] might be needed to detect progression and to identify patients with advanced fibrosis most in need of immediate treatment.

The main goal of treatment for chronic HCV is cure, and thus prevention of disease progression. Eradication of HCV, defined by a Sustained Virological Response (SVR), i.e. HCV RNA < 15 IU/mL 12 weeks after completion of antiviral therapy and thereafter, is associated with reduction of both all-cause and liver-related mortality from HCV[6,7]. Patients with cirrhosis are at more immediate risk of complications of liver disease.

The standard of care for chronic hepatitis C has been up to 2011 pegylated interferon alfa (IFN) and ribavirin for 24-72 weeks, with a SVR in 40 to 50% of treated individuals (a minority of those infected), and clinically significant adverse events. Between 2011 and 2013, the introduction of two first generation HCV protease inhibitors, boceprevir and telaprevir, to be used in combination with IFN and ribavirin, obtained a relatively modest increase in SVR (+ 20%) at the expense of major toxicities. Favorable responses to interferon-based treatments are less common in patients with cirrhosis compared with those without cirrhosis[8], and are still unsatisfactory when first-generation protease inhibitors are combined with interferon and ribavirin, further increasing the potential risks of adverse events[9]. As of today, numerous second-generation direct-acting antiviral agents (DAA) enabling the use of IFN-free, easily applicable, all-oral regimens have been approved in US by the Food and Drug Administration (FDA) and in the EU by the European Medicines Agency (EMA) and have entered clinical practice worldwide[10]. Omitting pegylated IFN and discarding boceprevir and telaprevir due to their unfavorable adverse events and tolerability profile has been made possible by an expedited design and competitive conduct of DAA combination trials striving for HCV treatments, fostered by FDA's "breakthrough" registration pathway[11].

The regimens approved for clinical use in EU countries by the EMA[12] currently encompass:

1. A nucleoside NS5B inhibitor (sofosbuvir), with ribavirin;
2. A nucleoside NS5B inhibitor (sofosbuvir) plus a protease inhibitor (simeprevir) or an NS5A inhibitor (daclatasvir), with or without ribavirin;
2. A fixed-dose combination of sofosbuvir plus an NS5A inhibitor (ledipasvir);
3. A fixed dose combination of a non-nucleoside NS5B inhibitor (dasabuvir) plus a protease inhibitor (paritaprevir, boosted with ritonavir) plus an NS5A inhibitor (ombitasvir), with or without ribavirin.

Except for *a*, recommended only for HCV genotype 2, all others cover all HCV genotypes, but are less effective against genotype 3. Reported rates of success, in terms of SVR, exceed 90% in all groups of patients, including those with cirrhosis. Other, even more effective DAA combinations are being developed[13] for use in the most difficult to treat and advanced patients, aiming for 100% of SVR in 100% of patients.

In a setting of restricted access to DAA (related to costs, actual availability and the wait for even better and universally applicable regimens), the selection of patients for immediate treatment or deferral entails strict adherence to established, validated and ethically accountable policies. In this article we will perform an ethical assessment addressing the issues linked to access to new therapies, prioritization and eligibility criteria, analyzing the meaning of the term distributive justice and the different approaches that can guide us regarding the matter.

Even if over time the price of new DAA will be reduced through competition and eventual patent expiration, the phenomenon of high drug costs will go on in the next decades and we need proper tools to face the problems of distributive justice that come with it[14].

Economical Impact and Access to Care

Enthusiasm for the new regimens has been dampened by their exceedingly high costs, a major obstacle to delivery. The extremely high price tag of DAA, unbearable for many health care

systems, has generated what has been defined as a "sticker shock" in most countries[15]. Moreover, the need for IFN-free combination regimens with two or more DAA for most of the patients and longer treatment duration for patients with cirrhosis causes a further increase of costs. This is why it is of uttermost importance to combine clinical evaluations of "real-life efficacy" of these regimens with pharmaco-economical analyses and Health Technology Assessment (HTA) reports, in order to reach a definite balance between cost-effectiveness and the actual margins of negotiation available to provide widespread access to therapy to all in need, avoiding both economic speculation and medical tourism to countries that provide these new drugs at lower cost.

However, all-oral HCV drugs on the horizon are expected to be cost-effective: recent studies have indicated that for genotype 1, the current DAA-based regimens are cost-effective[16], and recent discounting efforts promise to make them even more so.

In addition we must consider that chronic hepatitis C is a systemic condition and has been strongly associated with other pathologies such as diabetes mellitus, cardiovascular disease, psychiatric disorders, renal dysfunction and rheumatologic conditions; if we consider not only liver-related clinical outcomes, but also extra-hepatic complications, assessments of cost-effectiveness of HCV therapy could result even more positive[17]. In this sense, pharmaco-economics has pushed us towards thinking not in mere terms of price but rather in accounting terms, in order to evaluate sustainability and current assets together with the reduction of costs. Cost-effectiveness and cost are not considered in fact as equivalent: being cost effective does not guarantee the financial sustainability in the short term. Hence, since these treatments should be applied to so many persons over so brief a period, there would be a significant budgetary strain.

The current costs of DAA combinations active against HCV mean that on a global level far less patients than needed are being treated (only a minority of the estimated 130-150 million people infected world-wide are diagnosed and even fewer are assessed for eligibility and initiated on treatment) and that no population-wide public health benefit can be expected for some of the most heavily affected countries[18,19]. Even in the face of the excellent safety and efficacy and wide theoretical applicability of these regimens[20], their introduction is currently facing cost and access issues denying their use to many patients in need[21], suggesting policies of mixed use of IFN-containing and IFN-free regimens to reduce costs, even if the pressure to avoid IFN-containing regimens has become overwhelming in 2015.

In most countries the (at least early) favorite solution – e.g. in Italy – has been a stratification of patients for prioritization of treatment, which means allowing IFN-free DAA treatment only in patients with advanced fibrosis or cirrhosis, while keeping on hold persons with lesser stages of liver disease (so-called 'informed deferral' policies)[22]. A similar situation arose at the outset of the HIV/AIDS epidemics, until the availability of generic compounds removed the price obstacle.

The cost of new DAA treatments seems to be the most significant barrier to HCV eradication: surmounting it will require collaboration among healthcare providers, drug manufacturers, local and national governments and other stakeholders. We should, therefore, question about ethically proper margin profits for drug manufacturers and ways to limit the high price tags of drugs (patenting, treatment scale up). But most urgently we have to address the ethical issues linked to access to new therapies and to eligibility criteria. Even if over time the price of new DAA will be reduced through competition and eventual patent expiration, the phenomenon of high drug costs will go on in the next decades and we need proper tools to face the problems of distributive justice that come with it.

What Does Distributive Justice Mean in Medicine?

The continuing technical evolution of medicine has brought extraordinary benefits in terms of health and of Quality of Life (QoL), but has been accompanied by an exponential growth of the cost of drugs and medical devices. This entails that as individuals we all have a rightful aim towards the biggest benefit in terms of health for ourselves; but as a society, on the other hand, we need to strike a balance between obtaining the best possible result for each individual and the needs of the society as a whole. This means that the choice that maximizes population's health or has the best overall cost/effectiveness is not necessarily the best choice for a specific individual, and that the best choices may differ for different individuals[19]. National States, therefore, are often facing a huge problem of distributive justice. On the one hand they need to be able to guarantee

individual rights, among which the right to health in its broader sense, extending to compliance and QoL)[23]; on the other hand, they need to grant equal access to the resources and the sustainability of the distribution system. It is quite clear that the ultimate goal for a democratic society would be obtaining what is best for each individual, but in doing so it should aim not towards the best possible cure, but the best cure possible. This basic assumption is essential, even though it often leads to a conflict with the desires and aspirations of singles, especially since immediate access to information about new and potentially effective treatments is easily available to anyone. The prior considerations should make clear why it is necessary and urgent to perform an ethical assessment about access and prioritization of new DAA treatments.

An ethical assessment about health care policy means judging it in terms of justice/injustice. The principle of justice could be described as the moral obligation to act on the basis of fair adjudication between competing claims. As such, it is linked to fairness, entitlement and equality. Justice is concerned with the equitable distribution of benefits and burdens to individuals in social institutions, and how the rights of various individuals are realized. In healthcare ethics, justice can be subdivided into three categories: fair distribution of scarce resources (distributive justice), respect for people's rights (rights based justice) and respect for morally acceptable laws (legal justice)[24].

With regard to distributive justice, which rules the relationship between the society and its members, allocative choices can be made at two levels: a social level, named "macro-allocative", and an individual level, named "micro-allocative". Macro-allocative decisions are policy decisions about which programs and services should be offered in a context of scarcity and how public funding should be distributed between different levels of assistance: for example which part of the national budget must be directed to healthcare, how to distribute it into different programs, which diseases should come first, and so on. Micro-allocative decisions, also called patient-selection, are about selecting the patients who will receive a treatment, making a prioritization of the patients or of the treatments, therefore focusing on decisions that concern the single patient. In any case, while the fate of individual patients is not directly at issue in macro-allocative decisions, those decisions do affect individual patients indirectly.

In this article, we are focusing on micro-allocative issues linked to the new treatments for HCV reminding, however, the great importance of macro-allocative issues that should therefore be deeply analyzed.

Individualistic Libertarianism, Social Utilitarianism and Egalitarianism

The ethical assessment of a health care policy depends on the context and also on the ethical approach adopted, given that there is not a universally accepted ethical framework. There are three fundamental frameworks adopted as reference within an ethical assessment in this setting: individualistic libertarianism, social utilitarianism and egalitarianism. Depending on the ethical model adopted, the meaning of justice in healthcare, and the practical consequences will change.

Individualistic libertarianism privileges individual freedom more than social benefit. It aims to gain the maximum of freedom for each individual and conceives justice as the moral oblige not to damage the others. According to this theory, the State is compelled not to intervene in ways that limit individual freedom. When applied to the distribution of resources in healthcare, justice in liberalistic conception means at a macro-allocative level deleting every kind of public healthcare system and giving space to free marketplace. At a micro-allocative level it means that the selection of the patient and the prioritization for a treatment depends on the capability to pay and on an individual choice (individual autonomy).

Utilitarianism as a theory of justice is based on a principle of utility, approving every action that increases human happiness (by increasing pleasure and/or decreasing pain) and disapproving every action that diminishes it. According to the utilitarian approach, justice should strive to create the greatest happiness of the greatest number of people. A law is just if it consequences in a net gain in happiness, even at the expense of minorities. Utilitarianism still plays a major part in the democratic decision-making process; it is a secular theory requiring no reference to any natural rights or religious principles defensible by faith.

In macro-allocative justice, utilitarianism privileges financing those sectors that will increase social wellness and those areas of healthcare that will grant return to productivity for the patients. At a micro-allocative level the sentient patients, and especially those who are expected to return to productivity, will be preferred in the selection.

Egalitarianism is a theory that privileges social benefit at the expense of individual freedom, requiring the maximum intervention of the State and reducing free individual choice to the minimum, favoring equality for all the people. Egalitarian doctrines maintain that all humans are equal in fundamental worth or social status, advocating the removal of economic inequalities among people. The State should, therefore, intervene to guarantee minimum standards of care and assistance. At a macro-allocative level egalitarianism requires the maximum intervention of the State in healthcare policies, with more attention to the poorer/disadvantaged people. At a micro-allocative level it tends to guarantee equal access to cure and the same opportunities for everyone. We should make great care not to mistake *equality*, which can be intended as a mere leveling and equalization, with *equity*. What should be equal is the final result, not the mean used or the amount of resources invested. Gillon[24] emphasizes that justice is more than mere equality and that people can be treated unjustly even if they are treated equally. With reference to Aristotle [25,26], he argues that it is important to treat equals equally and unequals unequally in proportion to the morally relevant inequalities (the criterion for which is still being debated). Situations will always arise where decisions have to be taken and there are limited resources, different options and/or other conflicting moral concerns. Egalitarianism means therefore in the healthcare systems giving the same answer to the same individual need for care, in order to obtain equal results for all.

Many different countries in the world have adopted a model of *Welfare State*, e.g. in UK and Italy, based on the egalitarian conception of distributive justice, which envisages a public healthcare system with equal access to care for every individual. In order to give the same answer to the same individual health need, the allocation system is needs-based and it tends to give priority to the patients with greater need: this system satisfies the principle of justice while placing appropriate emphasis on medical need. According to this option, in these countries the ultimate goal for society as a whole is to obtain what is best for each individual, but in doing so, it aims not towards the best possible cure, but the best cure possible. This basic assumption is essential, even though it often leads to a conflict with the desires and preferences of individuals.

Scaling Individual's Health Need

The crucial problem is therefore identifying, quantifying and scaling the health need of the patients, according to the progression of the infection. Can we really be sure about the progression of HCV infection for each individual? Can we quantify the risk?

The patient group that benefits the most from the new DAA therapies is that with clinically evident cirrhosis, with decompensated cirrhosis and with other serious comorbidities. The next group includes asymptomatic patients with advanced fibrosis or cirrhosis, to be identified by an assessment of hepatic fibrosis based on non-invasive diagnostic measures. While advanced fibrosis are clearly at highest risk for short-term complications, it is not clear that persons with lesser degrees of fibrosis are not at risk[17].

Therefore, we still need data about the risks of treatment deferral, also considering that we have evidences that disease progression is not linear in chronic hepatitis C[27]: recent analyses have demonstrated that rates of fibrosis progression may be more accelerated than previously thought[28]. A treatment deferral could thus run the risk to allow progression to cirrhosis for a subset of patients, therefore increasing their future risk of hepatic decompensation or HCC[17]. The problem becomes more evident for patients with minimal or mild fibrosis, as the specific risk factors for disease progression have not been clearly defined yet, not allowing to have certain indications about the precise benefit and optimal timing of antiviral therapy in patients with early-stage disease. Moreover, in a prognostic setting, predictions are used to plan therapeutic choices based on the risk of a specific outcome, and estimates of probabilities are seldom based on a single predictor. In fact, physicians naturally integrate several patient's characteristics and symptoms to make a prediction: prediction is therefore inherently multivariable[29]. Although deterministic and probabilistic analyses try to take these aspects into consideration, they often fail to capture the full complexity of the clinical decision on the individual patient. In this setting, more detailed treatment comparisons could be gained by combining the different variables affecting the achievement of SVR, using multivariate risk modeling[30]. Last but not least, we should take into account symptoms of HCV, such as malaise, fatigue and abdominal pain, which – according to Pho et al[31] – might lower quality of life throughout the time that a patient is forced to wait for therapy.

According to Aronsohn and Jensen[22], an informed deferral is anyhow needed considering risks related to inaccurate staging of liver disease with a biopsy (sampling error), inability to predict progression of fibrosis and comorbidity changes over time. We also have to be aware that deferral requires a system of healthcare delivery that allows tracking and monitoring of patients in whom treatment is deferred, with serial non-invasive fibrosis measures while preventive care is provided[32].

Recent data show that the health benefit of waiting for IFN-free therapy instead of immediate IFN-containing regimen is lost when wait time for the new regimens is greater than 3 years for cirrhotic patients and 3.2 years for non-cirrhotic patients. Therefore, an analysis on how long it may be possible to defer IFN-free treatments without prejudice for a patient's health can be a useful tool, but cannot be used to justify the status quo and the adoption of a double track for treatment. In this sense, clinicians' analysis on therapeutic options and deferral "pros" and "cons" are giving us a definite timeline for facing and solving price issues of new treatments without prejudice for those who at the time being are not eligible for the new treatment.

Screening

Given the limited ability to risk-stratify early-stage patients and the possibility of accelerated disease progression, together with the high efficacy of new DAA, a compelling argument can be made to offer treatment to everyone, as recommended by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) HCV Guidance[33]. Although it can take HCV-infected individuals 20-30 years to develop serious health consequences, treating them as early as possible after diagnosis would probably minimize CHC-related morbidity and mortality[34]. On the other hand, overtreatment of potential non-progressors could raise the bar of costs beyond affordability for most countries, thus denying societal benefit (reduction of global disease burden) without individual benefits.

In addition, early treatment harnesses preventive potential by removing infected individuals from the pool of transmitters soon after infection, increasing the number of possible infections prevented and reducing associated costs. To date it is estimated that more than 90% of HCV infected individuals worldwide are unaware of their HCV positive status, also due to the fact that chronic hepatitis is asymptomatic until the developments of late-stage cirrhosis or HCC[35]. Therefore identifying and testing at risk populations would represent a critical step towards control and ultimately eradication of HCV infection, based on the concept that treating all patients regardless of fibrosis stage would be in the long-term the best cost-effective choice.

Several analyses emphasize the cost-effectiveness of a birth-cohort screening policy; while other studies portend that treating younger cohorts of HCV-infected individuals would maximize medical costs averted and quality-adjusted life years gained[34,36]. It has been estimated that in the USA birth cohort-based screening has the potential to identify up to 75% more HCV infections in a specific age group (individuals born between 1945 and 1965) compared to risk-based screening, depending on the percentage of the population that is tested[34]. However, the cost effectiveness of this screening strategy is especially sensitive to treatment uptake rates, requiring a certain threshold rate to generate sufficient cost savings and life expectancy gains to offset screening costs[34].

By converse, the current high price tag of new DAA keeps the financial stakeholders bound to stratification and prioritization. Moreover, no coherent strategies and resources to implement a population-wide screening and to systematically care for a large number of newly diagnosed HCV patients have been validated[37]. We definitely need to be aware of the difference between judging an intervention as cost-effective and having available the actual resources in the current moment to support the intervention. Should the price of DAA go down as predicted, the ultimate goal would become control of HCV in the general population, and hence universal screening would be needed, to allow for early intervention.

Some ethical issues arise when discussing universal screening, besides the obvious problems linked to privacy. False positives tests (i.e. anti-HCV positive who are HCV RNA negative) would cause an unnecessary psychological burden, while false negatives (i.e. HCV RNA positive missed because of a negative anti-HCV test, such as the saliva test) would reduce effectiveness of screening and foster a false sense of reassurance. Wrong screening results, as few as they might be, would also potentially jeopardize family and emotional relationships, employment, and insurance status. Most importantly, in the setting of possible access to cure, all infected persons

found by screening should be granted the possibility of an effective, tolerable and affordable treatment, regardless of the stage of their liver disease. Last but not least, should screening be made compulsory, individuals who refuse to be informed about their infection and health status would be forced to acknowledge the presence of infection.

Conclusions

As in many fields in medicine, the balance between individual rights to HCV care and societal benefit must be reached by taking into account factors as diverse as the natural history of the disease, its actual prevalence, our power to predict the course and the availability of an effective cure, and most of all the willingness of each person to be screened and eventually cured for the condition. Financial, organizational, industrial and political constraints cannot be held as primary decision factors, but should be held as cofactors regulating in the short term the ease of access to care.

Fine-tuning of the decision process to allocate therapies will in any case need a further evolution of knowledge on the long term effects of deferring or denying cure on the disease, and ultimately on the infection burden worldwide.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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