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Original Article

Implementation of Microelimination Strategy in Eradication of Chronic Hepatitis C Infection in Patients with Hemophilia in the Northern region of Serbia: Is Eradication Possible?

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Abstract. ***Background:*** **Treating HCV in people with hemophilia prevents the development of end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC) and greatly increases the quality of life for people living with hemophilia. There are many obstacles in reaching the WHO goal of globally eradicating HCV by 2030, mainly its scale, complexity, and implementation. That is why many countries have implemented a micro-elimination strategy: a pragmatic elimination approach in populations with the most efficacy. The aim of this publication is to present the morbidity and mortality rates, the clinical course and treatment outcomes of chronic HCV infection in people with hemophilia (PwH), as well as to show an example of a successfully conducted HCV micro-elimination strategy among people with hemophilia in the Province of Vojvodina.**
Methods**: A retrospective, single-center study, performed using medical documentation of all registered PwH in the Clinical Center of Vojvodina from 1994. until 2020. It included 74 hemophilia patients, out of which 32 were patients with hemophilia and chronic HCV infection.**
Results**: The mean age of HCV-positive positive people with hemophilia (PwH) was 42.3 years, with the duration of infection of 30-35 years. Co-infection with HIV was observed in 6.25% of cases. Furthermore, 18.75% of patients had spontaneous HCV elimination, and 75% were treated with antiviral protocols. Cirrhosis developed in 21.87% with an incidence rate of 0.6 per 100 patient-years. After treatment with Pegylated IFN and ribavirin (RBV), 58.3% achieved SVR. Side effects of IFN-based therapy regimens were recorded in 20.8% of treated (PwH). In 37.5% PWH, DAA protocols were administered, and these patients achieved SVR. HCV- PwH have a statistically higher mortality rate than non-infected people with hemophilia. Among the HCV-positive PwH, hemophilia-related deaths were 6.25%, and HCV-related deaths were 9.37%. Currently, in the Registry of PwH in Vojvodina, there are no patients with active HCV infection.**
Conclusion**: The micro-elimination strategy in the subpopulation of PwH was successfully implemented in Vojvodina by hematologists and infectious diseases specialists in close collaboration.**

Keywords: Hemophilia; Hereditary blood disorders; Viral hepatitis; Antiviral therapy; Hepatitis C; Hepatocellular carcinoma.

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Introduction. The prevalence of hepatitis C virus (HCV) positive cases ranks Serbia in the range of mid-endemic European countries.[1] Chronic HCV infection is the leading cause of a rising prevalence in end-stage liver disease (ESLD): cirrhosis and hepatocellular carcinoma (HCC).[2] Currently, the world is facing an epidemic of HCV-related complications in patients who received transfusions of blood and blood derivatives until the 1990s, making people with hemophilia (PwH) one of the most vulnerable populations.[3] Even though hemophilia has become the prime example for successful prevention in chronic illnesses using coagulation factors, the blood-borne transmission of HCV was nearly inevitable until the 1990s because of the technological processes involved in the development of blood derivatives, making this infection endemic in PwH.[4,5]

Until the discovery of direct-acting antivirals (DAA), chronic HCV infection was incurable for the 30 to 50% of patients treated with Interferon-based therapy regimens. PwH were frequently put in the group of non-responders, or worse, and doctors were unwilling to treat them with this regiments due to its side effects. DAA treatments improve the SVR rate up to 98%, and because of this, the world is on the verge of HCV eradication.[6] However, this goal may be prolonged due to the socio-economic factors in low-income countries.[2] Consequently, many authorities have supported a "step by step" micro elimination strategy for HCV: a pragmatic approach to identification and treatment of populations where it would have the highest efficacy. Thanks to the enormous prosperity of the preventive measures, mortality, and morbidity of PwH are greatly improved.[7] Unfortunately, HCV is the leading cause of death in PwH, and this group should be considered a priority according to the micro-elimination strategy.[8]

The aim of this publication is to present the morbidity and mortality rates, clinical course, and treatment outcomes of chronic HCV infection in PwH, as well as to show an example of a successfully conducted HCV micro-elimination strategy among this endangered subpopulation in the Province of Vojvodina, bringing us the one step closer to the World Health Organizations' (WHO) global goal of eradicating HCV by the year 2030.[9]

Material and Methods. This single-center study is retrospective and includes 74 hemophilia A and B patients who were followed in the tertiary healthcare system in the northern region of Serbia (the Province of Vojvodina) from 1994 to 2020.

Monitoring and bleeding prevention and treatment of PwH have been taking place in our institution since 1994 when the Registry of people with hemophilia was formed. The severity of hemophilia was classified as mild (5–40% of normal factor level), moderate (1–5% of normal factor level), or severe (<1% of normal factor levels).[4] According to the WFH recommendations for testing PWH for blood-borne diseases, all registered patients were tested for the presence of anti-HCV antibodies.[7]

Between 1994 and 2020, 32 PwH were identified as anti-HCV antibody positive. They were diagnosed and treated using the EASL recommendations for the Management of HCV infection.[9] Up to 2015, patients were treated with IFN based therapy regiment with partial success. In 2016, with the introduction of DAA therapy, the last 9 PwH with chronic hepatitis C were proclaimed priority in our medical center and successfully cured using the newer DAA regiment by December 2020 (**Figure 1**).

To present a successfully conducted HCV micro-elimination strategy among PwH in the northern region of Serbia, we examined in this study multiple factors: patient age, how HCV infection was detected, infection duration (time passed from the first exposure to blood products), co-infections (HIV, HbsAg, anti-HBc antibodies), number of HBV vaccinated PwH, HCV viral copies, HCV genotype, aminotransferase activity levels, presence of liver cirrhosis and HCC (confirmed by imaging diagnosis), HCV treatment options and outcomes (Sustained Virological Response – SVR), patient mortality. The study was approved by the local medical ethics committee.

Statistical analysis was performed using the student test (t-test) with the software program SPSS version 23. g. Categorical variables were presented as frequencies and percentages, and continuous variables as means and standard deviation (SD) or medians and interquartile ranges (IQR) for variables with skewed distributions. Statistical significance was set at p-value <0.05.

Results.

Patient Population. There were 74 hemophilia A and B

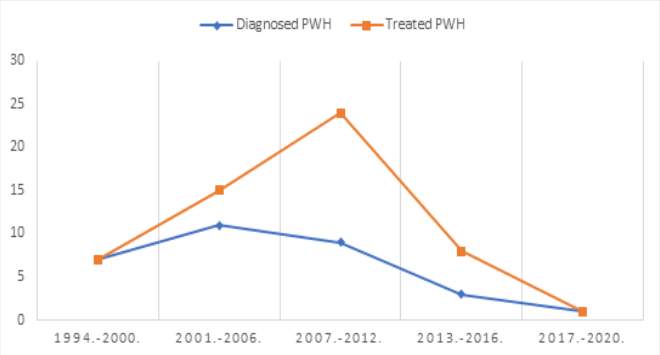

Figure 1. Diagnosis and treatment of HCV in patients with hemophilia in our center, from 1994. to 2020.

Table 1. Summary of patient population. Data are presented as percentages % (n) or mean ± SD.

Age, years	42.43 ±3.84
Male sex	100% (n=32/32)
Hemophilia type	
Hemophilia A	93.7% (n=30/32)
Hemophilia B	6.25% (n=2/32)
Hemophilia A severity	
Mild	36.6% (n=11/30)
Moderate	13.3% (n=4/30)
Severe	50% (n=15/30)

patients in our institution, of whom 32 (43.25%) were anti-HCV antibody positive, and this subgroup of patients will be further analyzed (**Table 1**). The prevalence of anti-HCV positivity in our population of persons with hemophilia was 0.43%. All anti-HCV antibody positive PwH were male, with a mean patient age of 42.4 years (42.43 ±3.84, n=32).

Following WHF recommendations for testing PwH for blood-borne diseases, we discovered 28/32 (87.5%) of anti-HCV antibody-positive patients, while 4/32 (12.5%) were found within ESLD etiology examinations. In addition, from first blood products exposure, patients were observed through a median follow-up time of 30 years (IQR 30–35).

Co-infection with HIV was observed in 2/32 (6.25%) PwH. Hepatitis B (HBV) viral infection markers were studied in 14/32 (43.75%): total HBc was present in 4/14 (28.6%) patients, while 3/14 (21.4%) were HbsAg positive. All seven patients were PCR HBV DNA negative. In total, 5/32 (15.6%) anti-HCV antibody positive PwH were HBV vaccinated.

Spontaneous HCV Elimination. Spontaneous HCV elimination was observed in 6/32 (18.75%) PwH, and it is determined using two consecutive negative PCR HCV RNA tests over six months.

Characteristics of Chronic HCV Infection. The biochemical and virologic parameters of 26/32 (81.25%) PwH with chronic HCV infection are shown in the table below (**Table 2**)

Cirrhosis developed in 7/26 (26.9%) of patients, and an incidence rate of 0.6 per 100 patient-years. Out of seven patients with liver cirrhosis, three are currently alive with compensated cirrhosis (Child-Pugh Score A) and have achieved SVR. HCC was present in 4/26 (15.4%) HCV-positive PwH in the Registry, and three patients with cirrhosis have died due to HCC (**Table 2**).

Treatment. From 1994. until today, our institution has treated 24/26 (92.3%) PwH with chronic HCV infection with antivirals (**Figure 1**). The mean age of PwH treated for HCV infection was 50.21 years (50.21 ±3.24, n=24). The average time PwH waited for antiviral treatment was 4.96 years (4.96 ±1.92, n=24).

Table 2. Characteristics of HCV infection in PWH in our cohort. HIV, human immunodeficiency virus; HBV, hepatitis B virus; ALT, aminotransferase; VL, viral load; HCC, hepatocellular carcinoma.

Co-infection	
HIV	6.25% (n=2/32)
HBV (anti-HBc)	28.57% (n=4/14)
HBV (HbsAg)	21.42% (n=3/14)
HCV	
Age at infection, years	50.21 ±3.236
Spontaneous clearance	18.75% (n=6/32)
Chronic infection	81.25% (n=26/32)
Genotype 1	50% (n=13/26)
Genotype 2	15.3% (n=4/26)
Genotype 3	34.6% (n=9/26)
Mixed 1a/1b genotype	3.84% (n=1/26)
Duration of HCV infection	30 years, IQR 30-35 years
Aminotransferase (ALT)	
Normal values	30.7% (n=8/26)
2x increase	46.15% (n=12/26)
10x increase	23.07% (n=6/26)
Viral Load (VL) HCV	
VL <400,000	15.3% (n=4/26)
VL >400,000	84.6% (n=22/26)
HCC	12.5% (n=4/32)

IFN based therapy was conducted in 20/24 patients (83.3%) – SVR was achieved in 14/20 (70%), while in 6/20 (30%) PWH, the response to this line of treatment was not satisfactory. Side effects of IFN-based therapy regiment were recorded in 5/20 (25%) of treated PwH. DAA treatment regimens were conducted in 9/24 (37.5%) – 5 of them were non-responders or had relapsed on IFN based therapy, and 4 of them were naïve (**Figure 2**).

Mortality. The cumulative mortality rate for people with hemophilia A and B in our center is 13.51%, and the yearly mortality rate is 0.09% per year. From 1994. until 2020, 9/32 (28.1%) of anti-HCV antibody positive PWH died, with an annual mortality rate of 1.07% per year. For non-infected PwH, the yearly mortality rate is 0.09%, and in total, 1/42 (2.3%) of non-infected PWH died. Thus, HCV-positive PwH have a statistically higher mortality rate than non-infected people with hemophilia (Fisher's exact test, p=0.0016, p<0.05, n=74) (**Table 3**).

At the time of death in anti-HCV antibody positive PwH, the average age is 53.7 years (53.7 ±6.74, n=9).

Among the deceased anti-HCV antibody positive PwH, hemophilia-related deaths were 2/32 (6.25%), and

Table 3. Fisher's exact test, mortality of HCV positive and HCV negative persons with hemophilia in our cohort. HCV, hepatitis C virus.

	Deceased	**Alive**	**Total**
HCV positive	9	23	32
HCV negative	1	41	42
			74
			p=0.0017, p<0.05

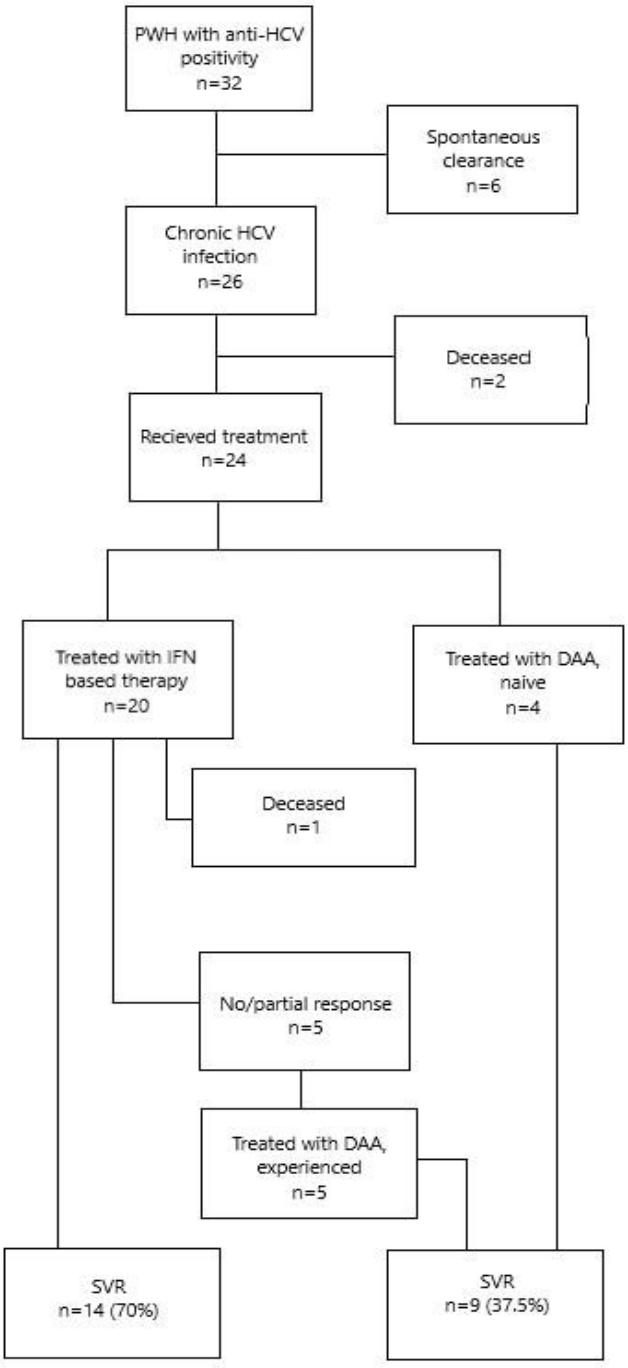

Figure 2. Summary of treatment outcomes in PWH with chronic HCV infection. HCV, hepatitis C virus; DAAs, direct-acting antivirals; IFN, interferon; SVR, sustained virologic response; PWH, persons with haemophilia; IFN, interferon; Peg IFN, pegylated interferon; RBV, ribavirine.

HCV-related deaths were 3/32 (9.37%), and the remaining 4/32 (12.5%) died from other causes.

Ending in December 2020, after 35 years of treating HCV-positive patients with hemophilia in our institution, we can conclude that in the northern region of Serbia, there are no active HCV infections in this population.

Discussion. The prevalence of HCV infection in persons with hemophilia in Serbia is thought to be around 0.37%, but until now, we did not have a definite number.[10] We can confirm that every patient with hemophilia A and B in the northern region of Serbia (the Province of Vojvodina) has been tested for anti-HCV antibodies and that the prevalence is 0.43% (43.25%). The majority of patients (87.5%) were screened for anti-HCV by the hematologist at the moment of registration in our institutions' Hemophilia Registry, unrelated to the severity of hemophilia. However, 12.5% of PwH were discovered late while diagnosing ESLD, and until then, they have never been included in the Registry or examined by a hematologist. In the rest of Serbia, only 57.3% of PwH have been tested for anti-HCV antibodies, and 37.5% were positive.[10] However, the exact prevalence of HCV infection (past or active) in PWH in Serbia is unknown. This "gap" in the prevalence of HCV among PwH in the different regions in Serbia supports the position of The European Hemophilia Consortium against centralized hemophilia supervision.[11] The recorded prevalence of anti-HCV antibody positive PwH in Vojvodina does not differ significantly from other European countries with a similar socio-economic status (Hungary, Slovenia, Croatia) during the '60s, '70s, and '80s but is expectedly lower than the most developed countries of the world (the USA 90%, Austria 80%, Italy 83%, Denmark 51% prevalence).[12] This is a paradox caused by poorly guided policies of donating blood (donating blood for profit, unprecise epidemiological surveys for donors etc.) and inadequate response of doctors and regulatory bodies at the beginning of the HCV epidemic.[13] Namely, in highly developed countries, coagulation factor concentrates were made out of a pool of 20-30 000 voluntary blood donors. By fault of inadequate triage, most of them belonged to the high-risk population for blood-borne diseases (mostly in the USA). Apart from that, not adhering to screening tests and viral inactivation processes resulted in a high risk of transmission, 5% per ordinated unit of factor concentrate until 1991. At the same time, the use of factor concentrates was far more flexible widespread in these countries.[8] In underdeveloped countries such as Serbia, hemophilia treatment was administered with restrictive protocols, cryoprecipitates, or fresh-frozen plasma, made from a much smaller pool of blood donors who were part of the local community.[14]

Spontaneous HCV clearance (seroconversion) is confirmed using two consecutive HCV RNA tests in the span of 6 months. Patients with spontaneous HCV clearance were defined as PwH with positive anti-HCV antibodies and negative HCV RNA (HCV Ab+/RNA-) without prior antiviral therapy. Spontaneous HCV elimination was confirmed in 18.75% of PwH, a lower rate than in most studies, where the rates range from 20% to 40%.[15] A good prognosis of HCV infection is determined by a complex set of interactions between

virus and host that is only partly understood. Male sex and genotype 1 are probably linked to a clearance rate that is lower than average.[16]

The prevalence of HIV/HCV co-infection of 6.2% (2/32) relates to neighboring countries (Slovenia 7%, rest of Europe 11%).[12] Paradoxically, even in this age of highly potent anti-retroviral treatment, PwH with HIV/HCV co-infection still have a high rate of progression into ESLD if the HCV infection goes untreated, mainly because of superimposed hepatotoxic effect and evolves metabolic syndrome.[17] Both patients in this review were cured, one in the PegIFB+RBV era and the others with DAA treatment. Testing voluntary blood donors for HBsAg was implemented in 1972; therefore, the prevalence of acute and chronic HBV infections is low in this population and ranges from 3%-11%.[18] Nonetheless, the prevalence of "occult" HBV is caused by nosocomial transmission.[19] Only 43.7% of patients in our institution are tested for HBV infection markers, even in the scenario of acutely aware hematologists and infectious disease experts to the consequences of blood-borne diseases. It has been proven that in the event of HCV/HBV co-infection, liver cirrhosis and HCC develop more frequently. Moreover, there is a possibility of reactivation of HBV during IFN or DAA treatment protocols.[20] Those facts implicate the need for all PwH to be tested for markers of HBV infection. The reach of vaccination against HBV is extremely low - 15.6% in our cohort, emphasizing the necessity of promoting vaccination in this group of patients.[21]

In the studied cohort, the distribution of HCV genotypes matches the distribution in the general population of Vojvodina. Mixed genotype (1a/1b) was found in 1/26 (3.8%) PwH. Most studies reported a greater frequency of mixed genotypes of HCV in infected PwH due to recombined HCV genomes in the event of long-lasting infections.[22,23] This phenomenon could affect the rate of resistance-associated substitutions and the genotype 1a resistance to DAA treatment protocols.[24] We have to indicate that this low percentage of mixed genotypes in our cohort could primarily result from unavailable molecular detection methods.

Using indirect diagnostic methods (serum markers such as Fib4, APRI score, ultrasound methods such as FibroScan, doppler ultrasound of the hepatic vein, etc.), liver cirrhosis was verified in 21.8% of patients. Until the advent of ultrasound elastography, the "golden standard" of diagnosing liver fibrosis and cirrhosis was a biopsy. In people with hemophilia, liver biopsy is almost always contraindicated from a cost-benefit assessment standpoint, which is why none of the patients in this study had undergone this invasive diagnostic procedure.[22,25]

Even though the HCV infections started in early childhood, liver cirrhosis was observed in 21.8% of patients. With the IQR 30–35 years, we observed that the duration of infection is the most important factor in the development of ESLD, in conjunction with co-infection (HIV/HBV), male sex, diabetes, obesity, and alcohol abuse.[26] The rate of liver cirrhosis is 0.6 per 100 patient-years in our study group. Sadly, in more than half of PwH suffering from liver cirrhosis, the diagnosis was made only after liver decompensation. The late diagnosis emphasizes the need for HCV testing for people at risk of infection who have received blood products before 1994 and multiple blood transfusions, especially people with hemophilia.[27] Even though chronic hepatitis C is the most important cause of ESLD today, it is mostly undiagnosed in the general population.[28]

In this cohort, we observed HCC in 12.5% of patients. Thus, the risk of HCC development in PwH is the same as in the general population with HCV. According to The Liver Disease patient registry (HEREPA) 48% of all HCC diagnosed in Serbia is caused by HCV infection (unpublished data).

The irony of PwH living long and productive lives thanks to improvements in the production of coagulation factor concentrates, but dying from a curable disease like HCV is frustrating. According to the National Inpatients Sample database USA (NIS), only 40-50% of PwH are treated for HCV infection.[8] The first HCV-positive Hemophiliac with CCV was treated with monotherapy of IFN alfa. During the following 25 years, treatment of HCV in PwH was conducted according to EASL protocols: PegIFN+RBV, and as a last resort DAA. As shown in Figure 1, in our center, HCV diagnosis and treatment rates were consistently equal throughout the years, which demonstrates the willingness of PwH to accept antiviral treatment protocols. A high rate of SVR was achieved in 73.6% of PwH treated with PegIFN+RBV in our cohort, in conjunction with an expected side-effects rate of 20.8%, which disproves healthcare providers' biases that PwH are difficult to treat with INF-based protocols.[4]

With the registration of highly efficient and safe DAA treatment by the Food and Drug Administration in 2013. and the European Medical Association in 2015, the goal of eradicating HCV by 2030. was set by the WHO.[29] However, the biggest obstacle in setting national strategies for eradication is financial - the price of DAA treatments is still unreachable for a large number of low-income countries.[30] In 2016, the European Directorate for Quality of Medicines (EDQM) stated that PwH should be given priority in DAA treatment protocols in national health budgets because of its benefit for PwH in reducing HCV morbidity and mortality, which is its leading cause. Also, ESLD and its sequelae greatly increase the cost of treatment: ESLD increases the risk of bleeding and the needing for invasive diagnostic and treatment procedures such as EGDS and paracentesis.[11]

In our study, 37.5% of infected PwH were treated with DAA's, and all achieved SVR. Treating HCV in PwH not only prevents the development of ESLD and HCC, but it also greatly increases the quality of life for people living with hemophilia, which is generally lower in PwH and depends on hemophilia severity, age, the use of orthopedic aids, and other comorbidities at first HCV infection.[30]

The mortality rate is unsurprisingly significantly higher in PwH with HCV, 1.07% per year, instead of 0.09% for HCV negative PwH, incidence of liver cirrhosis, and HCC in Vojvodina is not different from other regions in the world.[30]

After more than 35 years, the northern region of Serbia (Province of Vojvodina) has reached the WHO goal of micro-eliminating HCV well before 2030. There are many obstacles in gaining the WHO goal of globally eradicating HCV until 2030, mainly its scale, complexity, and implementation. That is why many countries have implemented a micro-elimination strategy: a pragmatic elimination approach in populations where it would have the highest efficacy. For the time being, this micro-elimination concept has proven realistic in the population of patients with hemophilia in northern Serbia, a well-defined subpopulation of HCV infected, under constant medical supervision.[6]

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