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**Original paper**

# Efficacy of HCV treatment in Poland at the turn of the interferon era – the EpiTer study

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## Abstract

**The aim of the study** was to analyze the efficacy achieved with regimens available for chronic hepatitis C (CHC) in Poland between 2013 and 2016.

**Material and methods:** Data were collected from 29 centers and included 6786 patients with available sustained virologic response (SVR) data between 1 January 2013 and 31 March 2016.

**Results:** The sustained virologic response rate for genotypes (G) 1a, 1b, 2, 3 and 4 was 62%, 56%, 92%, 67% and 56% respectively; 71% patients (*n* = 4832) were treated with pegylated interferon α (Peg-IFNα) and ribavirin (RBV), with SVR rates of 58%, 49%, 92%, 67% and 55% respectively. The sustained virologic response among 5646 G1 infected patients was the lowest with natural interferon α (7%, *n* = 70) or PegIFN (50%, *n* = 3779) with RBV, and improved in those receiving triple regimens of Peg-IFN + RBV combined with boceprevir (47%, *n* = 485), telaprevir (64%, *n* = 805), simeprevir (73%, *n* = 132) or sofosbuvir (70%, *n* = 23). The sustained virologic response with interferon-free regimens of sofosbuvir and RBV (*n* = 7), sofosbuvir and simeprevir (*n* = 53), and ledipasvir and sofosbuvir (*n* = 64) achieved 86%, 89% and 94% respectively. The highest SVR of 98% was observed with ombitasvir/paritaprevir combined with dasabuvir (*n* = 227). Patients infected with G3 (*n* = 896) and G4 (*n* = 220) received mostly Peg-IFN + RBV with SVR of 67% and 56% respectively. Interferon-free regimens were administered in 18 G3/G4 patients and all achieved an SVR. Sofosbuvir combined with Peg-IFN and RBV was administered to 33 patients with an SVR rate of 94%, and a similar rate was achieved among 13 G2 patients treated with interferon and RBV.

**Conclusions:** We observed significant differences in efficacy of HCV regimens available in Poland at the turn of the interferon era. The data will be useful as a comparison for therapeutic options expected in the next few years.

**Key words:** liver, hepatitis C, therapy.

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## Introduction

According to the recent data, hepatitis C virus (HCV) infection is estimated in about 3.2 million of the European Union inhabitants, and 200 000 are from Poland [1, 2]. Hepatocyte damage due to HCV infection stimulates liver fibrosis resulting in liver cirrhosis (LC) and can also be responsible for the development of hepatocellular carcinoma (HCC) [3-5]. Since no anti-HCV vaccine is available, the reduction of worldwide prevalence of HCV infection, as well as prevention of advanced liver disease in chronic hepatitis C (CHC) patients, can be achieved with an efficient antiviral therapy [6].

Until 2013 in Poland the only therapeutic option was treatment with pegylated interferon alfa (Peg-IFNα) and ribavirin (RBV). The sustained virologic response (SVR) rate of this regimen was about 40% in patients infected with the most prevalent HCV genotype (G) 1 and up to 70% in G2 or G3 infections [7-9]. In addition to insufficient efficacy, this regimen was limited by numerous adverse events leading to the treatment discontinuation and its failure. In 2011, the first generation of direct-acting antivirals (DAA), protease inhibitors boceprevir (BOC) and telaprevir (TVR), became registered in the European Union, and finally in 2013 it was reimbursed in a limited proportion of patients in Poland. Addition of these medicines to Peg-IFN and RBV improved SVR rates in G1 infected patients up to about 70%, but was not applicable for other genotypes [10]. Unfortunately, these regimens were still inefficient in non-responders to the Peg-IFN + RBV therapy, cirrhotics, and patients with IL28B genotype TT. It even worsened the safety profile compared to the Peg-IFN + RBV regimen, particularly in patients with advanced liver fibrosis [11].

New generation DAA, simeprevir (SMV), sofosbuvir (SOF), daclatasvir (DCV) as well as coformulated IFN-free regimens of SOF and ledipasvir (SOF/LDV) and ombitasvir/paritaprevir boosted with ritonavir combined with dasabuvir (OBV/PTV/r + DSV ± RBV) became available in Europe from 2014 and reimbursed in Poland in mid 2015. They are not only protease, but also polymerase and NS5A inhibitors and can be combined with each other to improve efficacy above 90% irrespectively of fibrosis, treatment history or host fac-

tors. The safety profile in the majority of patients is excellent, and the treatment usually does not exceed 12 weeks [5, 12-15].

The aim of the study was to analyze the efficacy achieved with very different regimens for treatment of CHC patients in Poland between 2013 and 2016, so at the age of significant changes in available therapeutic options.

## Material and methods

Data were collected with an Excel (Microsoft) based questionnaire filled in by 29 Polish centers from 15 voivodships involved in diagnosis and treatment of HCV-infected patients. All voivodships, except opolskie, were included in the database. The questionnaire contained information on the number of patients with efficacy data available between 1 January 2013 and 31 March 2016. Efficacy was determined by SVR defined by undetectable HCV RNA after at least 12 weeks of post-treatment follow-up. Submitted data were combined and efficacy was analyzed with respect to HCV genotypes and the administered therapeutic regimen.

## Results

As demonstrated in Table 1, a total of 6786 patients were included in the database. The large majority were infected with G1b (55.7%), followed by G1 without available subgenotyping (25.6%) and G3 (13.2%). Based on the proportion of G1b among patients with available subgenotyping, estimated prevalence of G1b in the studied population was calculated as 80.6%.

**Table 1.** Distribution of genotypes and efficacy (SVR) among 6786 patients with available efficacy data treated between 1 January 2013 and 31 March 2016 in 29 Polish centers

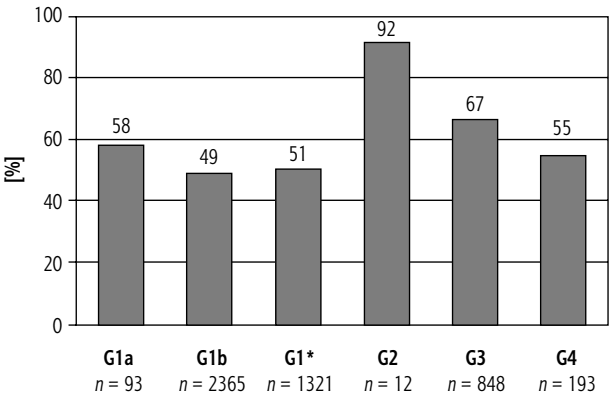
| Genotype | Patients in analysis, *N* | Distribution of genotypes, % | Patients cured, *n* | SVR (*n/N*) % |
|---|---|---|---|---|
| 1a | 126 | 1.9 | 78 | 62 |
| 1b | 3783 | 55.7 | 2105 | 56 |
| 1* | 1740 | 25.6 | 895 | 51 |
| 2 | 13 | 0.2 | 12 | 92 |
| 3 | 896 | 13.2 | 601 | 67 |
| 4 | 220 | 3.2 | 123 | 56 |
| 5 | 0 | 0 | 0 | 0 |
| 6 | 0 | 0 | 0 | 0 |
| Mixed | 8 | 0.1 | 1 | 13 |
| | 6786 | 100 | 3815 | 56 |

**Subgenotyping not available*

The sustained virologic response rate for all enrolled patients was 56%. The lowest SVR was for mixed genotypes (13%) and the highest for G2 (92%), but the number of patients in these two populations was very low and they were treated mostly with Peg-IFN + RBV (Table 1). Among patients infected with G1, the highest SVR was observed for G1a (62%). Despite the estimated high proportion of G1b among unidentified G1 patients, the SVR rate of 51% was lower compared to patients identified as G1b infected (56%). As shown in Table 1, SVR rates for G3 and G4 were 67% and 56% respectively.

Since 71% ($n$ = 4832) of patients included in the database were treated with Peg-IFN + RBV, SVR rates for particular genotypes in patients treated with this regimen were usually lower compared to general data. However, once again the highest efficacy was demonstrated for G2 and G3, but the SVR rate for G1b was almost equal to G1 infected without subgenotyping (Fig. 1).

Treatment efficacy of different regimens in the large number of 5646 patients infected with genotype 1 is demonstrated in Figure 2. A unique group of 70 patients treated with natural interferon alfa (natural IFN) achieved an extremely low SVR rate of 7%. The regimen with Peg-IFN + RBV, which was standard for many years, provided therapeutic success in 50% of them. Relatively low SVR of 47-64% was achieved with the IFN-based triple regimens containing the first generation DAA – BOC or TVR (Fig. 2). Efficacy achieved with the second wave DAA (SMV or SOF) but still IFN-based regimens was about 70%. Significant improvement with an SVR rate exceeding 80% was achieved with IFN-free therapeutic options, and the highest SVR rate of 98% was observed in patients treated with OBV/PTV/r + DSV ± RBV (Fig. 2).




**Subgenotyping not available*

**Fig. 1.** Sustained virologic response rate after treatment with Peg-IFN + RBV in 4832 patients infected with different HCV genotypes, between 1 January 2013 and 31 March 2016 in 29 Polish centers

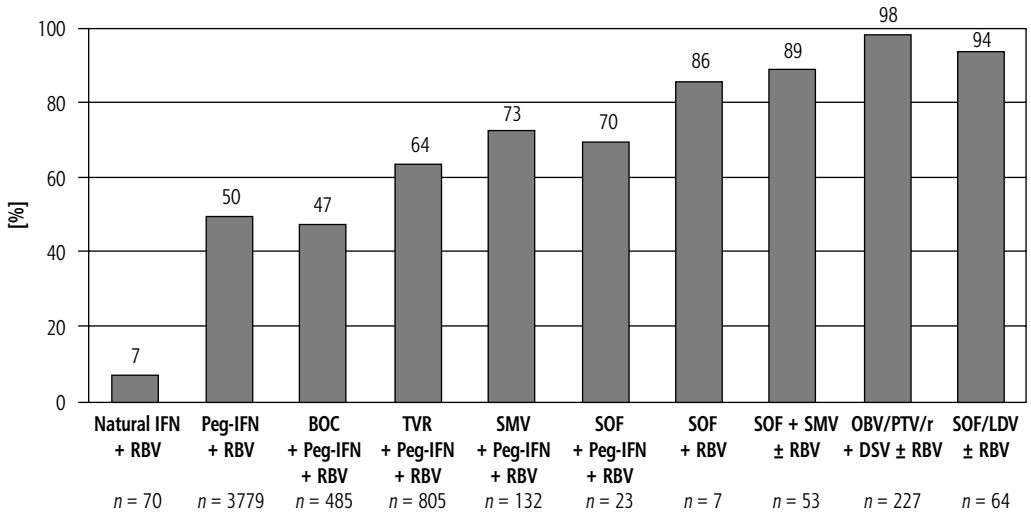



**Fig. 2.** Sustained virologic response rates achieved after treatment with different regimens in 5646 patients infected with HCV genotype 1, between 1 January 2013 and 31 March 2016 in 29 Polish centers

Efficacy of particular regimens in 1129 patients infected with genotypes 2, 3 and 4 is shown in Table 2. The large majority of patients infected with G3 and G4 received Peg-IFN + RBV; therefore overall efficacy was 67% and 56% respectively. However, different IFN-free therapeutic options were administered in 18 G3/G4 patients, and all of them achieved an SVR. Sofosbuvir + Peg-IFN + RBV is currently the most popular regimen in Poland for treatment of G3 infected patients. In the analyzed period it was administered to 33 patients, with an SVR rate of 94%. Similar efficacy of 92% was achieved among 13 patients infected with G2 treated with Peg-IFNα or non-Peg-IFNα and RBV without any DAA. Interestingly, there were documented 6 cases of triple IFN-based therapy containing SMV in G4 infected patients, which failed in all except one patient (Table 2).

## Discussion

Lower SVR in undetermined G1 compared to G1b patients was due to the different regimens administered. Subgenotyping was not obligatory before availability of interferon-free regimens, so it is obvious that

**Table 2.** Sustained virologic response rates achieved after treatment with different regimens in 1129 patients infected with HCV genotypes 2, 3 and 4, between 1 January 2013 and 31 March 2016 in 29 Polish centers

| | Genotype 2 | | Genotype 3 | | Genotype 4 | |
|---|---|---|---|---|---|---|
| | ***n*** | **SVR** | ***n*** | **SVR** | ***n*** | **SVR** |
| **Natural IFN + RBV** | – | – | 11 | 0% | 1 | 0% |
| **IFN + RBV** | 1 | 100% | – | – | – | – |
| **Peg-IFN** | – | – | – | – | 2 | 0% |
| **Peg-IFN + RBV** | 12 | 92% | 848 | 67% | 193 | 55% |
| **TVR + Peg-IFN + RBV** | – | – | – | – | 1 | 100% |
| **SMV + Peg-IFN + RBV** | – | – | – | – | 6 | 17% |
| **SOF + Peg-IFN + RBV** | – | – | 33 | 94% | 3 | 33% |
| **OBV/PTV/r ± RBV** | – | – | – | – | 12 | 100% |
| **SOF/LDV ± RBV** | – | – | 1 | 100% | 2 | 100% |
| **SOF + DCV + RBV** | – | – | 1 | 100% | – | – |
| **SOF + RBV** | – | – | 2 | 100% | – | – |
| **Overall** | 13 | 92% | 896 | 67% | 220 | 56% |

all patients not subgenotyped for G1 were treated before mid 2015 with less efficient interferon-based therapeutic options. This explanation was supported by similar response rates (49% vs. 51%) in patients treated with Peg-IFN + RBV. However, it should be taken into consideration that efficacy of IFN-based therapies can be affected by numerous other factors including history of previous treatment, IL28B genotype and stage of the disease, which were not analyzed in our study.

Figure 2 provides unique information on the natural IFN + RBV regimen which was still administered between 2013 and 2016 to 70 patients. According to our knowledge, this old-fashioned therapy was administered mostly to patients with strong contraindications to Peg-IFN, usually in treatment of patients with advanced fibrosis. However, an SVR rate of 7% even in a very difficult to treat population is insufficient to support use of this regimen in the era of IFN-based therapy.

Our data confirmed similar response rates for G1 and G4 in a large number of patients. We observed a relatively low SVR for G3 (67%). According to the literature, it was expected at the level of 70-80% [7]. In contrast, the SVR rate among 13 identified G2 patients reached 92%, which was higher than expected, but the value of this finding is limited due to the low number of patients.

The lower than expected SVR rate achieved with the triple regimens containing the first generation DAA, particularly BOC, can be explained by the extremely difficult to treat population of cirrhotics and non-responders to Peg-IFN + RBV enrolled in these regimens. Similar efficacy data were previously reported in real world studies such as CUPIC and ADVEX [10, 11].

There was a limited number of patients with available efficacy data after interferon-free regimens. They were treated mostly with medication provided as an "early access" by pharmaceutical companies in 2014 and 2015, and the majority of these patients were included in the real world studies AMBER and HARVEST. Therefore it is not surprising that SVR rates of OBV/PTV/r + DSV ± RBV and SOF/LDV for G1 infected patients are similar to those already reported [14, 15]. They are also similar to available real world data from other countries and confirm the superiority of the two mentioned regimens compared to the combination of SOF + SMV ± RBV or SOF + RBV in the G1 population [16, 17].

A large majority of patients infected with other than G1 genotypes were treated with the Peg-IFN + RBV regimen ($n$ = 1053). Sofosbuvir + Peg-IFN + RBV treatment was administered to 33 patients infected with G3, with 94% efficacy, which is similar to that demonstrated in the BOSON study and supports the rationale for current recommendations of the Polish HCV Expert Group for G3 management [18, 19]. Also worth mentioning was a group of 12 patients infected with G4 treated with OBV/PTV/r ± RBV, which achieved a 100% response rate, similar to that observed in clinical trials and real world experience [15, 20]. Altogether, 18 patients infected with G3 or G4 were treated with different interferon-free regimens, and all of them cleared the virus. Of course, the numbers are not meaningful, but such high efficacy indicates a tendency we should expect in the future study containing many more patients treated without interferon.

In this study we observed significant differences in efficacy of HCV therapeutic options available in Poland between 2013 and 2016, at the turn of the interferon age. It was probably the last moment we were able to collect a large number of patients treated with interferon-based regimens, and therefore these data will be useful as a comparison for interferon-free regimens which are already available and those expected in the next few years.

## Disclosure

Authors report no conflict of interest.

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