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Original Article

Micro-elimination of HCV as a possible therapeutic strategy: our experience and a review of literature

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Abstract

Background: Serbia has an intermediate estimated prevalence of chronic hepatitis C (CHC) infection, approximately 1.13%, with hepatitis C remaining one of the leading causes of liver-related morbidity and mortality in Serbia with impaired quality of life and overwhelming cost of treating its complications As the availability of new treatment options and resources for screening remains limited, micro-elimination of CHC becomes a top priority.

Methods: Review of the available published data related to the clinical and epidemiological situation of the hepatitis C infection in Serbia, including the unpublished data from the databases of four major reference centres in Serbia (Clinical Center Serbia, Clinical Center Niš, Clinical Center Vojvodina and Clinical Center Kragujevac).

Results: Currently in Serbia, micro-elimination appears to be realistic in the patients with haemophilia, who represent a small, well-defined subpopulation, under constant monitoring by the healthcare system. Other feasible targets for micro-elimination of CHC infection in Serbia are patients on hemodialysis, prisoners and people who inject drugs.

Conclusions: Micro-elimination is feasible in Serbia, especially in the subpopulation of patients with haemophilia. This may represent an initial step towards achieving the WHO objective to eliminate hepatitis C infection by 2030.

Key words: hepatitis C infection; micro-elimination; Serbia.

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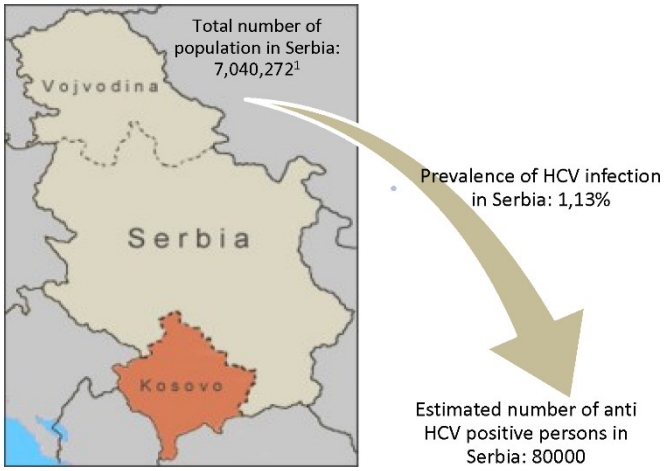
Background

Infection with hepatitis C virus (HCV) remains one of the leading causes of liver-related morbidity and mortality in Serbia. However, there are no available official epidemiological data on the incidence and prevalence of the infection in Serbia, except the study by Mitrović *et al*., showing prevalence around 1.13% in the general Serbian population [1]. According to the official statistical data the population of Serbia is 7,040,272 [2] (since 1st January 2017, with no data for Kosovo and Metohija), thus providing an estimated number of patients with HCV infection in Serbia of approximately 80,000 [3], shown in Figure 1.

Data availability and treatment options for hepatitis C infection in Serbia

The main source of data for patients who had undergone antiviral treatment, are the databases of the reference healthcare institutions in Serbia, where the treatment and follow up of the patients were performed. The estimated number of treated patients by the time of the publication is 3,682 [4]. Considering the success rates of previously available antiviral treatment (pegylated interferon and ribavirin), varying from 52% - 65% [4,5], depending on genotypes and the degree of fibrosis, it seems that, so far in Serbia, 2,074 patients could have been successfully treated.

Figure 1. Prevalence HCV infection in Serbia.



Source of the map of Serbia: https://commons.wikimedia.org/wiki/Atlas_of_Serbia.

However, according to the unpublished information from the databases of four major reference centres in Serbia (Clinical Center Serbia, Clinical Center Niš, Clinical Center Vojvodina and Clinical Center Kragujevac, shown in Figure 2), a total of 6,425 patients were diagnosed with chronic hepatitis C (CHC). So far only 53% out of the total number of diagnosed patients had undergone antiviral treatment, shown in Figure 3 [6]. Available data show that, also due to under-diagnosis and under-treatment, CHC in Serbia is far from elimination. It has been suggested by the experts from the treatment centres, to achieve this goal, a partnership is required between health care providers, policy-makers, patient organizations and industry, to develop and implement local elimination strategies for Serbia [7].

According to the databases of the four Serbian reference centres, the predominant HCV genotype is 1 (G1) found in 65.05% of patients followed by genotype G3 in 24.99%, G4 in 4.49%, G2 in 4.20%, and mixed genotype infection in 1.27% of the patients (Figure 4) [6]. Most of the patients (57.31%) do not have a significant degree of fibrosis, severe fibrosis is found in 9.67% and cirrhosis in 14.1% of patients [6]. Available scarce published data for Serbia including two decades of clinical observations, show that the following factors are negative predictors of sustained virologic response and had most certainly negative effect on the overall success rates with the dual therapeutic protocol: (predominance of unfavourable genotypes especially genotype 1 and advanced fibrosis or cirrhosis) [6,8,9-11]. These conclusions are in concordance with overwhelming published data from high-income countries, with advanced surveillance strategies and reliable epidemiological data for chronic hepatitis C infection [12-14].

Liver transplant surgery remains mostly inaccessible therapeutic procedure in Serbia, so most of the patients with unfavourable treatment outcome do not have other treatment options, apart from symptomatic treatment [4,15]. The occurrence of malignant alteration is not rare, and an increase of the number of patients with hepatocellular carcinoma in all reference centres has been recently observed. Available data show significant number of patients with hepatocellular carcinoma with CHC infection (approx. 300) in Serbia, which makes up to 4.7% of the total number of patients diagnosed with CHC [8].

The WHO objective to eliminate HCV infection by 2030 urges proactive screening, diagnosis and treatment of patients with CHC infection [16]. This strategy defines elimination as an 80% reduction in new HCV infections and a 65% reduction in HCV mortality [17,18]. Such a strategy is understandable, taking into consideration the availability of new DAA therapy with

Figure 2. Reference centers in Serbia for treating patients with HCV infection: Novi Sad, Belgrade, Kragujevac, Nis.

Source of the map of Serbia: https://commons.wikimedia.org/wiki/File:Serbia_Map.png.

direct-acting antivirals (DAA), whose treatment efficiency exceeds 95% [17].

However, the limiting factor in the elimination strategy, particularly in developing countries, is the cost of new therapeutic protocols. Serbia has a National Hepatitis plan [19]. For now, DAA treatment is restrictive and limited only to the patients with the most advanced liver disease and co-morbidities, who make up a small percentage of the total number of persons with CHC infection in Serbia [20].

Therefore, it is necessary to have a more pragmatic approach in the strategy for the elimination of this infection in Serbia, by defining the most vulnerable subpopulation, but also extending treatment availability of DAAs, which could result in a significant reduction and elimination of HCV infection.

Target groups for possible micro-elimination in Serbia

After thorough examination of available epidemiological data for different subpopulations of patients in Serbia who are at risk of HCV infection, the following groups were identified: people who inject drugs (PWID), persons with haemophilia, persons in penitentiary institutions haemodialysis patients.

People who inject drugs (PWID) with CHC infection

According to the published EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) data from 2017, an estimated number of addicts who are actively using narcotics in Serbia is around 20,500 persons [21]. The same source, however, with data from 2014, estimates that the number of people with anti-HCV antibodies in this population ranges between 60-80% (about 14,000 people) [22]. In Serbia, there are no available community-based syringe or needle exchange programs, and opioid substitution therapy (OST) has a very low involvement rate of less than 10% [21]. These are important factors which explain that a very small percentage of people (especially among injecting drug users) are aware of their HCV status, especially because they are neglected by the healthcare system and the availability of anonymous anti-HCV testing is limited. Although HCV existence has been confirmed in this population, numerous problems such as stigmatisation, lack of information and availability of specialised treatment centres, often interfere with successful treatment and follow-up. Despite this, previous experiences with dual therapeutic protocols in this subpopulation are excellent, with success rates close to the general population. Published data show sustained

Figure 3. Relationship between estimated number of people with HCV infection and cured patients in Serbia.

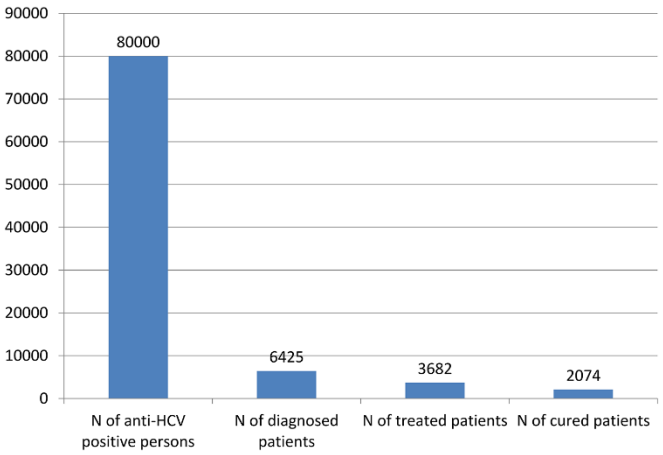


Figure 4. Distribution of genotype HCV in Serbia.

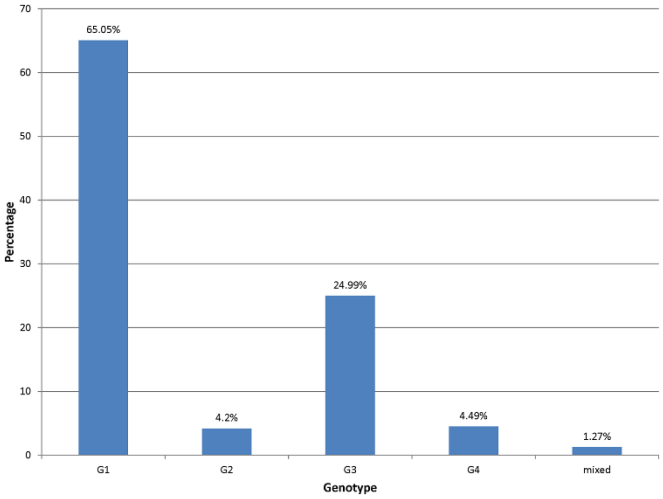
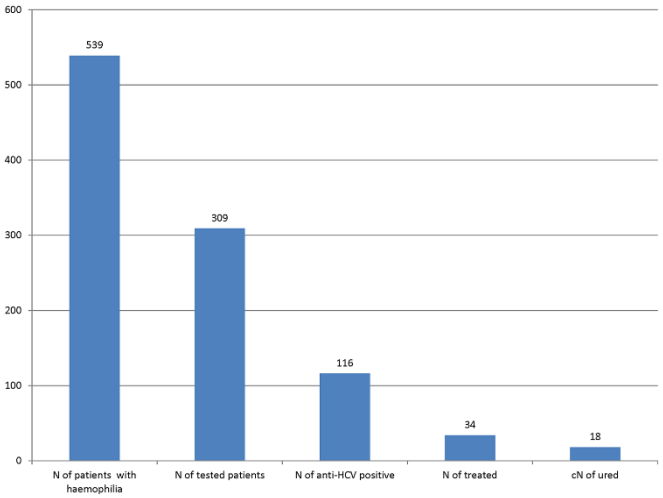


Figure 5. Existing data on patients with haemophilia and HCV infection in Serbia.



virologic response (SVR) in this subpopulation of 67.7% [23,24]. Possible explanation for exceptionally high SVR, in spite of numerous previously mentioned difficulties, is presence of positive predictors in this subpopulation, such as younger age, absence of other co-morbidities (including hepatitis B and HIV co-infection) and less severe liver damage [23]. However, given the estimated number of patients and the unreliable data concerning PWID in Serbia, this remains an important limiting factor in perceiving the true epidemiological situation of HCV infection in this particular group of patients. Therefore, without further strategies including improved surveillance, community-based needle exchange programmes and wider availability of testing, the micro-elimination of HCV infection in this group of patients in Serbia is, at this moment, a challenging goal.

Patients with haemophilia and CHC infection

During the 1990s and before the introduction of routine screening blood products for HCV infection, a substantial number of patients with haemophilia were infected with the virus. Left untreated, long-term HCV infection results in chronic liver disease and may progress to severe fibrosis, liver cirrhosis, hepatocellular carcinoma (HCC), and death. Although there is solid data to show that there is no difference in the progression to end- stage liver disease (ESLD) in patients with haemophilia when compared to CHC patients without inherited blood disorders, unfortunately, overall mortality of patients with haemophilia is reported to be five times higher than that of the general population [26]. There are also publications suggesting even a 16 times higher mortality risk due to liver-related morbidity in patients with haemophilia and CHC, compared with the general population, due to the development of liver failure, cirrhosis and HCC [27]. Therefore, antiviral therapy, especially in the new DAA era is an imperative in this group of patients, especially taken in account the severe burden of the healthcare system with the life-long substitution therapy for haemophilia and possible complications of untreated HCV infection. Estimated annual treatment cost for patients with severe haemophilia in Serbia is between 100,000-200,000 EUR per patient [28,29]. However, these patients in Serbia have a very poor quality of life, especially due to consequences of untreated and/or unrecognised HCV infection. The use of modern anti-HCV therapy would provide a better quality of life for people with severe haemophilia.

According to the data obtained from the Registry of Congenital Coagulopathies of the Republic of Serbia, kept at the Blood Transfusion Institute, the number of registered persons with haemophilia in Serbia, as of 30th September 2018, is 539 (454 with haemophilia A and 85 with haemophilia B) [30]. Although testing for HCV infection in these patients is not mandatory, it can be strongly recommended, bearing in mind the high risk of exposure to this infection [31]. According to this Registry, the total number of patients with haemophilia, who have been tested for the presence of anti-HCV antibodies is 309 (which is 57.3% of total number of registered patients with haemophilia) and 116 of them, are anti-HCV positive, which accounts for 37.54% of the total number of tested persons with haemophilia (Figure 4). However, there is no data if these anti-HCV patients with haemophilia have detectable viremia. There is an apparent discrepancy between number of tested and untested individuals with haemophilia, due to local guidelines, which dictate mandatory anti-HCV testing only in patients with severe disease who received blood derivatives. Patients with milder forms of haemophilia are left to the health officials to decide on individual basis whether to perform anti-HCV testing in patients who had never received blood derivatives and transfusions. Due to the significant improvements in the treatment of haemophilia and the use of recombinant products it is understandable that there is only one anti-HCV positive person registered with haemophilia in Serbia under the age of 18 [30]. There is no data whether this person has a detectable viremia, or on subsequent confirmatory tests for all 116 HCV-reactive patients with haemophilia.

To estimate the approximate number of people with haemophilia and active HCV replication, we analysed available (unpublished) data from regional centres for the treatment of patients with haemophilia (Clinical Center Serbia, Clinical Center Niš, Clinical Center Vojvodina and Clinical Center Kragujevac) [32]. Experience in the treatment of these patients with dual therapeutic protocols is not extensive. Until now, the dual therapeutic protocol with pegylated interferon and ribavirin has been used for the treatment of 29 persons with haemophilia (15 patients with G1, 7 patients with G2, 7 patients with G3). The SVR with this protocol was 44.83%, probably due to a slightly higher prevalence of G2 infection (24% of this population). After the introduction of direct-acting antivirals (DAAs) additional 5 patients were treated with generic drugs from this group (in total 34 patients were treated for HCV infection, as shown in Figure 5). All treated patients had achieved SVR [32].

However, the estimated number of patients with haemophilia and HCV infection in Serbia, who are candidates for the treatment with new DAA drugs, is 98, according to the existing data on the current number of tested and anti-HCV positive persons with haemophilia. Due to the well-organised healthcare centres for the treatment of haemophilia in Serbia and the epidemiological data which is regularly updated at the Registry of the Blood Transfusion Institute of the Republic of Serbia, it is possible to carry out micro-elimination in this well-defined group of patients. These patients are constantly visible in the healthcare system, due to the need for the continuous application of the substitution therapy, therefore, testing them for the presence of active HCV replication is the first and necessary step in the micro-elimination process. The use of DAAs, with expected 95% success, would quickly lead to the elimination of HCV infection in this group of patients, especially as there have been no recorded transmissions and new patients with HCV infection and haemophilia in recent years (which is supported by the data that there is only 1 registered person with anti-HCV positive antibodies under the age of 18 in Serbia) [30]. The elimination of HCV infection in this subpopulation of patients would significantly reduce costs of the healthcare system in the years to come, as there would be no additional costs due to liver-related complications with a very uncertain outcome.

Prison inmates with CHC infection

Although there is no precise epidemiological data about the prevalence of HCV infection among prison inmates in Serbia, clinical data indicates significant prevalence of HCV infection in this subpopulation. Simonović *et al*. analysed the success of antiviral therapy in this subpopulation [33]. Most of the patients with CHC were younger (<40 years), with no significant co-morbidities, however, with numerous epidemiological risk factors for HCV infection. Treatment success rates in this group of patients are comparable and somewhat better than in the general population reaching up to 62.5% [33]. A dominant way of transmission of the infection was intravenous drug use, which was identified in 93.8% of patients in this study, most patients had a baseline moderate fibrosis which might have contributed to the success of the treatment [33]. This population largely overlaps with the most significant population of HCV patients, who are PWID. An observed difference in the population of PWID in the prisons is that in prison conditions these patients are more motivated to be treated. Also, considering the close follow-up after these individuals in the prison settings, the compliance of this population is expected to be high, including possibilities for prolonged follow-up. The micro-elimination of HCV infection in this group of patients would significantly reduce the number of patients with HCV infection in the general population. It has been suggested that harm reduction (including more available OST), HCV screening and better availability of treatment in prisons could be a crucial step in eliminating HCV as a public health threat [34]. However, the unresolved problem of financing the treatment of this group of patients for the time being, presents a very important limiting factor, since in Serbia the source of funding for treatment in the prison is different from that of the general health system.

Patients on hemodialysis and CHC infection

Patients with chronic renal failure requiring hemodialysis are also a subpopulation with a slightly higher prevalence of HCV infection, especially in the early 1990s. In the publication of Nikolić *et al*., screening of patients in a hemodialysis centre in Belgrade in 1991 showed 44% of anti-HCV positive patients [35].

Experience in treating these patients with the dual therapeutic protocol is not extensive. The reason for this was an opinion of the Commission of the National Health Insurance Fund for the approval of antiviral therapy for CHC (2003-2010) to offer treatment solely to patients who are immediate candidates for a kidney transplant and are formally introduced into the kidney transplant list. However, very few patients in Serbia had fulfilled all the mentioned criteria. Most of the patients were treated with the dual therapeutic protocol using pegylated interferon and ribavirin, with very modest SVR ranging from 30% to 46% [36,37]. The unfavourable treatment outcomes od dual protocol including numerous serious side effects during antiviral treatment (primarily anaemia) have, by the end of 2017, considerably reduced the total number of patients on hemodialysis with CHC on antiviral treatment in the last five years. Untreated/unsuccessfully treated CHC infection in this subpopulation has certainly increased the burden of healthcare services due to the need of these patients for hemodialysis on separate devices. On the other hand, the presence of active chronic HCV infection additionally aggravated the general health of these patients, due to the further progression of the liver disease.

So far there has been only one published case report in Serbia from 2018. for a successfully treated hemodialysis patient (with G1 HCV infection and no

liver fibrosis) with DAA protocol, who had a previous virological relapse after unsuccessful interferon treatment [38].

Considering that the new DAA therapy has very few adverse effects, the micro-elimination of HCV infection in patients on hemodialysis would have at least three positive effects. First the need for special hemodialysis devices would be reduced and would eliminate an important epidemiological risk factor for HCV infection. Finally, this would considerably improve the quality of life of these patients, and third an SVR could lead to a successful outcome of kidney transplantation. Although this group of patients is suitable for the micro-elimination of HCV infection, it is unknown how many hemodialysis patients have an active replication of HCV. According to the available data from 2012 the total number of hemodialysis patients in Serbia is 4,225 and the estimated prevalence of HCV infection is approximately 7.2% (304 hemodialysis patients with HCV infection in Serbia) [39]. An additional problem in the further evaluation of HCV infection in this population of patients is the large number of dialysis centres throughout Serbia (63 centres) with only 4 reference centres where HCV infection that can confirm the infection with PCR testing. All this creates aggravating conditions, but not insurmountable circumstances, for micro-elimination of HCV infection in this subpopulation.

Conclusion

HCV micro-elimination in a defined patient population such as patients with haemophilia, patients on dialysis, incarcerated individuals, PWID, is a key and feasible step towards achieving the HCV elimination goals set by the WHO. Taking into consideration the above data, it seems that in Serbia this goal would be easiest to implement in persons with hemophilia, as a first step. This small group is clearly defined and under the constant monitoring of the healthcare system. The remaining considered groups of patients (hemodialysis patients, prisoners and PWID) could be the next target group for micro-elimination of HCV infection in Serbia, but it is necessary to obtain more accurate epidemiological data. Potentially, the implementation of micro-elimination in the above defined patient populations, may be a first step towards broadening the access to HCV treatment and care in Serbia, which would bring Serbia closer to the achievement of the WHO objective.

Authors contribution

KB, JSB, PM, JJ contributed to drafting the manuscript; MŽ, MI, JM, CT, SP provided the necessary data about the treated patients, JJ critically revised the manuscript for intellectual content. All authors read and approved the final to be submitted manuscript.

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