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Review paper

New therapeutic options for HCV in Central Europe

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Abstract

New therapeutic options became available in 2015 in the European Union. We present the availability of interferon-free regimens with direct acting antivirals (DAA) in four Central European countries – the Czech Republic, Hungary, Poland and Slovakia – which despite similar historical, geographical and economic situations demonstrate different systems for access to anti-HCV (hepatitis C virus) medication. Treatment of patients in the Czech Republic was based in 2015 on an exceptional individual reimbursement procedure, but regular reimbursement procedures are expected in 2016. In Hungary the decision for treatment is balanced against budget limitations and the national Priority Index system reflecting stage of liver disease, activity of the disease and predictive factors. A reimbursed interferon (IFN)-free therapeutic program for all genotypes, without restrictions related to hepatic fibrosis and treatment history, is already available in Poland. In Slovakia patients with advanced fibrosis are currently selected for possible IFN-free therapy in 2016.

Key words: HCV, treatment, Central Europe.

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Introduction

New therapeutic options became available in 2015 because of several interferon-free regimens registered by the European Medicine Agency (EMA) for the European Union. Unfortunately, registration does not mean wide access and reimbursement by national health funds or private health insurance companies. Therefore availability of treatment for chronic hepatitis C (CHC) is different in particular countries and is usually limited by the degree of hepatic fibrosis and previous treatment history. In this article we present the availability of treatment based on direct acting antivirals (DAA) in four Central European countries: the Czech Republic, Hungary, Poland and Slovakia. Despite similar historical, geographical and economical situations, different systems supporting CHC treatment were implemented to provide access to innovative treatment. This article was prepared as part of the Central European Hepatologic Collaboration (CEHC).

Czech Republic

Regular availability and reimbursement of new DAA in the Czech Republic depend on several conditions:

- each particular compound must be registered by the EMA and by our national State Institute for Drug Control (SIDC),
- reimbursement of each particular drug is based on agreement of SIDC, manufacturer and insurance companies (General Insurance Company and Union of Insurance Companies). This agreement defines the price of each drug,
- there must exist national rules how to use each drug.

Keeping in mind all these conditions it is clear that an undefined and unpredictable time period exists when the drug has the EMA and SIDC registrations but does not have reimbursement (condition #3). As all compounds used in interferon (IFN)-free drug regimens had registration of EMA within 2014 or 2015, we were facing a "reimbursementless" time period for these two years. The Czech legal system gives physicians the option to request the patient's insurance company for exceptional reimbursement within this period. These requests must contain all relevant data on the patient's disease and, of course, must be in concordance with indications approved by the EMA and SIDC. If the request is approved, the physician is able to begin the therapy in a particular case and this therapy is fully reimbursed.

By this exceptional reimbursement we treated approximately 400 patients in 2015 in the Czech Republic. The majority of these patients were cirrhotics, compensated as well as decompensated, and patients listed for transplantation or patients after liver transplantation.

Now, in December 2015, we are approaching really regular reimbursement of all DAA used in IFN-free regimens. The #1 drugs expected to enter the regular market on January 1, 2016 are Exviera and Viekirax by Abbvie, likely immediately followed by Harvoni and Daklinza (February – March 2016). Only a limited number of large volume centers (likely 15-17) will be provided with the special budgets for IFN-free regimens. Therefore, these centers are supposed to centralize all patients indicated for IFN-free treatments (approx. 400-500 patients in 2016).

The Czech Society of Hepatology released updated national guidelines in October 2015. These are strictly based on European Association for the Study of the Liver (EASL) Guidelines published in April 2015 (www.ces-hep.cz), and they serve as a basis for the reimbursement system described above [1, 2].

Hungary

Approximately 70 000 people are infected with the hepatitis C virus (HCV) in Hungary, more than half of whom are not aware of their infection. Early recognition and effective treatment of related liver injury may prevent consequent advanced liver diseases (liver cirrhosis and liver cancer) with their complications and increase work productivity and life expectancy of the infected individual on one hand, and could prevent the transmission of the virus as well as substantially reduce the long-term financial burden of related morbidity from the socioeconomic point of view.

Available since 2003 in Hungary, pegylated interferon (Peg-IFN) + ribavirin (RBV) dual therapy can kill the virus in 40-45% of previously untreated (naïve), and in 5-21% of previous treatment-failure patients. Addition of a direct acting first generation protease inhibitor drug (boceprevir or telaprevir) to the dual therapy increases the chance of sustained clearance of the virus to 63-75% and 59-66%, respectively. These two protease inhibitor drugs have been available and financed for a segment of Hungarian patients since May 2013. From 2013 to 2015, other direct acting antivirals were registered for the treatment of chronic hepatitis C in different combinations, including short duration (8-12 weeks) interferon-free regimens, with a potential efficacy over 90% [3].

Indication of therapy includes exclusion of contraindications to the drugs and demonstration of viral replication with consequent liver injury, i.e., inflammatory and or fibrosis in the liver. For initiation of treatment as well as for on-treatment decisions, accurate and timely molecular biology tests are mandatory. In staging of liver damage (fibrosis) non-invasive methods (transient elastography and biochemical methods) are acceptable to avoid concerns of patients related to liver biopsy.

The professional decision for treatment is balanced against budget limitations in Hungary, and priority is given to those with urgent need using a national Priority Index system reflecting the stage of liver disease as well as additional factors (activity and progression of liver disease, predictive factors and other special circumstances).

All treatments that are covered from a pre-defined budget by the National Health Insurance Fund are to be centrally approved. These treatments are restricted to the most cost-effective combinations based on the cost per sustained viral response value in different patient categories with consensus between professional organizations, the Insurance Agency and patient organizations. More expensive therapies might be available upon co-financing by the patient or a third party. Interferon-free treatment and shorter therapy duration are preferred as much as financially feasible. A separate budget is allocated to cover interferon-free treatments for the most-in-need interferon ineligible/intolerant patients, and for those who have no other interferon-based therapy option (Table 1).

Poland

The current reimbursement program created by the National Health Fund (NFZ) allows the treatment of about 3500 patients every year. According to a recent analysis [5] the annual treatment rate in Poland should

Table 1. Interferon-free combinations for chronic HCV hepatitis in Hungary (2015-2016) [2, 4]

Direct acting antivirals	Genotype	Treatment duration (weeks)	Comments
SOF + RBV	G2 (G3)	12 (24)	Neg. predictors or G3: 24 weeks
SOF + SMV ± RBV	G1, G4	12	Neg. predictors or G1a: + RBV
SOF + LDV ± RBV	G1, G3, G4	8-12 (24)	Treatment experienced, cirrhotic: + RBV (or 24 weeks); G3: + RBV, 24 weeks
SOF + DCV ± RBV	G1, G3, G4	12 (24)	24 weeks therapy – costly
OBV/PTV/r + DSV ± RBV	G1	12-24	G1a or cirrhosis: + RBV G1a and Peg-IFN + RBV: null response: + RBV, 24 weeks
DCV + ASV*	G1b	24	NS5A L31 or Y93 polymorphism: not recommended
DCV + SMV ± RBV	G1b	12-24	Peg-IFN + RBV not reagent: + RBV, 24 weeks
GZV + EBV*	G1, G4, G6	8-12	
GZV + EBV + SOF*	G3	8-12	

**Not licensed by EMA (European Medicines Agency), SOF – sofosbuvir, RBV – ribavirin, SMV – simeprevir, LDV – ledipasvir, DCV – daclatasvir, OBV – ombitasvir, PTV – paritaprevir, /r/ – ritonavir, DSV – dasabuvir, ASV – asunaprevir, GZV – grazoprevir, EBV – elbasvir, Peg-IFN – pegylated interferon*

be increased by 4-fold to achieve > 90% reduction of HCV infections by the year 2030. Additionally it is essential to provide access to highly effective therapeutic options.

Until 2015 the NFZ therapeutic program for HCV treatment management reimbursed triple therapy containing boceprevir and telaprevir to a limited number of patients with advanced fibrosis, who failed previous interferon based dual therapy or were treatment naïve with IL28B genotype TT. As a result only 20% of patients had access to triple therapy, there was no reimbursement for the interferon-free regimen, and a large majority of patients were still treated with a suboptimal combination of pegylated interferon α (Peg-IFN-α) and ribavirin (RBV). Moreover, the only approved method of fibrosis evaluation was liver biopsy.

From November 2014 some pharmaceutical companies provided early access to innovative medication for about 400 patients, mostly with advanced hepatic fibrosis. We included these patients in real life studies on efficacy and safety (AMBER, HARVEST), that up to now in interim analysis have demonstrated a 99% sustained virologic response rate with ombitasvir/paritaprevir/ritonavir (OBV/PRV/r) and dasabuvir (DSV) ± RBV, 90% with sofosbuvir/ledipasvir (SOF/LDV), 84% with SOF + Peg-IFN-α + RBV and 79% with SOF + simeprevir (SMV) [6].

A new version of the NFZ therapeutic program started in May 2015 and provided reimbursed SMV containing triple therapy for all genotype 1 and 4 infected patients even with minimal fibrosis and irrespective of IL28B status. Additionally, hepatic fibrosis evaluation became possible with elastography. From July 2015 the first interferon-free regimen with OBV/PRV/r + DSV ± RBV became available irrespective of fibrosis (even in patients without fibrosis) or previous treatment history in genotype 1 and 4 infected patients. In September the second interferon-free combination containing asunaprevir (ASV) and daclatasvir (DCV) for genotype 1 was included in the NFZ therapeutic program. Finally in November SOF for possible combination with RBV and Peg-IFN-α in genotypes 2-6, and SOF/LDV in genotype 1 were approved for reimbursement. However, the most important were the prices which were negotiated by the Health Ministry at a level only slightly higher than Peg-IFN-α + RBV. Therefore it is very likely that from 2015 there will be no patients on IFN-based treatment except genotype 3 infected who will be treated with SOF + Peg-IFN-α + RBV (Table 2).

According to available sales and tender data we can assume that in 2015 about 3000 patients can start treatment with interferon-free regimens, mostly OBV/PRV/r + DSV ± RBV.

In June 2015 the National Plan for HCV elimination was submitted to the Health Ministry by the National Consultant for Infectious Diseases and the Polish Group of HCV Experts. This plan assumes implementation of wide access to highly effective IFN-free therapeutic options and testing of populations identified as a high risk for HCV infection including:

- recipients of blood transfusion before 1992,
- intravenous drug users (ongoing and past),
- hospitalized more than 3 times during the life,
- history of imprisonment,
- tested for HIV infection,
- elevated ALT,
- diagnosis or suspicion of any hepatic disorder.

Table 2. Regimens available and reimbursed in 2015 for treatment of chronic hepatitis C in Poland

Regimen	Genotypes						
	1a	1b	2	3	4	5	6
OBV/PTV/r ± DSV ± RBV	x	x					
OBV/PTV/r ± RBV					x		
ASV + DCV		x					
SOF/LDV	x	x					
SOF + Peg-IFN + RBV			x	x	x	x	x
SOF + RBV			x	x	x	x	x

OBV – ombitasvir, PTV – paritaprevir, /r/ – ritonavir, DSV – dasabuvir, RBV – ribavirin, ASV – asunaprevir, DCV – daclatasvir, SOF – sofosbuvir, LDV – ledipasvir, Peg-IFN – pegylated interferon

According to recently published analysis to achieve > 90% reduction of HCV prevalence in Poland, it will be necessary to diagnose and treat 15 000 HCV cases annually with efficacy exceeding 90% [7].

Slovakia

Slovakia, a member of the European Union, is a country with limited economic resources compared to wealthier countries. This also affects the health care budget.

Recently, therapeutic options with practically 100% efficiency for the treatment of chronic hepatitis C have become available. The cost of these regimens, based on the active substance, is 3 to 4 times higher than previous treatment regimens. This puts tremendous pressure on the resources of the health care system. This pressure is further increased by patients who are well aware of a highly effective treatment available for CHC and they of course request such treatment.

We estimate that there are about 35,000 people infected with the HCV in Slovakia [8]. The most common genotype is genotype 1 (70-80%), most of which is 1b. The rest is mainly genotype 3, while other genotypes are rare. The treatment of chronic viral hepatitis B and C in Slovakia has been centralized in centers for the treatment of viral hepatitis since 1995. These centers are codified through the decree of the Ministry of Health of the Slovak Republic. Currently there are 23 centers, including centers for children and youth.

Classical treatment with Peg-IFN-α plus ribavirin (PR treatment) was used until 2012. Later on the first generation of protease inhibitors (PI) boceprevir and telaprevir became available and health insurance companies started to reimburse them. Because of the increased cost associated with the new molecules, we applied a prioritization system for the first time. This system was developed by our experts organized in the working group for viral hepatitis, which is part of the Slovak Society of Hepatology. This new system was based on the fact that it first and foremost treated patients at high risk and those who could not wait for new molecules. This system also introduced new concepts to facilitate communication between Health Care Providers (HCP) and health insurance companies. For PR treatment we introduced the abbreviation "2K" (combination of two drugs) and for PR and PI treatment the abbreviation "3K". After negotiations with health insurance companies and collecting data from centers we developed a consensus about the number of patients who required treatment with 3K at 120 to 130 per year since 2013. This also applies to 2015, but boceprevir and telaprevir were replaced by simeprevir, which has been reimbursed since March 2015.

Interferon-free 3D combination treatment has been approved in Slovakia since September 2015, followed by the approval of the sofosbuvir and ledipasvir regimen. Due to the expected high number of patients requiring an IFN-free regimen, the working group for viral hepatitis reevaluated the strategy in order to prioritize patients who need IFN-free treatment. The working group has set up the parameters through which all CHC patients requiring an IFN-free regimen have been divided into three main groups: Emergency, Urgent and Remaining.

The Emergency group includes all patients on waiting lists for orthotopic liver and renal transplant, patients after orthotopic liver and renal transplant, and patients with advanced liver diseases (i.e. stage F4 – liver cirrhosis), who were identified as high-risk according to the CUPIC criteria (albumin below 35 g/l and/or platelet counts below 100×10^9/l) [9]. Patients within the CUPIC criteria after the failure of 3K therapy or with significant extra-hepatic manifestations were also included. Our plan is to treat all patients in the Emergency group by the end of 2015.

Currently, the working group for viral hepatitis is starting the collection of Urgent patients. Patients are subject to the following inclusion criteria: all patients with advanced fibrosis F3/F4 and/or after failure of 3K therapy (F3/F4). We plan to treat these patients during 2016. The group of Remaining patients requiring an IFN-free regimen will be treated according to economic possibilities.

We are continuing with the 2K treatment regimen in Slovakia in the group of patients who meet the following criteria: F0-F3, IL 28B C/C. Some patients could be treated with 3K therapy with SMV.

Conclusions

Treatment of patients in the Czech Republic was based in 2015 on an exceptional individual reimbursement procedure, but regular reimbursement procedures are expected in 2016. In Hungary the decision for treatment is balanced against budget limitations and the national Priority Index system reflecting stage of liver disease, activity of the disease and predictive factors. A reimbursed IFN-free therapeutic program for all genotypes, without restrictions related to hepatic fibrosis and treatment history, is already available in Poland. In Slovakia patients with advanced fibrosis are currently selected for possible IFN-free therapy in 2016.

Disclosure

Authors report no conflict of interest.

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