Utilization and Cost of Peginterferon Plus Ribavirin Combination Therapy in the Management of Chronic Hepatitis C Virus in Europe

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BACKGROUND

- Hepatitis C virus (HCV) is a global public health problem, affecting approximately 3% of the world's population.[1]
- Nearly three-quarters of all HCV cases progress to chronic infections.
- Commonly used treatments for chronic HCV include peginterferon alfa-2a (PEG2A) or peginterferon alfa-2b (PEG2B) combination therapies with ribavirin.
- Prescribing patterns and costs of treatments in real-world clinical practice in Western Europe have not been widely examined.

OBJECTIVE

To document real-world utilization patterns and costs of PEG2A plus ribavirin (PEG2A+R) and PEG2B plus ribavirin (PEG2B+R) combination therapy in the management of chronic HCV in Western Europe.

METHODS

Study Design

Retrospective abstraction of patient chart data

Data Source

- Deidentified patient charts abstracted by physicians in five European countries: United Kingdom (UK), France, Germany, Italy, and Spain.
- Physicians recruited by Kantar Health (formerly TNS Healthcare) from their Global Access Panel, one of the largest online physician panels in the world, with a membership of over 70,000 physicians from around the world.
- A chart review approach provided several advantages:
  - Detailed demographic and prescription use data not easily available in existing databases in Europe.
  - Rich clinical information (pathology reports, genotyping, and other laboratory results) that cannot be obtained from other data sources in Europe.
  - All outcomes assessed in a standardized manner across the five countries of interest.
- Cost information not available in patient charts; therefore, country-specific treatment costs estimated at patient level using combination of drug prices (provided by Novartis), treatment duration, and (for patients on PEG2B+R) body weight.

Inclusion Criteria

Physicians

- At least 15 chronic HCV patients seen in the practice annually
- A practice period of 2 to 35 years

Patients

- Age ≥ 18 years
- Diagnosis of chronic HCV within the past 5 years
- No evidence of hepatitis B or HIV/AIDS
- No treatment as part of randomized clinical trial
- Presence of HCV genotype information
- Treatment with PEG2A+R or PEG2B+R
- ≥ 1 year follow-up post-treatment initiation
- Presence of HCV RNA laboratory result at time of treatment initiation (± 30 days)

Outcome Measures

All outcomes assessed over entire duration of treatment and stratified by country.

- Baseline physician and patient characteristics
- Prescription drug utilization patterns for PEG2A+R and PEG2B+R:
  - Number and percentage of patients initiating each regimen
  - Reason for treatment initiation
  - Length of time between diagnosis and treatment initiation
  - Number of prescriptions
  - Duration of treatment (total number of days between treatment initiation and treatment completion or discontinuation)
  - Reason for discontinuation of treatment
  - Treatment compliance
  - Sustained viral response
  - Cost of prescriptions

Statistical Analyses

- Analyses carried out using SAS® (Version 9) statistical software
- Descriptive statistics:
  - Mean values, standard deviations (SDs), medians, and ranges of continuous variables
  - Frequency distributions for categorical variables

RESULTS

Physician Characteristics

- 240 physicians (~ 48 in each country) recruited to abstract patient charts.
- Physicians were in practice for 15 years on average.
- Physicians saw 142 HCV patients annually, of whom approximately 76 were treated with peginterferon and ribavirin combinations.
- Hepatology, gastroenterology, and internal medicine were the predominant physician specialties observed, representing 22%, 30%, and 25%, respectively, of all physicians recruited.

Patient Characteristics (Table 1)

- A total of 804 patients (~160 per country) identified.
- Approximately 65% were male with mean age of 46 years.
- Combined, genotypes 1 and 4 represented 53.4% of the total study sample; genotypes 2 and 3 were a combined 46.6% of the study sample.
- Nearly 48% of patients were married (ranging from 30% in the UK to 67% in Italy).
- 35% of all patients had at least a secondary school education, and 15% had a college degree or higher education.
- Over 50% of patients in France were past intravenous drug users.

Table 1. Characteristics of the Study Sample

Characteristic	UK	Germany	France	Italy	Spain	Total (All Countries)
Number of patients	148	172	174	164	146	804
Gender						
Male	93 (62.8%)	108 (62.8%)	125 (71.8%)	99 (60.4%)	98 (67.1%)	523 (65.0%)
Female	55 (37.2%)	64 (37.2%)	49 (28.2%)	65 (39.6%)	48 (32.9%)	281 (35.0%)
Age						
Mean (SD)	42.2 (10.8)	44.4 (10.4)	46.4 (11.0)	49.2 (11.7)	44.4 (8.7)	45.6 (10.8)
Median	42	45	46	49	43	45
Range	19, 71	21, 71	21, 77	22, 74	24, 67	19, 77
Nonmissing Obs (n)	119	168	174	162	136	759
Age category						
< 18	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
18-24	5 (3.4%)	3 (1.7%)	5 (2.9%)	1 (0.6%)	1 (0.7%)	15 (1.9%)
25-34	27 (18.4%)	30 (17.4%)	18 (10.3%)	19 (11.6%)	17 (11.6%)	111 (13.8%)
35-44	40 (27.2%)	45 (26.2%)	56 (32.2%)	37 (22.6%)	59 (40.4%)	237 (29.5%)
45-54	32 (21.8%)	65 (37.8%)	58 (33.3%)	53 (32.3%)	40 (27.4%)	248 (30.9%)
55-64	13 (8.8%)	22 (12.8%)	23 (13.2%)	38 (23.2%)	18 (12.3%)	114 (14.2%)
65+	2 (1.4%)	3 (1.7%)	14 (8.0%)	14 (8.5%)	1 (0.7%)	34 (4.2%)
Unknown	28 (19.0%)	4 (2.3%)	0 (0.0%)	2 (1.2%)	10 (6.8%)	44 (5.5%)
Genotype						
Genotype 1,4	68 (46%)	86 (50%)	97 (55.7%)	86 (52.4%)	92 (63.0%)	429 (53.4%)
Genotype 2,3	80 (54%)	86 (50%)	77 (44.3%)	78 (47.6%)	54 (37.0%)	375 (46.6%)
Ethnic origin						
White	103 (69.6%)	159 (92.4%)	0 (0.0%)	161 (98.2%)	135 (92.5%)	558 (69.4%)
African origin	21 (14.2%)	3 (1.7%)	0 (0.0%)	3 (1.8%)	4 (2.7%)	31 (3.9%)
Asian	2 (1.4%)	2 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	5 (0.6%)
Other	17 (11.5%)	6 (3.5%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	24 (3.0%)
Not asked	5 (3.4%)	2 (1.2%)	174 (100%)	0 (0.0%)	5 (3.4%)	186 (23.1%)
Marital status						
Married	44 (29.7%)	68 (39.5%)	82 (47.1%)	109 (66.5%)	79 (54.1%)	382 (47.5%)
Widowed	7 (4.7%)	3 (1.7%)	8 (4.6%)	3 (1.8%)	2 (1.4%)	23 (2.9%)
Divorced/ separated	30 (20.3%)	31 (18.0%)	32 (18.4%)	9 (5.5%)	21 (14.4%)	123 (15.3%)
Single	40 (27.0%)	49 (28.5%)	46 (26.4%)	33 (20.1%)	24 (16.4%)	192 (23.9%)
Other	0 (0.0%)	2 (1.2%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	3 (0.4%)
Unknown	27 (18.2%)	19 (11.0%)	5 (2.9%)	10 (6.1%)	20 (13.7%)	81 (10.1%)
Educational attainment						
Primary	18 (12.2%)	35 (20.3%)	53 (30.5%)	40 (24.4%)	64 (43.8%)	210 (26.1%)
Secondary	45 (30.4%)	83 (48.3%)	42 (24.1%)	73 (44.5%)	38 (26.0%)	281 (35.0%)
College or higher	22 (14.9%)	21 (12.2%)	54 (31.0%)	25 (15.2%)	15 (10.3%)	137 (17.0%)
Unknown	63 (42.6%)	33 (19.2%)	25 (14.4%)	26 (15.9%)	29 (19.9%)	176 (21.9%)
Intravenous drug use						
Current user	9 (6.1%)	11 (6.4%)	0 (0.0%)	0 (0.0%)	5 (3.4%)	25 (3.1%)
Past user	71 (48.0%)	62 (36.0%)	88 (50.6%)	44 (26.8%)	53 (36.3%)	318 (39.6%)
Never used	46 (31.1%)	74 (43.0%)	68 (39.1%)	106 (64.6%)	72 (49.3%)	366 (45.5%)
Unknown	22 (14.9%)	25 (14.5%)	18 (10.3%)	14 (8.5%)	16 (11.0%)	95 (11.8%)

Treatment Patterns (Tables 2, 3a, 3b)

- PEG2A+R initiated by 69% of patients, while PEG2B+R initiated by 31% of patients.
- Over 70% of patients on PEG2A received 180 mcg/week of PEG2A + 800 or 1,000 mg/day of ribavirin, with almost equal distribution between the groups; use of 1,200 mg ribavirin was less common.
- With the exception of Italy, the most common dose of PEG2B was 1.5 mcg/kg/ week of PEG2B + 1,000 mg/day of ribavirin.
- Mean therapy duration for both PEG2A+R and PEG2B+R was 35 weeks with little variation by country.

Table 2. Distribution of Peginterferon and Ribavirin Combination Regimens

	UK	Germany	France	Italy	Spain	Total (All Countries)
Number of patients						
PEG2A+R	122	121	126	85	97	551
PEG2B+R	26	51	48	79	49	253
PEG2A+R regimens						
180 mcg/week PEG2A + 800 mg/day ribavirin	52 (42.6%)	49 (40.5%)	38 (30.2%)	36 (42.4%)	24 (24.7%)	199 (36.1%)
180 mcg/week PEG2A + 1,000 mg/day ribavirin	32 (26.2%)	37 (30.6%)	49 (38.9%)	34 (40.0%)	38 (39.2%)	190 (34.5%)
180 mcg/week PEG2A + 1,200 mg/day ribavirin	29 (23.8%)	23 (19.0%)	29 (23.0%)	14 (16.5%)	28 (28.9%)	123 (22.3%)
Other	1 (0.8%)	3 (2.5%)	2 (1.6%)	0 (0.0%)	0 (0.0%)	6 (1.1%)
Unknown	8 (6.6%)	9 (7.4%)	8 (6.3%)	1 (1.2%)	7 (7.2%)	33 (6.0%)
PEG2B+R regimens						
1.5 mcg/kg/week PEG2B + 800 mg/day ribavirin	3 (11.5%)	14 (27.5%)	12 (25.0%)	33 (41.8%)	19 (38.8%)	81 (32.0%)
1.5 mcg/kg/week PEG2B + 1,000 mg/day ribavirin	13 (50.0%)	25 (49.0%)	20 (41.7%)	26 (32.9%)	23 (46.9%)	107 (42.3%)
1.5 mcg/kg/week PEG2B + 1,200 mg/day ribavirin	10 (38.5%)	10 (19.6%)	12 (25.0%)	19 (24.1%)	7 (14.3%)	58 (22.9%)
Other	0 (0.0%)	2 (3.9%)	4 (8.3%)	1 (1.3%)	0 (0.0%)	7 (2.8%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3a. Treatment Duration and Reasons for Discontinuation by Country and Treatment Regimen

	UK		Germany		France		Italy		Spain		Total (All Countries)	
	PEG2A+R	PEG2B+R	PEG2A+R	PEG2B+R	PEG2A+R	PEG2B+R	PEG2A+R	PEG2B+R	PEG2A+R	PEG2B+R	PEG2A+R	PEG2B+R
Number of patients	122	26	121	51	126	48	85	79	97	49	551	253
Duration (weeks) of therapy												
Mean (SD)	33.9 (17.8)	27.7 (14.0)	40.1 (20.5)	35.8 (18.8)	38.2 (19.8)	35.3 (14.1)	36.5 (14.9)	35.2 (13.6)	35.0 (15.0)	37.4 (13.8)	37.0 (18.2)	35.1 (15.0)
Median	28	24	47	31	42	28	35	27	32	46	38	28
Min	1	4	5	1	0	12	2	8	3	12	0	1
Max	104	54	168	80	158	79	71	57	75	57	168	80
Distribution												
< 4 weeks	4 (3.3%)	1 (3.8%)	0 (0.0%)	1 (2.0%)	1 (0.8%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	2 (2.1%)	0 (0.0%)	8 (1.5%)	2 (0.8%)
4.1-12 weeks	11 (9.0%)	2 (7.7%)	3 (2.5%)	4 (7.8%)	7 (5.6%)	1 (2.1%)	3 (3.5%)	1 (1.3%)	3 (3.1%)	2 (4.1%)	27 (4.9%)	10 (4.0%)
12.1-16 weeks	3 (2.5%)	0 (0.0%)	3 (2.5%)	2 (3.9%)	1 (0.8%)	0 (0.0%)	2 (2.4%)	2 (2.5%)	3 (3.1%)	1 (2.0%)	12 (2.2%)	5 (2.0%)
16.1-24 weeks	25 (20.5%)	11 (42.3%)	28 (23.1%)	9 (17.6%)	40 (31.7%)	16 (33.3%)	11 (12.9%)	21 (26.6%)	25 (25.8%)	11 (22.4%)	129 (23.4%)	68 (26.9%)
24.1-40 weeks	10 (8.2%)	2 (7.7%)	15 (12.4%)	9 (17.6%)	13 (10.3%)	8 (16.7%)	24 (28.2%)	20 (25.3%)	15 (15.5%)	5 (10.2%)	77 (14.0%)	44 (17.4%)
40.1- 48 weeks	25 (20.5%)	3 (11.5%)	35 (28.9%)	10 (19.6%)	36 (28.6%)	13 (27.1%)	19 (22.4%)	16 (20.3%)	27 (27.8%)	17 (34.7%)	142 (25.8%)	59 (23.3%)
> 48 weeks	19 (15.6%)	2 (7.7%)	26 (21.5%)	13 (25.5%)	27 (21.4%)	5 (10.4%)	21 (24.7%)	17 (21.5%)	12 (12.4%)	8 (16.3%)	105 (19.1%)	45 (17.8%)
Unknown	25 (20.5%)	5 (19.2%)	11 (9.1%)	3 (5.9%)	1 (0.8%)	5 (10.4%)	4 (4.7%)	2 (2.5%)	10 (10.3%)	5 (10.2%)	51 (9.3%)	20 (7.9%)
Reason for treatment discontinuation												
Patient completed planned treatment regimen	76 (62.3%)	16 (61.5%)	101 (83.5%)	43 (84.3%)	95 (75.4%)	34 (70.8%)	72 (84.7%)	64 (81.0%)	60 (61.9%)	37 (75.5%)	404 (73.3%)	194 (76.7%)
Lack of viral response	16 (13.1%)	3 (11.5%)	6 (5.0%)	5 (9.8%)	12 (9.5%)	7 (14.6%)	7 (8.2%)	7 (8.9%)	12 (12.4%)	4 (8.2%)	53 (9.6%)	26 (10.3%)
Patient request	5 (4.1%)	5 (19.2%)	1 (0.8%)	2 (3.9%)	3 (2.4%)	0 (0.0%)	5 (5.9%)	3 (3.8%)	6 (8.2%)	0 (0.0%)	22 (4.0%)	10 (4.0%)
Adverse event(s), including lab abnormalities	9 (7.4%)	1 (3.8%)	6 (5.0%)	1 (2.0%)	5 (4.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	6 (6.2%)	4 (8.2%)	26 (4.7%)	7 (2.8%)
Noncompliance	3 (2.5%)	0 (0.0%)	3 (2.5%)	0 (0.0%)	1 (0.8%)	2 (4.2%)	0 (0.0%)	0 (0.0%)	2 (2.1%)	1 (2.0%)	9 (1.6%)	3 (1.2%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (6.3%)	4 (8.3%)	1 (1.2%)	2 (2.5%)	4 (4.1%)	0 (0.0%)	15 (2.7%)	6 (2.4%)
Multiple reasons	11 (9.0%)	1 (3.8%)	4 (3.3%)	0 (0.0%)	2 (1.6%)	0 (0.0%)	0 (0.0%)	3 (3.8%)	5 (5.2%)	3 (6.1%)	22 (4.0%)	7 (2.8%)

- By genotype, mean therapy duration for genotypes 1 and 4 was approximately 42 weeks (regardless of therapy regimen), compared with only 31 weeks and 27 weeks for genotypes 2 and 3 in PEG2A+A and PEG2B+R patients, respectively.
- As expected, the most commonly observed cutoffs for treatment duration were 24 weeks (the predominant cutoff seen in genotypes 2 and 3) and 48 weeks (the predominant cutoff in genotypes 1 and 4), but a nontrivial proportion of patients in all countries (18.5% overall) received therapy for more than 48 weeks.
- Completion of planned regimen was by far the most common (~75% of patients) reason for therapy cessation.

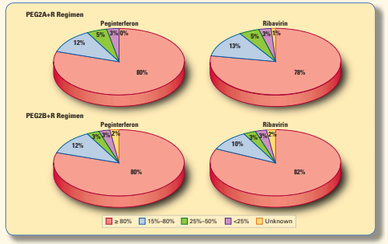
Table 3b. Treatment Duration, by Genotype and Treatment Regimen

	Genotype 1/4		Genotype 2/3	
	PEG2A+R	PEG2B+R	PEG2A+R	PEG2B+R
Number of patients	303	126	248	127
Duration (weeks) of therapy				
Mean (SD)	41.8 (17.7)	42.9 (14.6)	30.7 (16.9)	27.2 (10.9)
Distribution				
< 4 weeks	6 (1.9%)	8 (6.4%)	2 (0.8%)	2 (1.6%)
4.1-12 weeks	16 (5.3%)	3 (2.4%)	11 (4.4%)	2 (1.6%)
12.1-16 weeks	8 (2.6%)	10 (7.9%)	4 (1.6%)	2 (1.6%)
16.1-24 weeks	31 (10.2%)	8 (6.4%)	98 (39.5%)	58 (45.7%)
24.1-40 weeks	28 (9.2%)	49 (38.9%)	49 (19.8%)	36 (28.4%)
40.1-48 weeks	117 (38.6%)	39 (31.0%)	25 (10.1%)	10 (7.9%)
> 48 weeks	77 (25.4%)	0 (0.0%)	28 (11.3%)	6 (4.7%)
Unknown	20 (6.6%)	9 (7.1%)	31 (12.5%)	11 (8.7%)

Treatment Compliance (Figure 1)

- Physician reported compliance was documented separately for peginterferons and ribavirin.
- High degree of compliance (took medication ≥ 80% of the time) reported for 80% of patients on average.
- No significant difference in compliance rates between peginterferons and ribavirin.

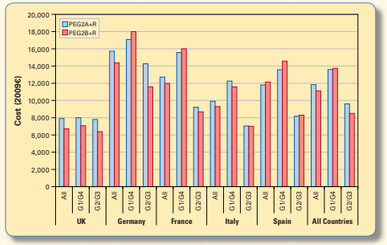
Figure 1. Compliance Rates



Treatment Costs (Figure 2)

- Mean weekly treatment costs for PEG2A+R ranged from €212 to €429 depending on the ribavirin dose.
- Mean weekly treatment costs for PEG2B+R ranged from €203 to €459 depending on the ribavirin dose and body weight.
- Germany had the highest drug costs while UK had the lowest.
- Mean total regimen costs were estimated at €11,827 per patient for PEG2A+R (ranging from €7,904 in the UK to €15,724 in Germany) and €11,109 per patient for PEG2B+R (ranging from €6,709 in the UK to €14,376 in Germany).
- In general, total regimen costs were substantially higher for patients with genotypes 1 and 4 (€13,591 and €13,736 for PEG2A and PEG2B, respectively) compared with genotypes 2 and 3 (€9,601 and €8,504, respectively).

Figure 2. Cost of Treatment With Peginterferon and Ribavirin Combination Regimens



G1, G2, G3, and G4 = genotypes 1, 2, 3, and 4, respectively. Genotypes 1 and 4 and genotypes 2 and 3 are grouped together.

CONCLUSIONS

- Peginterferon-based regimens, although a mainstay of chronic HCV management, are costly, particularly for patients with genotypes 1 and 4.
- Public health systems bearing the high economic burden of chronic HCV treatment should be mindful of these costs when considering formulary access for alternative treatments.

ACKNOWLEDGMENTS

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