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Comparative effectiveness of 8 versus 12 weeks of Ombitasvir/Paritaprevir/ritonavir and Dasabuvir in treatment-naïve patients infected with HCV genotype 1b with non-advanced hepatic fibrosis

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ABSTRACT

Purpose: Since 2017 treatment-naïve patients infected with genotype 1b of hepatitis C virus and minimal or moderate fibrosis can be treated with Ombitasvir/Paritaprevir/ritonavir + Dasabuvir (OPrD) for 8 weeks according to updated Summary of Product Characteristics. The aim of our study was to assess the comparative efficacy of 8 and 12-weeks therapy with OPrD in large cohort of patients eligible for 8 weeks regimen treated in real-world setting.

Materials and methods: We analysed data of 3067 HCV genotype 1b infected patients treated with OPrD between 2015 and 2017. Final analysis included patients with none, minimal or moderate fibrosis (F0–F2).

Results: A total of 771 patients were enrolled in the study, including 197 (26%) treated for 8-weeks and 574 patients fulfilling criteria for 8-weeks but assigned to 12-weeks regimen. Majority of patients had no or minimal fibrosis (F0–F1). Longer treatment duration was more often administered in patients with moderate fibrosis, comorbidities, concomitant medications. SVR was achieved in 186 (94%) patients treated for 8 weeks and 558 (97%) for 12 weeks (p = 0.07). After exclusion of lost to follow-up patients, sustained virological response (SVR)

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rate reached 95% and 99%, respectively (p = 0.01). We were not able to identify factors associated with non-response.

Conclusions: This real-word experience study confirmed similar, high effectiveness of 8 and 12-weeks regimens of OPrD in genotype 1b HCV infected patients with non-advanced fibrosis. Despite of reduced SVR rate after 8-weeks regimen, there is no need to extend therapy to 12-weeks in vast majority of such patients and no need to add ribavirin.

1. Introduction

Chronic hepatitis C virus (HCV) infection is one of leading causes of liver disease, affecting approximately 71 million people globally. The most prevalent worldwide is genotype (GT) 1, particularly its subtype 1b, which is predominant in Europe [1]. According to the most recent analysis GT1b is responsible for more than 80% HCV infections in Poland [2]. Therefore at the beginning of the interferon-free era there was a need of highly effective and tolerable regimen for treatment of patients infected with this GT. The first available option was ombitasvir/paritaprevir/ritonavir and dasabuvir (OPrD), which was approved in the European Union for the treatment of GT1b infected patients for 12 weeks, regardless of liver fibrosis and treatment history [3]. Since 2017, treatment-naïve patients with chronic GT1b HCV infection with minimal or moderate fibrosis can be treated with OPrD for 8 weeks. This update of Product Characteristics was based on the results of a relatively small Garnet study, which was not supported by any large real world experience (RWE) study [4]. Shortening of the treatment can reduce therapy costs, improve patients comfort and adherence to treatment. So, if it does not cause sustained virological response (SVR) reduction and can be confirmed in additional study, 8 weeks therapy should be recommended as an optimal regimen.

The aim of our study was to assess the comparative efficacy of 8 and 12-week regimens of OPrD in patients eligible for 8 weeks therapy in RWE setting.

2. Patients and methods

2.1. Study design

The analysis was a part of the EpiTer-2 database, a retrospective, investigator-initiated, manufacturer-independent study evaluating antiviral treatment of HCV infected patients in routine clinical practice, that included 22 Polish hepatitis treating centres [5,6]. The choice of the regimen was entirely at the discretion of the treating physicians. Patients were treated in line with reimbursed therapeutic program of the Polish National Health Fund and in accordance with the recommendations of the Polish Group of Experts for HCV [7]. According to the protocol of national therapeutic program, patients receiving OPrD regimen were monitored every 4 weeks for haematology, ALT and bilirubin level and additionally HCV RNA were measured at the end of treatment (EOT) and final follow-up visit. HCV RNA detection level varied across study centres depending on the assay used but was always < 15 IU/mL as recommended by national guidelines [7]. The study was supported by the Polish Association of Epidemiologists and Infectiologists.

2.2. Patients

Among 6228 patients included in the EpiTer-2 database, treated for chronic HCV infection between 1 July 2015 and 31 December 2017, a total number of 3067 patients infected with GT1b received OPrD, that included 771 patients with none, minimal or moderate fibrosis (F0–F2). In this population 197 patients received 8-weeks regimen, whereas remaining 574 patients eligible for shorter treatment duration were assigned to 12-weeks regimen. Decision on the length of treatment was at the discretion of the treating physician based on the Summary of Product Characteristics for Viekirax and Exviera (updated in March 2016), that also included ribavirin (RBV) co-administration. We decided to have 12 weeks regimen with RBV arm in the analysis to demonstrate possible effect of RBV addition.

2.3. Data analysis

Data concerning baseline variables included demographics, prior treatment status, stage of liver fibrosis (based mostly on stiffness in elastography), comorbidities, concomitant medications, HIV and HBV coinfections, severity of the disease, history of decompensation and hepatocellular carcinoma, laboratory parameters, treatment regimen, therapy course, efficacy and safety, were collected retrospectively and submitted online by questionnaire administered by Tiba sp. z o.o.

The efficacy end point was the SVR defined as undetectable HCV RNA at least 12 weeks after the end of treatment. The safety of antiviral therapy was assessed by analysing the most common and most severe documented adverse events, as well as the rate of treatment discontinuation, its modification and deaths.

2.4. Statistical analysis

The results are expressed as mean ± standard deviation (SD) or n (%). P values of < 0.05 were considered to be statistically significant. Comparisons between groups were performed with analysis of non-parametric test. The significance of difference was calculated using the Fischer's exact test for categorical variables and by the Mann Whitney *U* test for continuous variables. Multivariate analysis was performed using logistic regression with SVR as dependent variable, fibrosis (F0-1 vs F2), sex and comorbidity as qualitative predictors and age, HCV-RNA and serum albumins as quantitative predictors. Statistical analyses were performed using GraphPad Prism 5.1 (GraphPad Software, Inc., La Jolla, CA, USA).

3. Results

The mean age of the cohort was 47 ± 15 years, and 43% were males. As shown in Table 1, 49% of the analysed population presented comorbidities with the most frequent arterial hypertension, and 41% were treated with co-medications. Longer treatment duration was statistically significantly more often administered in older patients with comorbidities and concomitant medications. The majority of patients had no or minimal fibrosis, and their proportion in the group treated for 8 weeks (84%) was statistically significantly higher compared to patients treated for 12 weeks (61%). The most common method of liver fibrosis assessment was transient elastography applied in 56% of patients (Table 1).

As shown in Fig. 1, overall SVR rate calculated according to the intent-to-treat (ITT) analysis was achieved in 186/197 (94%) patients treated for 8 weeks and 558/574 (97%) treated for 12-weeks (p = 0.07). After exclusion of lost to follow-up patients (modified ITT (mITT) analysis), SVR rate reached 95% and 99%, respectively (p = 0.01). Among those treated with OPrD for 12 weeks, 53 patients (9.2%) received additionally RBV, which did not improved the efficacy and even caused insignificant reduction of SVR rate compared to patients treated with OPrD without RBV in both intent-to-treat (ITT) (93% vs 98%, p = 0.05) and modified ITT (mITT) analysis (96% vs 98%,

Table 1
Baseline characteristics of patients treated with OBV/PTV/r + DSV for 8 weeks or 12 weeks (eligible for 8 weeks).

Parameter	OBV/PTV/r + DSV		
	8 weeks n = 197	12 weeks n = 574	p
Gender, females/males, n(%)	123 (62.4%)/ 74 (37.6%)	321 (56%)/ 253 (44%)	0.11
Age [years] mean ± SD; min.-max.	42 ± 13; 20-77	49 ± 15; 17-82	< 0.001
Females	43 ± 13; 20-71	50 ± 15; 23-82	< 0.001
Males	41 ± 14; 23-77	47 ± 14; 17-79	< 0.001
BMI mean ± SD; min-max	25 ± 4; 17-43	25 ± 4; 16-50	0.13
Comorbidities, n(%)	60 (30%)	322 (56%)	< 0.001
Any comorbidity	18 (9%)	146 (25%)	< 0.001
Hypertension	5 (2.5%)	35 (6.1%)	0.06
Diabetes	2 (1%)	26 (4.5%)	0.03
Renal disease	2 (1%)	12 (2.1%)	0.52
Autoimmune diseases	2 (1%)	8 (1.4%)	1.00
Non-HCC tumors other	47 (24%)	239 (41.6%)	< 0.001
Concomitant medications, n(%)	56 (28%)	259 (45%)	< 0.001
Liver fibrosis, n(%)			
F0	4 (2%)	0	
F1	161 (82%)	351 (61%)	< 0.001
F2	32 (16%)	223 (39%)	
OLTx experienced, n(%)	0	0	N/A
HCC history, n(%)	0	4 (0.7%)	N/A
Liver fibrosis assessment, n(%)			
biopsy	16 (8%)	186 (32.4%)	
TE	130 (66%)	309 (53.8%)	
SWE	51 (26%)	78 (13.6%)	< 0.001
ARFI	0	1 (0.2%)	
HIV coinfection	1 (0.5%)	9 (1.6%)	0.46
HBV coinfection			
HBsAg(+)	0	4 (0.7%)	N/A
HBsAg(−)/anti-HBctotal(+)	16 (8%)	62 (10.8%)	0.34
ALT IU/L, mean ± SD	61 ± 57	64 ± 50	0.17
Bilirubin mg/dL, mean ± SD	0.67 ± 0.36	0.69 ± 0.4	0.54
Albumin g/dL, mean ± SD	4.2 ± 0.5	4.1 ± 0.4	0.02
Albumin < 3 g/dl, n (%)	1 (0.5%)	2 (0.3%)	1.00
Creatinine mg/dL, mean ± SD	0.83 ± 0.49	0.96 ± 1.1	0.30
Hemoglobin g/dL, mean ± SD	14.0 ± 1.9	14.4 ± 1.9	0.01
Platelets, x1000/μL, mean ± SD	228 ± 65	220 ± 64	0.12
Platelets < 100 000/μL, n (%)	2 (1%)	9 (1.6%)	0.73
HCV RNA x10^6 IU/ml, mean ± SD	1.9 ± 3.1	1.98 ± 6.5	0.42
HCV RNA > 6x10^6 IU/ml, n (%)	16 (8%)	31 (5.4%)	0.17

Abbreviations: OBV - ombitasvir; PTV - paritaprevir; r - ritonavir; DSV - dasabuvir; BMI - body mass index; SD - standard deviation; HCC - hepatocellular carcinoma; HCV - hepatitis C virus; F - fibrosis; OLTx - orthotopic liver transplantation; TE - transient elastography; SWE - shear wave elastography; ARFI - acoustic radiation force impulse; HIV - human immunodeficiency virus; HBV - hepatitis B virus; HBsAg - hepatitis B surface antigen; anti-HBc - antibody to the hepatitis B core antigen; ALT - alanine aminotransferase; HCV RNA - hepatitis C virus ribonucleic acid.

p = 0.29) (Fig. 1). A comparison carried out between the patients treated for 8 or 12-weeks without RBV revealed SVR rates of 94% vs 98% (p = 0.03) in ITT, and 95% vs 98% (p = 0.02) in mITT analysis, respectively (Fig. 1). The only factor associated with SVR in multivariate analysis was 8 week therapy (p = 0.02), with additional trend towards higher SVR in female patients (p = 0.06). The likelihood of SVR was irrespective of age, HCV-RNA, serum albumin, fibrosis advancement (F0-1 vs F2) as well as the presence of comorbidity.

All 9 non-responders from the 8-weeks arm demonstrated viral load below 6 million U/l. All except one demonstrated minimal fibrosis (F1) and 8 were males (Table 2). In the analysed cohort 7 patients (3 males and 4 females) did not respond to 12-weeks OPrD regimen. Two of them had liver fibrosis F1 and five F2; among those with moderate fibrosis (F2) two received therapy with RBV (Table 3).

We were not able to identify the factors associated with non-response to OPrD ± RBV regimen, except for 2 patients in the 8-weeks group, of whom one did not respond to previous pegIFN and RBV therapy and the other one stopped the therapy for 1 week (between 4th and 5th week) because of alcohol abuse.

The majority of patients completed the treatment course as scheduled. The therapy was discontinued by 8 patients and modified in 5 others, mostly due to RBV dose reduction in the patients scheduled for 12 weeks regimen with RBV. Approximately 20% of the total study population experienced at least one adverse event (AE) during the therapy and it was affected by the presence of RBV in the regimen. The most common were weakness/fatigue, sleep disorders, headache and pruritus. Serious AE were reported only in the 12-weeks regimen subpopulation, mainly among patients treated without RBV. There were no deaths reported (Table 4).

4. Discussion

In the present study, we found a statistically significantly higher response to the 12-week OPrD therapy than the 8-week therapy among patients who completed the treatment. The study included patients treated for 12 weeks before the Summary of Product Characteristics changes allowed for shortening of their treatment to 8 weeks. Moreover, as mentioned above the final decision on the regimen, that included possible RBV co-administration and the length of treatment was at the physician discretion. Therefore some patients with none or minimal fibrosis received the 12 weeks regimen.

As mentioned above, shortening of treatment with OPrD was possible based on the Garnet study, which included 166 patients treated for 8 weeks. It was carried out as a single arm, open label study and provided SVR rate of 98% [4]. The only RWE study published up to now with results of 8 weeks OPrD regimen in 200 patients demonstrated SVR rate of 96% [8]. Based on these two studies we can assume that SVR rate achieved after 8 weeks was similar to that demonstrated in our study. However, it must be mentioned, that both of these studies were single arm, so did not compare 8 vs. 12 weeks regimens in patients eligible for shortened therapy because of not advanced liver fibrosis. However such a comparison was carried out in our study.

In the largest RWE study, published by Backus et al. [9], 8 weeks therapy with ledipasvir/sofosbuvir (LDV/SOF) carried out in 1333 patients allowed to achieve SVR in 92% patients. Unfortunately, almost all RWE studies on efficacy of OPrD included patients treated for 12 weeks or longer and SVR rates ranged from 86% to 99% SVR [9–18].

Our present study included patients infected with HCV GT1b, without advanced fibrosis, which met criteria for shortening the treatment to 8 weeks according to both Product Characteristics and current experts recommendations [7,19]. However, the weakness of our study included differences in patients characteristics since among patients treated for 8 weeks there were significantly more females, the patients were younger, demonstrated less advanced fibrosis, had less comorbidities and co-medications. These factors theoretically support better response to treatment, but it was not confirmed with the final efficacy analysis. It was clearly demonstrated that adding RBV to the 12 weeks regimen did not improve efficacy and even caused insignificant reduction of SVR rate and the only factor associated with SVR reduction in multivariate analysis was the 8 week therapy.

It was documented previously [11], that measurement of the viral

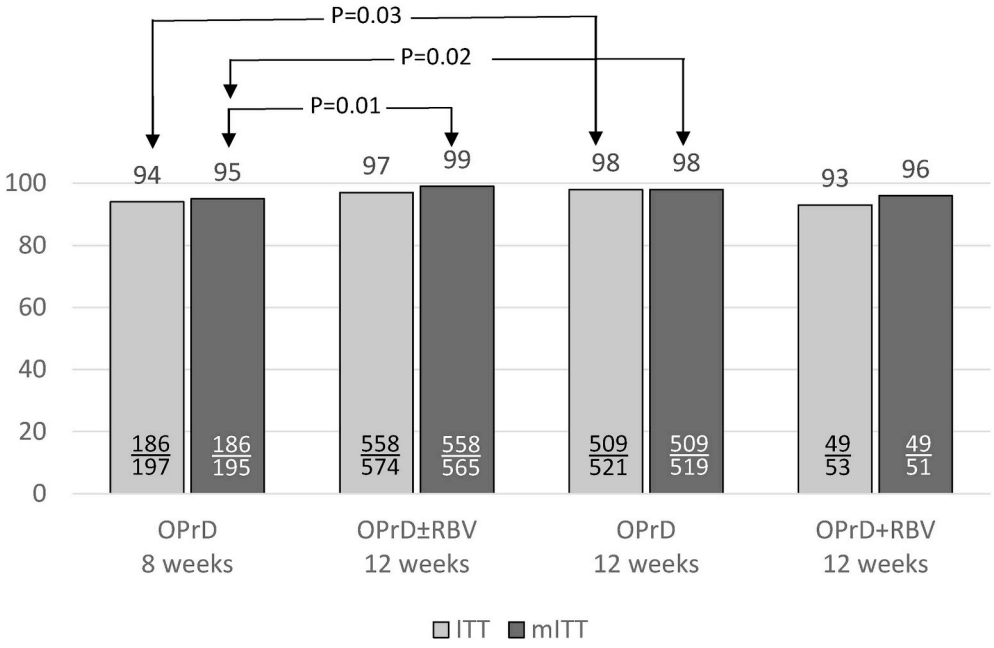

Fig. 1. Treatment effectiveness (SVR rate) of OPrD with and without RBV administered for 8 or 12 weeks, calculated according to ITT and mITT analysis; only statistically significant differences were indicated.
Abbreviations: SVR - sustained virological response; OBV - ombitasvir; PTV - paritaprevir; r - ritonavir; DSV - dasabuvir; RBV - ribavirin; ITT - intent-to-treat; mITT - modified intent-to-treat.

Table 2
Characteristics of 9 non-responders to 8 weeks regimens.

patient	regimen	fibrosis	Baseline HCV RNA x10^6 IU/ml	EOT	Comment (possible reason, chance of SVR if extended)
Female 1	OPrD	1	0.07	TD	none
Male 1	OPrD	1	1.02	TND	none
Male 2	OPrD	2	1.81	TD	none
Male 3	OPrD	1	4.63	TND	none
Male 4	OPrD	1	5.98	TND	none
Male 5	OPrD	1	1.30	TD	Treatment stopped for 1 week (4–5wk) because of alcohol abuse
Male 6	OPrD	1	2.90	TD	none
Male 7	OPrD	1	4.50	TND	none
Male 8	OPrD	1	5.60	TD	none

Abbreviations: HCV RNA - hepatitis C virus ribonucleic acid; EOT - end of treatment; SVR - sustained virologic response; OPrD - ombitasvir, paritaprevir, ritonavir and dasabuvir; TD - target detected; TND - target not detected; pegIFN - pegylated interferon; RBV – ribavirin.

Table 3
Characteristics of 7 non-responders to 12 weeks regimens.

patient	regimen	fibrosis	Baseline HCV RNA x10^6 IU/ml	EOT	Comment (possible reason, chance of SVR if extended)
Female 1	OPrD	1	0.51	TND	none
Female 2	OPrD	2	7.46	TND	none
Female 3	OPrD	2	2.68	TD	none
Female 4	OPrD + RBV	2	0.52	TND	none
Male 1	OPrD	1	4.75	TND	none
Male 2	OPrD	2	3.38	TND	none
Male 3	OPrD + RBV	2	3.21	TND	none

Abbreviations: HCV RNA - hepatitis C virus ribonucleic acid; EOT - end of treatment; SVR - sustained virologic response; OPrD - ombitasvir, paritaprevir, ritonavir and dasabuvir; TD - target detected; TND - target not detected; RBV – ribavirin.

load at the end of direct-acting antiviral (DAA) treatment does not predict the final response. Patients with detectable but not quantifiable HCV RNA at the EOT, can finally either achieve or not achieve SVR. Therefore the majority of the RWE studies even do not provide the EOT

Table 4
Treatment course, modification and discontinuation, safety data according to regimen.

Parameter	8 weeks n = 197	12 weeks n = 521	12 weeks + RBV n = 53
Treatment course, n(%)			
Therapy discontinuation	3 (1.5%)	4 (0.8%)	1 (1.9%)
Therapy modification	0	0	5 (9.4%)
Patients with at least one AE	25 (13%)	97 (19%)	21 (40%)
Serious adverse events	0	4 (0.8%)[a]	1 (1.9%)[b]
Most common AEs (> 2%)			
Weakness/fatigue	8 (4%)	40 (8%)	11 (21%)
Sleep disorder	4 (2%)	10 (2%)	3 (5.7%)
Headache	9 (5%)	6 (1%)	3 (5.7%)
Pruritus	5 (3%)	14 (3%)	0
Laboratory abnormalities			
Elevated ALT, > ULN	0	1 (0.2%)	0
Bilirubin, > 1.5 ULN	1 (0.5%)	2 (0.4%)	2 (3.8%)
Hemoglobin, < 9.5 g/dl	0	2 (0.4%)	0
eGFR, < 60 ml/min/1.73m^2	0	1 (0.2%)	0
Death in treatment course	0	0	0

Abbreviations: RBV - ribavirin; AE - adverse event; ULN - upper limit of norm; eGFR - estimated glomerular filtration rate.
[a] Allergic reaction, headache, ALT elevation (hospitalization), weakness.
[b] Weakness.

viral load information. Since the protocol of the national therapeutic program includes HCV RNA examination at the EOT we are able to provide this unique information. As it was demonstrated in Tables 2 and 3, non-responders after both 8 and 12 weeks regimens had either detectable or non-detectable HCV RNA at the EOT.

There were 4 patients with hepatocellular carcinoma (HCC) but without cirrhosis, which was uncommon but possible if cirrhosis was diagnosed using liver biopsy. Our patients were diagnosed for the disease advancement using liver elastography, which is affected by several factors additional to fibrosis, such as inflammation, steatosis or blood circulation. Therefore non-cirrhotics with HCC are more likely to be found with elastography which is currently an approved technique for the liver advancement evaluation.

It should be noted that almost all patients (8/9) who experienced treatment failure in the 8-week arm were males. According to the recent studies males are less likely to be non-adherent, but on the other hand heavy drinkers, who are usually male more often discontinue therapy,

that can result in lower response rate [18,20,21]. From our data, we were not able to find a clear reason of non-response, particularly in patients treated for 8 weeks. Unfortunately, EpiTer-2 database does not include detailed, day-by-day adherence data, but it provides information on discontinuation or modification of treatment. Based on this information we found that between 2 males with clarified possible reasons of no response only 1 stopped the treatment for one week, whereas the other patient was non-responder to previous interferon based therapy, which as a matter of fact should not affect response to interferon-free treatment. It is worth to mention that 5 of 9 non-responders from the 8-weeks regimen arm had detectable viral load at the EOT compared to only 1 of 7 in the 12-weeks regimen arm. The most probable reason of non-response in these patients was non-adherence, but we were not able to establish why it was more frequent among patients treated for 8 weeks.

5. Conclusions

Concluding, we confirmed high effectiveness of both 8 and 12-weeks OPrD regimens in GT1b HCV infected patients with non-advanced fibrosis. Despite of reduced SVR rate after 8 weeks regimen, there is no need to extend the therapy to 12-weeks in vast majority of such patients and no need to add RBV. However the decision on shortening the treatment to 8 weeks should take into account the risk of lower response rate demonstrated in males.

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Author contribution

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Declaration of competing interest

Dorota Zarębska-Michaluk – Sponsored Lectures: AbbVie, Gilead, Merck; Anna Piekarska – Consultancy: AbbVie, Gilead, Merck, Roche; Jerzy Jaroszewicz – Consultancy: AbbVie, BMS, Gilead; Research funding: Merz, Roche; Jakub Klapaczyński – Sponsored Lectures Gilead; Włodzimierz Mazur – Consultancy: AbbVie, BMS, Gilead, Janssen, Merck, Roche; Research funding: AbbVie, Gilead, Merck, Roche; Rafał Krygier – Consultancy - AbbVie, Gilead, Promed; Teresa Belica-Wdowik – Consultancy: AbbVie, Gilead; Research funding: AbbVie; Barbara Baka-Ćwierz – Consultancy: AbbVie, Gilead, Roche; Research funding: AbbVie, Roche; Ewa Janczewska – Consultancy: AbbVie, BMS, Gilead, Janssen, Roche; Research funding: AbbVie, Allergan, BMS, Gilead, Janssen, Merck, Roche, Vertex, Tobira; Krzysztof Tomasiewicz – Consultancy: AbbVie, Alfa Wasserman, BMS, Gilead, Janssen, Merck, Roche; Research funding: AbbVie, BMS, Gilead, Janssen, Merck, Roche; Aleksander Garlicki – Consultancy: AbbVie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Roche, Sanofi Pasteur; Research funding: Amgen, Janssen, Pfizer; Agnieszka Czauż-Andrzejuk – Research funding: AbbVie, Merck; Dorota Dybowska – Sponsored Lectures: Abbvie. Waldemar Halota – Consultancy: AbbVie, BMS, Gilead, Janssen, Merck, Roche; Research funding: AbbVie, Gilead, Roche; Małgorzata Pawłowska – Consultancy: AbbVie, BMS, Gilead, Janssen, Merck, Roche; Research funding: AbbVie, Gilead, Roche; Krzysztof Simon – Consultancy: AbbVie, Gilead, BMS, Merck, Janssen, Alfa-Wassermann, Baxter, Bayer, Roche; Research funding: AbbVie, Allergan, Bayer, EISAI, Gilead, Intercept, Janssen, Tobira, Pfizer; Olga Tronina – Consultancy: AbbVie; Research funding: Janssen; Robert Flisiak—Consultancy: AbbVie, Alfa Wasserman, BMS, Gilead, Janssen, Merck, Roche; Research funding: AbbVie, Gilead, Janssen, Merck, Roche; Paweł Pabjan, Beata Dobracka, Beata Lorenc, Magdalena Tudrujek-Zdunek, Marek Sitko, Jolanta Citko, Łukasz Laurans, Zbigniew Deroń, Iwona Buczyńska, Jolanta Białkowska – none declared.

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