

Chronic Hepatitis C – in Risk Groups in Eastern Europe: a Global Public-health Problem

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Abstract:

Hepatic diseases are the sixth most common cause of death in the European Union. The World Health Organization has adopted a global strategy to eliminate viral hepatitis as a serious public health threat by 2030. Approximately one quarter of patients with CHC (chronic hepatitis C) has developed cirrhosis of the liver. It is a precancerosis with a high risk of developing hepatocellular carcinoma. From an epidemiological point of view, injection drug use (IDU) is the most significant way of transmitting HCV infection. Patients with an increased risk of transmitting HCV infection, active IDUs, homosexuals with risky sexual practices, women planning to conceive, patients undergoing hemodialysis and prisoners should all be treated in preference. This population of patients is threatened by an addiction itself as well as by infections, repeated reinfections or mixed infections, concomitant mental disorders or diseases, and multiple associated disorders. To the fulfilment of the WHO strategy on HCV elimination/eradication would certainly contribute a nationwide screening in individual European countries and active collaboration with general practitioners who could treat patients with HCV by themselves - that is, without help of specialists, with pan-genotypic drugs.

Introduction

The most common public health priorities within the European Union include: environmental health, addictions, chronic diseases, care for the elderly, health inequalities. Public health priorities in the Slovak Republic include especially environmental health, non-communicable diseases occurring on a mass scale and addictions (1).

Hepatic diseases are the sixth most common cause of death in the European Union (Eurostat data). **Along with metabolic diseases** (NAFLD - non-alcoholic fatty liver disease, NASH - non-alcoholic steatohepatitis), **viral liver diseases are considered to be the most frequently occurring liver disease** (2, 3).

The World Health Organization has adopted a global strategy to eliminate viral hepatitis as a serious public health threat by 2030. This strategy covers both, hepatitis B (HBV) and hepatitis C (HCV). Its goals include a 90% reduction of consequences and a 65% reduction of mortality due to HBV/HCV by 2030.

Worldwide prevalence of HCV infection (hepatitis C) is about 2% in the normal population. Worldwide, about 150 million people are infected with hepatitis C virus. Every year, approximately 350-700,000 people die for causes related with HCV infection (4).

The highest prevalence of HCV is traditionally reported in Egypt, where it reaches 15%. Eastern European countries report

a prevalence up to 3.5%, US 1.68%.

In developing regions, HCV infection is still spreading due to an existing huge reservoir of infection with asymptotically infected people without diagnosis or treatment. At the same time, developing countries have an inadequate blood donation testing system; a low level of using single-use medical devices which contributes to hepatitis C spreading. Migration of infected people from developing countries brings the risk of transmission.

Chronic hepatitis C (CHC) is a pre-cancerosis with a high risk of developing hepatocellular carcinoma. In Slovakia, an epidemiological study found that the prevalence of anti-HCV antibodies in adults over 15 years was 1.52%, with chronic infection confirmed by evidence of virus replication in 0.67% (5). It accounts for over 30,000 chronically infected patients, out of which, according to the number of reported diseases, only a minor part was diagnosed. Similar data on underdiagnoses of viral hepatitis

have also been reported in other countries which highlights the need for active screening of this infection.

HCV is transmitted by *parenteral* routes. Prevention is an extremely important part of the health care and it should focus on people infected with HCV as well as on people with risky behaviours. Primary prevention aims to a reduction of the risk of getting the HCV infection and its transmission to other people; **secondary prevention** deals with reducing the risk of liver damage in HCV positive individuals (6). Table no. 1 lists the risk factors for the transmission of HCV infection.

From an epidemiological point of view, intravenous drug use is the most significant way of spreading HCV infection. According to the epidemiological data analysis, around 10 million intravenous drug users (IDUs) worldwide were anti-HCV positive. There are about 2.3 million infected IDUs in Eastern Europe, about 2.6 million infected IDUs in Eastern and South East Asia, China

Tab. 1 Risk factors for the transmission of HCV infection

High risk of transmission:
<ul style="list-style-type: none"> - Anamnesis of intravenous drug use - Contaminated blood, blood products or organs transplanted before year 1990 - Imprisonment - Needle stick or sharp injuries - Performances (e.g. injection administration, vaccination, surgery, transfusion, rituals) including a repeated use or sharing of contaminated tools in countries with a high HCV prevalence - Non-sterile contaminated tattoos or piercing - Repeated hemodialysis - Sharing personal items contaminated with blood of HCV infected person (e.g. razor blades, manicure scissors, toothbrushes) - Sharing contaminated intranasal cocaine tools - HBV infection - HIV infection - Children whose mothers are infected with HCV - Undiagnosed liver disease
Moderate risk of transmission:
<ul style="list-style-type: none"> - Sexual partner with HCV infection - Frequent change of sexual partners - Sexually transmitted diseases including HIV and lymphogranuloma venereum

reports 1.6 million, Russia 1.3 million and the US 1.5 million infected IDUs.

Approximately 70-80% of all infected IDUs are infected with HCV during the first year of drug addiction (7). Transmission between the IDUs is not only linked to contaminated injecting instruments. Other personal items related to the preparation of the drug solution for injection (filters, spoons) are also a source of transmission (8, 9).

In 2016, in the Slovak Republic, 237 cases of CHC (morbidity 4.4/100,000 inhabitants) were reported to the Regional Public Health Offices, representing a decrease of 25.9% compared to 2015. Diseases occurred in all regions of the SR with a maximum in the Banska Bystrica (6.1), Trencin (5.8) and Trnava (5.5) Regions. The lowest morbidity was reported in the Presov (2.4), Kosice (3.0) and Zilina (3.7) Regions.

Diseases were reported mostly in age groups above 15 years. One case occurred in the age group of 5-9 years. The highest morbidity occurred in the age group of 25-34 years, in which 82 persons (morbidity 9.8/100,000) got ill and in 35-44 year olds with 58 cases (morbidity 6.6).

In patients epidemiological anamneses were found: 97 x intravenous drug application, 25x healthcare facilities, 12x transfusion, 18x tattoo, 1 x piercing, 84x cause was not found (10).

Providing adequate health care to people who use injection drugs is very specific. This population of patients is threatened by an addiction itself as well as by infections, repeated reinfections or mixed infections, concomitant mental disorders or diseases, and multiple associated disorders. These are often the so-called marginalized patients, socially stigmatized and isolated (1, 11).

Successful diagnosis and treatment of viral hepatitis in drug addicts unconditionally requires effective collaboration and functional interconnection of not only health care professionals, but of the wide range of

professionals and institutions involved in the care of this patient - social workers, volunteers working within governmental and non-governmental organizations, self-help groups and foundations, family members and friends of the drug addicts (1).

In the Western world, about 25-30% of people infected with HIV have chronic HCV infection. There is a higher prevalence in Southern and Eastern Europe compared to Northern and Western Europe, as well as is in larger cities where it rises to 50-90%. The need for CHC (chronic hepatitis C) treatment in co-infected persons is greater than in those with CHC infection alone. Progression of liver disease is much faster in people with HCV/HIV co-infection (twice the risk of developing liver cirrhosis). Deaths related to liver disease are the second most common cause of death in HIV-positive patients. Successful HCV treatment can also improve tolerability of antiretroviral (HAART) therapy by reducing the risk of hepatotoxicity (12, 13).

Chronic hepatitis C is **not spread** by sneezing, coughing, water, food, sharing dishes or cups, hugging. People with HCV infection should not be discriminated at work, nor isolated from visiting schools and pre-school facilities. **Acute infection** occurs as a mild illness, often without icterus or even asymptotically. Therefore, the number of reported cases is only a fraction of the actual number of new cases. There is also a problem to reliably distinguish acute cases from chronic hepatitis C (14).

Chronic hepatitis C, which develops in about 80% of cases, goes on for a long time without symptoms or with minimal symptoms (its course can mimic influenza - fatigue, lassitude, pain in the muscles and joints, loss of appetite, rarely occurs vomiting, raised temperature). These symptoms are usually attributed to other causes, as well as is a possible increased aminotransferase activity, which often only slightly

exceeds the upper limit of physiological values (15).

Approximately one quarter of patients with CHC has developed cirrhosis of the liver. Assumptions say that the proportion of patients with CHC in the stage of liver cirrhosis will increase dramatically. Estimates talk about more than a third of patients. In the US, about 37% of patients will have hepatitis C in the stage of cirrhosis in 2020.

However, CHC may also occur without increased or with just intermittently increased ALT activity. Therefore, the screening of anti-HCV in individuals who belong to any of the risk groups, even if they have normal ALT activity (1, 15), is fully justified.

In some countries, in addition to persons who are or have been at risk of being infected with hepatitis C virus, screening recommendations also involve anti-HCV testing in age groups where epidemiological surveys revealed the highest number of infected people. According to epidemiological data, in Slovakia it currently refers to persons between the ages of 50 and 60 years. It would be appropriate to target the screening activities on this group as well (3).

HCV positive patients: must not donate blood, organs, tissues or sperm; must not share with other people sharp tools that could potentially be contaminated with blood (e.g. razor blades, manicure scissors, toothbrushes); should cover open wounds and scratches to prevent people from coming in contact with their blood; should avoid having tattoos and piercing done in unprofessional salons. HCV positive people should inform their sexual partners about the disease and use barrier protection. A sexual partner of a HCV positive person should have the antibodies to HBV (hepatitis B), HCV and HIV infection examined. Patients with HCV infection should completely eliminate consumption of alcohol (due to worsening of the liver fibrosis progression), avoid other

hepatotoxic substances, including the so-called “plant products”.

Studies of the natural history of the disease have found that in 55-85% of people with acute hepatitis C it develops into chronicity. Spontaneous excretion of the virus is more common in infected children and young women than in people who have developed acute hepatitis at a higher age. The risk of CHC progression into cirrhosis of the liver is 5-25% over the period of 25-30 years.

Factors associated with the progression of liver damage in chronic HCV infection include: **a)** transmission of infection in higher age (the risk increases after the age of 40-45); **b)** alcohol consumption over 50 g per day (16); **c)** obesity and liver steatosis for any other reason; **d)** co-infection with HBV and/or HIV; **e)** higher degree of liver damage (F2 - fibrosis of level 2 and higher). To evaluate the alcohol intake, usually the dose of pure alcohol – ethanol – is being calculated. Studies have manifested that a daily intake of ethanol between 30-50 g is an amount that proves to worsen the course of chronic HCV infection as it accelerates the progression of liver fibrosis. Daily marijuana use also has negative effects on the course of CHC (17). On the contrary, drinking coffee (more than 2 cups a day) has a positive effect on the liver (18).

CHC can also cause *extrahepatic manifestations* including mixed cryoglobulinaemia, type II and III. The main manifestation is systemic vasculitis, which is clinically manifested as palpable purpura, joints pain and arthritis, fatigue, peripheral neuropathy and glomerulonephritis. Most people with essential mixed cryoglobulinemia are infected with CHC. Since early symptoms of cryoglobulinemia may include simple proteinuria and renal dysfunction without actual symptoms of cryoglobulinaemia or liver disease, all people with proteinuria and cryoglobulinemia should be screened

for CHC even if they have no clinical and/or biochemical manifestations of liver disease. Symptomatic cryoglobulinemia is an indication for the treatment of HCV, independently of the degree of liver disease (19).

Other extrahepatic manifestations of CHC include: hematologic malignancies (B-cell non-Hodgkin lymphoma: B-NHL), renal failure, depression, cognitive impairment, dermatological diseases (hyaline, porphyria cutanea tarda), thyroid disorder, type 2 diabetes mellitus, rheumatic diseases and cardiovascular diseases.

The goal of CHC treatment is to cure HCV infection in order to: prevent HCV-associated liver diseases and extrahepatic manifestations including necroinflammation, fibrosis, cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma (HCC), severe extrahepatic manifestations and deaths; improve the quality of life and eliminate the stigma; to prevent further transmission of HCV infection (20). Eradication – curing the HCV infection will help patients improve survival, prevent development of complications and allow regression of fibrosis even in an advanced stage of liver disease.

Until 2011, pegylated IFN (interferon) and ribavirin combination therapy could have been considered the gold standard in CHC treatment. Success of the treatment was relatively low. In the treatment of the HCV genotype 1 (which is the most common genotype in Europe and in our country) the sustained virological response was less than 50%.

A disadvantage of interferon-based treatment of CHC was, in addition to relatively low efficacy, a relatively long duration of treatment (usually 48 weeks of treatment), complicated dosing regimens and the need to monitor the virologic response during treatment. This treatment was also accompanied by frequent adverse effects and for some groups of patients (e.g. patients with

decompensated cirrhosis) it was contraindicated.

In 2011, first two new molecules (telaprevir, boceprevir) from the group of directly acting antivirals were registered for genotype 1. These new molecules were used in triple therapy in combination with pegylated interferon and ribavirin, resulting in an increase in treatment success to approximately 63-75%.

A development of other drugs from a group of directly active antiviral agents brought new prospects for CHC treatment. These are new molecules that interfere with the replication cycle of hepatitis C virus. According to the mechanism of action we divide them into 3 groups: NS3 / 4A protease inhibitors; NS5B polymerase inhibitors; NS5A protein inhibitors.

The most recent trend in CHC treatment is the use of several direct-acting antivirals without IFN, so called interferon-free or IFN-free regimens. These treatment regimens have resulted in: an increase in treatment efficacy to over 90% of the sustained virologic response, efficacy on several or all HCV genotypes, an increased safety of treatment and a significant decrease in adverse effects; shortening of the treatment regimens from standard 48 weeks to 12 weeks; simplified dosing; simplified patient monitoring during treatment; unified treatment regimens. In most patients, after successful antiviral treatment there is an overall improvement in their health independently of the degree of liver damage (21, 22, 23).

However, after completing the CHC treatment, increased attention should be given to patients who had advanced liver fibrosis or cirrhosis prior to beginning the treatment, who had started treatment in a higher age and who had a high body mass index (BMI). In these patients the degree of hepatic impairment should be monitored by non-invasive methods (hepatic fibrosis may persist).

Achieving a sustained virological response (SVR) reduces the risk of decompensated cirrhosis, but does not completely eliminate the risk of HCC (hepatocellular carcinoma). In these patients, we need to perform HCC surveillance every 6 months.

The introduction of non-interferon-based therapy into practice has also brought the need to monitor drug interactions between new direct-acting antiviral drugs and other drugs that the patient is taking: e.g. statins, fibrates, cardiovascular drugs, immunosuppressants, antiretrovirals and others. It is necessary to be careful when modifying the dose or administering new drugs during antiviral treatment of CHC, and consult a specialist in these cases.

Patients with an increased risk of transmitting HCV infection, active IDUs, homosexuals with risky sexual practices, women planning to conceive, patients undergoing hemodialysis and prisoners should all be treated in preference. After successful treatment, patients should be informed about the possible HCV reinfection if they continue with risky activities.

According to WHO, the main obstacles to the implementation of the strategy for viral hepatitis elimination are: low percentage of diagnosed persons (about 20%) and high prices of antiviral drugs (24, 25, 26). The largest drug-price barrier is emerging in middle-income countries, e.g. in Brazil, China, Colombia, Mexico, Kazakhstan or Turkey. **WHO plans to prepare and implement a global system for monitoring the viral hepatitis elimination process (27).**

To the fulfilment of the WHO strategy on HCV elimination/eradication would certainly contribute a nationwide screening in individual European countries and active collaboration with general practitioners who could treat patients with HCV by themselves - that is, without help of specialists, with pan-geno-

typic drugs. Specialists would deal with the more serious cases of HCV infection in various centers (ineffective HCV treatment, presence of coexisting diseases, suspicion of advanced fibrosis through non-invasive tests: FibroScan ≥ 10 kPa or FibroTest > 0.58). The French Hepatology Society also inclines toward this view. A real-world example of functioning CHC treatment is Australia, where the annual number of treated patients exceeds their options of treatment by specialists (28, 29).

If we do not implement the screening programs at present, in 2 or 3 years patients with CHC already diagnosed will be cured, but on the other hand, many undiagnosed CHC patients will remain in the population. Without facilitating access to treatment and active collaboration with general practitioners, swift eradication of HCV from the population will not be possible in our conditions.

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