The public health and HTA perspective on modern treatment methods of hepatitis C

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The hepatitis C remains a serious health problem and a public health threat. The new pharmacological treatment regimens seem to offer a breakthrough in fighting this disease and possibly even a promise to eradicate it, however at a very high cost. The health technology assessment of the novel therapies is associated with several problems which are presented in this paper.

THE HEPATITIS C AS A HEALTH PROBLEM AND A PUBLIC HEALTH ISSUE

The hepatitis C virus (HCV) was discovered in 1989 as a causal agent of the particular type of viral hepatitis, which had been called "non-A, non-B hepatitis" before that discovery. It is a blood borne virus and there is a major role of the iatrogenic factors in its transmission which includes the use of injectable drugs, the inadequate sterilization of medical equipment and the transfusion of unscreened blood and its products. The virus can be also transmitted sexually or from mother to baby. From 15 to 45% of people clear the infection spontaneously by their immune system. The incubation period is from half a month to six months. The symptoms include fatigue, jaundice, grey-colored faeces, dark urine, joint pain, nausea, vomiting, abdominal pain and decreased appetite. However, 80% of people don't exhibit symptoms after the infection. The diagnosis includes serological testing for anti-HCV antibodies and nucleic acid testing for HCV-RNA, as well as assessment of the liver damage (fibrosis and cirrhosis) through biopsy and non-invasive tests [1].

The hepatitis C has been extensively spreading from the 1940's and 1950's in Japan through the 1960's to 1980's in North America and Western Europe. In the 1970's it was a major cause of chronic hepatitis in transfusion recipients [2]. Worldwide the hepatitis C causes approximately 25% of all cases of liver cirrhosis and cancer. The chronic infection is the main cause of chronic liver disease in the USA and Western Europe but the regions with the highest prevalence are East and Central Asia as well as North Africa. The incidence of hepatitis C in the European Union is 8.7 per 100,000. The hepatitis C is the cause of large reduction in life expectancy and health-related quality of life. There are estimations that for a 43-year old patient with mild hepatitis the reduction in survival is up to three years. However, in the case of moderate hepatitis it jumps to nine years, while in compensated cirrhosis even to 16 years [3, 4, 5, 6].

According to the WHO from 135 to 150 (170 in some other estimates) million people worldwide are chronically infected with hepatitis C; 80% of whom live in middle-income and low-income countries. The mortality rate due to hepatitis C is from 350 to 500 thousand deaths per year [1]. By 2007, HCV infection had superseded HIV infection as a cause of death in the USA [5].

THE DEVELOPMENT OF THE HEPATITIS C PHARMACOLOGICAL TREATMENT METHODS

The major efforts in the hepatitis C treatment are being put into the achievement of a sustained virological response (SVR) after completion of the anti-HCV pharmacological therapy. By this means the progression of the disease is being slowed down. As the main parameter of monitoring the changes in viremia, the SVR is defined as undetectable (or below the lower limit of quantification) HCV RNA at 12–24 weeks after cessation of treatment [7]. As a biomarker indicative of the viral clearance instead of a "true" or finite endpoint like e.g. mortality or existence of a disease, the SVR is considered the best available indicator of viral clearance [8].

Initially the chronic HCV treatment was based on the interferon (IFN) alpha, to which the ribavirin (RBV) was later added. The further improvements included the replacement of IFN with its pegylated form called the pegylated interferon (peg-IFN) and then addition of the initial protease inhibitor direct-acting antiviral (DAA) therapies, like telaprevir or boceprevir. The newest therapeutic regimens are IFN-free and they include medicines like sofosbuvir, ledipasvir, paritaprevir, ombitasvir, dasabuvir [9]. The gradual development of the hepatitis C pharmacological treatment methods

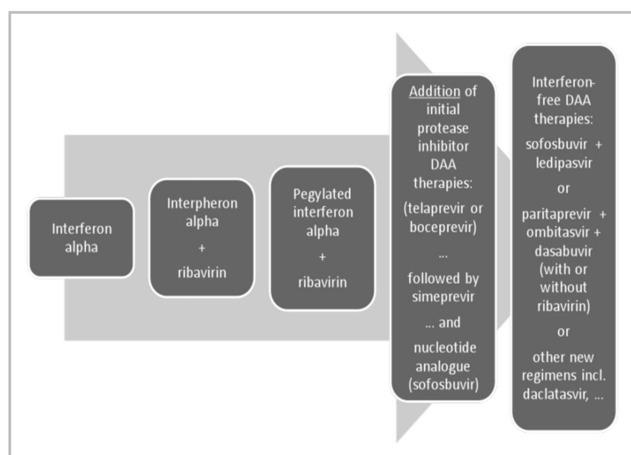

Figure 1.
The development of the hepatitis C pharmacological treatment methods [based on: 9].

(starting from IFN to the newest medicines) has been presented in Figure 1. It reflects the efforts to increase the efficacy as well as the tolerability of the antiviral pharmacotherapies. However, the improvements in clinical outcomes of the hepatitis C treatment are being achieved with a significant cost, putting a heavy burden onto the patients and/or the third-party payers worldwide.

THE HTA ISSUES ASSOCIATED WITH THE HEPATITIS C TREATMENT

There are several issues which are important when the health technology assessment (HTA) approach is taken to assess the novel anti-HCV therapies.

The new treatments offer the achievement of higher SVR rates or the new options of IFN-free regimens for those patients who cannot tolerate IFN or respond poorly to their previous therapies. As far as the clinical effectiveness assessment is concerned, the human genetic predispositions have to be taken into consideration (the pharmacological interventions depend on the HCV genotype). The patient's genetic predispositions allow to predict the positive response to treatment. The assessed intervention could be either a single new medicine or its combination with RBV or other new medicines. The novel pharmacological interventions which undergo the HTA lack the peg-IFN as well as the non-peg-IFN. The analyzed populations depend on treatment naivety or kind of former treatment. The comparators include the standard treatment methods, like boceprevir plus peg-IFN plus RBV.

During the next stage of the HTA process (the economic analysis) the cost-effectiveness is being assessed for the different HCV genotypes. The specific factors which can be included in sensitivity analysis are e.g. the cost of pharmaceuticals, the alcohol intake or the patient characteristics (age, phase of liver fibrosis). On one hand the new pharmacological treatment methods of HCV seem efficacious but on the other they tend to be extremely expensive. The new medicines do not seem to actually reduce overall spending and it appears to be a serious obstacle, generally being not welcome among the payers [10].

For many new pharmacological regimens the cost-effectiveness ratio exceeds the conventional thresholds pertaining to the additional QALY gained, like three times GDP per capita or other in different jurisdictions. Although the new medicines can be more economically attractive in subgroups of patients at the higher liver fibrosis stages or being younger at the time of treatment initiation, the application of differentiated cost-effectiveness ratios can raise ethical concerns.

The economic analyses of the novel hepatitis C treatments have several limitations. They include lacking data on real-world effectiveness and uncertainty of prices due to the price negotiations or the confidential risk-sharing schemes. There are also several factors related to the clinical heterogeneity which can influence the cost-effectiveness estimations. They include: gender, age, HIV coinfection and other comorbidities, patients' genetic IL28B polymorphism or liver fibrosis [11].

In the last stages of the HTA of the novel hepatitis C therapies the budget impact analysis is being performed. It is worth mentioning that the extremely high prices of new medicines can substantially increase short-term overall drug expenditures. It has also to be taken into consideration that the possibility to avoid the peg-IFN-based regimens which are unpleasant for patients can intensify the HCV screening, which can result in an increasing demand for the new, expensive pharmacotherapies.

Whether the hepatitis C can be eradicated remains the debatable issue [12]. There are several factors which favour or prohibit the hepatitis C eradication and the positive forecast for the HCV patients – they have been presented in Figure 2.

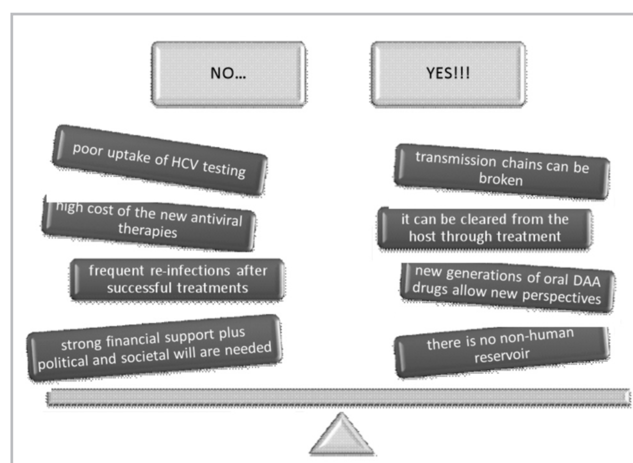

Figure 2.
The factors which favour or prohibit the hepatitis C eradication [based on: 12].

There are several lessons taken from the experiences with fighting the global HIV/AIDS epidemics which could be considered helpful in HCV eradication efforts, especially among the low and middle income countries [6]. The mobilization of civil society to demand a human rights-based approach to treatment access seems to be crucial. The activity of inter-governmental agencies and foundations are also important. Other mechanisms include generic competition, voluntary or compulsory licensing or tiered pricing. Despite the normally high market prices achieved in high income countries for DAA therapies (over USD 100,000 per treatment) the actual production cost for a 12-weeks regimen is estimated at less than USD 250 [6].

CONCLUSIONS

- The new pharmaceuticals seem to offer a breakthrough in hepatitis C treatment.
- The possibility of the hepatitis C eradication has become a non-fiction issue but it depends on many factors.

- The high cost of new medicines is currently a major obstacle in widening patients' access to treatment.
- The HTA offers invaluable assistance in rational scientific approach to introduction of new hepatitis C regimens.

DISCLAIMER

The views and opinions expressed in this article are those of the Author and not the institutions he is associated with.

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AUTHOR'S RESUME

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