https://doi.org/10.22416/1382-4376-2018-28-6-15-26

Real-Life Experiences with Telaprevir in the Treatment of Chronic Genotype 1 Hepatitis C — The TEPS Study

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As one of the first Direct Acting Antivirals (DAA), the protease inhibitor Telaprevir (TVR) was available in the European Union from 9/2011 until 9/2016 as a new treatment option for chronic Hepatitis C.

Aim. To assess the implementation of therapy stopping rules or shortening of the treatment and their impact on sustained virological response (SVR), as well as the safety and efficacy of the TVR-based therapy during routine daily treatment of patients in Germany.

Materials and Methods. 802 patients were assessed (272 treatment naïve, 520 pre-treated) in the non-interventional, multi-center study.

Results. 56.6 % of the patients achieved SVR. SVR rate was higher in patients with relapse after previous treatment (68.0 %) than in patients with a previous null-response (31.1 %) and in previously untreated patients (58.1 %). Stopping rule conditions were fulfilled by 3.2 % of patients and it was implemented in 65.4 % of these. 34.3 % of the patients fulfilled the conditions for a therapy shortening. This rule was adhered to in 48.4 % of these, in 34.5 % it was not adhered to. Thus recommendations were not always being followed. Therapy shortening was considered more frequently in previously untreated (54.8 %) than for previously treated patients (24.2 %). Stopping rule application but not shortened treatment reduced therapy costs.

Conclusion. The TVR-based therapy represented a breakthrough at that time. Further DAAs have been added as therapeutic options since, increasing the complexity of treatment choice and correct implementation. They represent both an opportunity and a challenge for all those involved.

Keywords: Hepatitis C, Direct Acting Antivirals (DAA), stopping rule, shortening of treatment, Sustained virological response (SVR)

Conflict of interest: T. Berg reports research grants from Abbvie, Roche, BMS, Gilead, Novartis, Merck/MSD, Intercept, Janssen, Novartis, Sequana Medical, und Pfizer and financial compensation for talks/advisory boards from Abbvie, Alexion, Bayer, Boehringer Ingelheim, BMS, Gilead, GSK, Intercept, Janssen, MSD/Merck, Merz, Novartis, Sequana Medical and Roche. P. Buggisch reports financial compensation for speakers bureaus or advisory boards from AbbVie, BMS, Janssen, Gilead, MSD, Roche. D. Hueppe has received financial compensation for talks and advisory boards from Abbvie, BMS, Boehringer-Ingelheim, Echosens, Falk, Gilead Sciences, Janssen-Cilag, MSD Sharp&Dohme/Merck, Roche Pharma. S. Maus has received financial compensation for talks from AbbVie, Gilead, Janssen and MSD and for advisory boards from AbbVie and MSD. H. Wedemeyer has received financial support for research from AbbVie, Abbot, Gilead and BMS as well as financial compensation for talks/advisory boards from Abbot, AbbVie, BMS, Falk Foundation, Gilead, IST, Janssen, Schering-Plough, Novartis and Roche Diagnostics. G. Teuber has received financial support for clinical studies from Janssen and MSD, and reports financial compensation for talks and/or advisory boards (some including travel costs) from Janssen, Roche, Gilead, BMS, MSD, and AbbVie. T. Lutz has received research grants from AbbVie, BMS, Gilead Sciences, Glaxo-Smith-Kline / ViiV, Janssen-Cilag, Merck, Sharp & Dohme and Tibotec Janssen. K. Stein reports financial compensation for an advisory board from Janssen. S. Wegner is employee of Janssen. H. Hinrichsen reports financial compensation for talks and advisory boards from Janssen.

For citation: Berg T., Buggisch P., Hueppe D., Mauss S., Wedemeyer H., Teuber G., Lutz T., Stein K., Wegner S., Hinrichsen H. Real-Life Experiences with Telaprevir in the Treatment of Chronic Genotype 1 Hepatitis C — The TEPS Study. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2018;28(6):15–26. https://doi.org/10.22416/1382-4376-2018-28-6-15-26

Практический опыт применения Телапревира при лечении хронического гепатита С генотипа 1: Исследование TEPs

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Ингибитор протеазы Телапревир (ТПВ) является одним из первых противовирусных препаратов прямого действия (ППВП) и применялся в странах Евросоюза при лечении хронического гепатита С в качестве нового метода с сентября 2011 года по сентябрь 2016 года.

Цель: Оценить применение правил остановки (прекращения) или сокращения периода терапии и их влияние на устойчивый вирусологический ответ (УВО), а также безопасность и эффективность противовирусной терапии на основе ТПВ при рутинном применении в Германии.

Материалы и методы. В неинтервенционном мультицентровом исследовании участвовали 802 пациента (272 пациента, ранее не получавшие, и 520 пациентов, ранее получавшие противовирусные препараты).

Результаты. Устойчивый вирусологический ответ (УВО) был достигнут у 56,6 % пациентов. Доля пациентов с УВО среди пациентов с рецидивом после предыдущего лечения была выше (68,0 %), чем у пациентов с предыдущим нулевым ответом (31,1 %) и у пациентов, ранее не получавших противовирусные препараты (58,1 %). Критериям прекращения терапии соответствовали 3,2 % пациентов, из них у 65,4 % лечение было остановлено. Критериям сокращения терапии соответствовали 34,3 % пациентов. Это правило было применено в отношении 48,4 % из них, у 34,5 % оно не соблюдалось. Таким образом, не всегда соблюдались рекомендации по прекращению или сокращению терапии. Чаще терапию сокращали в группе пациентов, ранее не получавших лечения (54,8%), чем в группе пациентов, получавших противовирусную терапию в анамнезе (24,2%). Именно применение правил прекращения терапии, а не сокращение ее продолжительности, позволило снизить затраты на лечение.

Заключение. Терапия на основе ТПВ в свое время стала прорывом в лечении гепатита С. Позже были предложены новые варианты ППВП для терапии, что усложнило выбор и точность применения препаратов. ППВП привнесли одновременно как новые возможности, так и новые сложности.

Ключевые слова: гепатит С, противовирусные препараты прямого действия (ППВП), правила прекращения лечения, сокращение лечения, устойчивый вирусологический ответ (УВО)

Конфликт интересов: Т. Берг сообщает о получении грантов в следующих компаниях: Abbvie, Roche, BMS, Gilead, Novartis, Merck/MSD, Intercept, Janssen, Novartis, Sequana Medical и Pfizer, а также о получении финансового вознаграждения за прочитанные лекции в компаниях Abbvie, Alexion, Bayer, Boehringer Ingelheim, BMS, Gilead, GSK, Intercept, Janssen, MSD/Merck, Merz, Novartis, Sequana Medical and Roche. П. Бугеш сообщает о финансовом вознаграждении за прочитанные лекции и проведенные консультации в компаниях AbbVie, BMS, Janssen, Gilead, MSD, Roche. Д. Хюппе получал финансовое вознаграждение за выступления с докладом и консультационные услуги в следующих компаниях: Abbvie, BMS, Boehringer-Ingelheim, Echosens, Falk, Gilead Sciences, Janssen-Cilag, MSD Sharp&Dohme/Merck, Roche Pharma. Ш. Маусс получал финансовое вознаграждение за выступления с докладом в компаниях AbbVie, Gilead, Janssen и MSD, а также за оказанные консультационные услуги в AbbVie и MSD. Х. Ведемейер получал финансовую поддержку на проведение исследований в компаниях AbbVie, Abbot, Gilead и BMS, а также финансовое вознаграждение за выступление с докладом / консультационные услуги в Abbot, AbbVie, BMS, Falk Foundation, Gilead, IST, Janssen, Schering-Plough, Novartis и Roche Diagnostics. Г. Тойбер получил финансовую поддержку на проведение клинических исследований в Janssen и MSD, а также финансовое вознаграждение за выступление с докладом / консультационные услуги (включая транспортные расходы) в компаниях Janssen, Roche, Gilead, BMS, MSD и AbbVie.

Т. Лутц получал исследовательские гранты в компаниях AbbVie, BMS, Gilead Sciences, Glaxo-Smith-Kline / ViiV, Janssen-Cilag, Merck, Sharp & Dohme и Tibotec Janssen. К. Штайн сообщает о финансовом вознаграждении за консультационные услуги в компании Janssen. С. Вегнер является сотрудником в компании Janssen. Х. Хинрихсен сообщает о получении финансового вознаграждения за выступления с докладом и консультационные услуги в компании Janssen.

Для цитирования: Для цитирования: Берг Т., Бугеш П., Хюппе Д., Маусс Ш., Ведемейер Х., Тойбер Г., Лутц Т., Штайн К., Вегнер С., Хинрихсен Х. Практический опыт применения Телапревира при лечении хронического гепатита С генотипа 1: Исследование TEPs. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2018;28(6):15–26. https://doi.org/10.22416/1382-4376-2018-28-6-15-26

Introduction

According to the World Health Organization approximately 170 million patients worldwide [1] are chronically infected with hepatitis C virus (HCV). The predominant hepatitis C genotype in Germany is Genotype 1, accounting for approximately 60 % of infections [2]. Early HCV infections are often asymptomatic and thus frequently remain undiscovered. Roughly 80 % of acute HCV infections become chronic, meaning that the HCV-RNA can be detected over more than 6 months. During the chronic HCV infection liver fibrosis or cirrhosis often depicts the basis for the development of a hepatocellular carcinoma (HCC).

Due to the associated increased morbidity and mortality, the chronic hepatitis C requires treatment. The risk of HCC occurrence decreased through the elimination of HCV, the progression of the liver disease, as well as prevention of possible extrahepatic manifestations [3].

For a period of more than 10 years the standard treatment for HCV genotype 1-infected patients in Germany was the dual treatment with pegylated interferon alpha and ribavirin [3] with SVR rate of 40–50 % [4].

In 2011, one of the first Direct Acting Antivirals (DAAs), the protease inhibitor Telaprevir (TVR) became available as a new treatment option for chronic HCV infection. Compared to the dual treatment with pegylated interferon alpha plus ribavirin, the TVR-based triple therapy was characterized by significantly improved SVR rate and the possibility for a shortened therapy duration under certain circumstances [5]. Also for those patients, who have not achieved SVR with a dual treatment (relaps, partial responder, null-responder), significantly higher cure rates could be achieved using TVR-based triple therapy [6].

Roughly 50–60 % of the TVR treated patients achieved an anticipated extended rapid virological response (eRVR; HCV RNA not detectable at week 4 and 12 of the triple therapy) and thereby qualified for a reduced therapy duration (24 weeks) with an expected SVR rate of 90–95 % [7]. Patients without an eRVR can nevertheless still expect SVR rates of 64 %, however, with a 48-week therapy duration [7, 8].

The treatment experiences derived from the clinical studies up to now have resulted in a clear therapy concept with stringent rules [9]. The TVR treatment at that time was to be started in combination with peg-interferon alpha and ribavirin and discontinued after maximally 12 weeks.

As with every new therapy concept, the handling of interactions and adverse effects during routine treatment represents a new challenge with often unknown problems, the results from non-interventional studies in real-world settings can help to overcome those problems by careful monitoring, documentation and assessment of daily experience. The goal of this monitored, non-interventional study was to evaluate the implementation of the stopping rules and the rules for shortening of the therapy, as well as the safety and efficacy of the telaprevir-based therapy during the daily treatment routine in Germany. This is relevant to provide a basis for the comparison between the advent of new DAAs based therapies and today's therapy options with respect to costs, efficacy and safety and the impact of meaningful use of resources. This includes the implementation of product characteristics into the label and results from health services research about a medication that bridged and thereby facilitated a fundamental change in how to treat chronic hepatitis C patients.

Methods

In this prospective, non-interventional, multicentre observational study, the telaprevir-based triple treatment was investigated with both treatment naïve patients and previously treated patients with a chronic Genotype 1 HCV infection under real-world conditions in Germany. The patients were treated with a combination of telaprevir, ribavirin and peg-interferon. The observation period covered the total treatment period plus a follow-up of 24 weeks after the end of the treatment.

The data were documented non-interventionally, i.e. there was no study-specific prescribed treatment regimen. The decisions on inclusion of a patient, as well as on the choice of treatment were at the discretion of the treating physicians and were consistent with the normal treatment practice at the study centre. All study data were entered into an eCRF by the study centres and independently monitored.

Hepatologists, infectiologists, general practitioners with hepatological specialization and specialized

centres participated in the study to representatively reflect the spectrum of everyday routine therapy practice in Germany.

Two rules were investigated to study the adaptation of physicians to new treatment regimens. The rules in relation to the total duration of the treatment were oriented towards the previous HCV treatment and required HCV-RNA PCR measurements after 4 and 12 weeks and were defined as follows:

- **Rule on the shortening of the therapy time** (response-guided therapy, RGT):
  - For patients with undetectable HCV-RNA at week 4 and 12 (eRVR), the treatment with TVR was discontinued after 12 weeks and the patients received peg-interferon alpha and ribavirin alone for a further 12 weeks resulting in a total treatment duration of 24 weeks.
  - Patients with detectable HCV-RNA in either week 4 and/or week 12 the treatment with TVR was discontinued after 12 weeks and the patients received a treatment with peg-interferon alpha and ribavirin alone for a further 36 weeks resulting in a total treatment duration of 48 weeks.
  - For all patients with liver cirrhosis the treatment with TVR was discontinued after 12 weeks, and even if HCV-RNA was not detectable in the weeks 4 and 12, it was recommended to treat the patients with peg-interferon alpha and Ribavirin alone for a further 36 weeks resulting in a total treatment duration of 48 weeks.
  - For pre-treated adults with previous partial (partial responder) or lacking response (null responder) the treatment with TVR in combination with peg-interferon alpha und ribavirin was to be started and continued over 12 weeks, followed by peg-interferon alpha and ribavirin alone (without TVR) for a further 36 weeks resulting in a total treatment duration of 48 weeks.
- **Stopping Rule.** As with an insufficient virological response a SVR is very improbable, the following approach was recommended:
  - For patients with a HCV-RNA >1000 IE/ml at week 4 of treatment it was recommended to permanently discontinue the treatment with TVR, peg-interferon alpha and ribavirin.
  - For patients with a HCV-RNA >1000 IE/ml at week 12 of treatment TVR medication was completed and it was recommended to also permanently discontinue the treatment with Peg Interferon alpha and Ribavirin.

The response to treatment was defined through undetectable HCV-RNA levels over the course of the observation. The usual time intervals to be documented were 4, 12, 24 and 48 weeks after start of the TVR-based therapy, as well as 24 weeks following the end of treatment, if feasible.

The selection of patients was performed according to the following selection criteria:

- Men and women of at least 18 years of age,
- Diagnosed with chronic hepatitis C of Genotype 1,
- Therapy with TVR-based treatment regime,
- Signed patient information and consent forms were available before the start of the documentation.

Patients who participated in a clinical study during the observation period were excluded from the protocol. Some patient data from this study were also analyzed in another real-world cohort in Germany [10].

Predictive factors for the treatment success were exploratively assessed by means of a logistic regression analysis. Thereby the outcome variable SVR24 was initially tested univariately against all individual factors. In the final model, only the effects with a p-value of ≤ 0.1 were included.

The final model consisted of a multiple logistic regression analysis with a stepwise parameter selection. The null hypothesis for each of the tested explanatory variables was that in the final model (with a pre-set level for all included explanatory variables) the variable has no effect on the SVR24. The alternative hypothesis was that the effect was unequal to zero. Here, it was assumed that effects with a p-value of ≤ 0.1 have a significant influence on therapy success.

Results

Data from 802 patients, who fulfilled all inclusion criteria and received at least one dose of telaprevir-based therapy, were analyzed (full analysis set). Of these 272 patients were therapy naïve, 520 were previously treated and for 10 patients previous treatment was unknown.

The mean age of the patients was 49.3 ± 10.7 years. With a mean age of 51.3 years previously treated patients were somewhat older than untreated patients with a mean age of 45.6 years (Table 1). 62.6 % of the patients were male, 37.4 % were female. The mean body-mass index (BMI) was 26.3 kg/m^2.

Therapy

The mean therapy duration was 11.4 ± 2.9 weeks for TVR, 31.4 ± 14.8 weeks for ribavirin and 30.9 ± 14.5 weeks for the peg-interferon. 97.9 % of the patients reported compliance to the TVR intake frequency of every eight hours.

93.1 % of all patients received a concomitant medication during the observation period, in the majority to reduce the therapy-induced adverse reactions. 4.2 % of the patients required additional HCV medication.

30.2 % of the patients discontinued the TVR-based therapy prematurely, this occurred more frequently in pre-treated patients (34.0 %) than in untreated patients (23.2 %). The main reasons for the premature discontinuation were poor efficacy (36.8 %), adverse reactions (29.3 %) and patient request (15.3 %).

Description of baseline parameters

The mean duration of the HCV infection was 9.4 years, 6.7 years for previously untreated patients and 10.9 years for previously treated patients.

The HCV subtype was 1a for 36.9 %, and 1b for 50.2 %. A 1a/1b co-infection was present in 0.6 % of the patients (12.2 % unknown). 30.7 % of the patients had a fibrosis at baseline, split into 23.9 % of the previously untreated and 34.8 % of the previously treated patients. According to the information provided by the physician, liver cirrhosis was present in 14.8 % of the patients before start of therapy (with 8.5 % of the previously untreated and with 18.3 % of the previously treated patients).

An HIV co-infection was present in 8.7 % of patients at baseline, 0.8 % of patients had a hepatitis B virus co-infection.

In 50.5 % of the patients the transmission pathway of the HCV infection was known. Among the known transmission pathways, the most frequent were i.v. drug use and receiving blood-based products (31.6 % and 9.6 % respectively in previously untreated patients, 18.5 % and 16.7 % respectively in previously treated patients). Risk factors for a progression of the HCV disease were found in more than half of all patients; the most frequent were nicotine consumption (24.3 %) and significantly increased transaminases (20.5 %).

520 of the 802 patients (64.8 %) were pre-treated, of these 88.9 % received a combination therapy consisting of interferon and ribavirin, 2.9 % an interferon mono-therapy and 8.3 % a different type of therapy. Pre-treatment had resulted in 38.5 % of the patients in a relapse and in 38.3 % in a non-response.

IL28B genetics was documented in 59.6 % of the patients. The determined IL28B genotypes were CC in 17.2 %, CT in 62.1 % and TT in 20.7 %.

Concomitant diseases were specified in 65.7 % of the patients. The most frequent concomitant diseases were psychiatric (16.6 %) and endocrine diseases (15.8 %). The most important baseline parameters are represented in table 1.

Primary endpoint

Stopping Rule

Criteria for application of the stopping rule, i.e. a detectable HCV-RNA (>1000 IE/ml) at week 4 and/or week 12, was present in 26 of the 802 patients (3.2 %). The stopping rule was correctly applied in 17 (65.4 %) of these patients (two-sided 95 %-confidence interval [44.3 %; 82.8 %]). In 6 patients (23.1 %) the rule was falsely not applied, and for 3 of the eligible patients (11.5 %) the adherence to the rule remained unknown (fig. 1). For the 6 patients, whose treatment was continued the mean treatment duration was 18.6 weeks with a maximum of 34.6 weeks. One of the 6 patients (16.7 %) who was treated further despite applicability of the stopping rule achieved an SVR 24 weeks after the end of treatment.

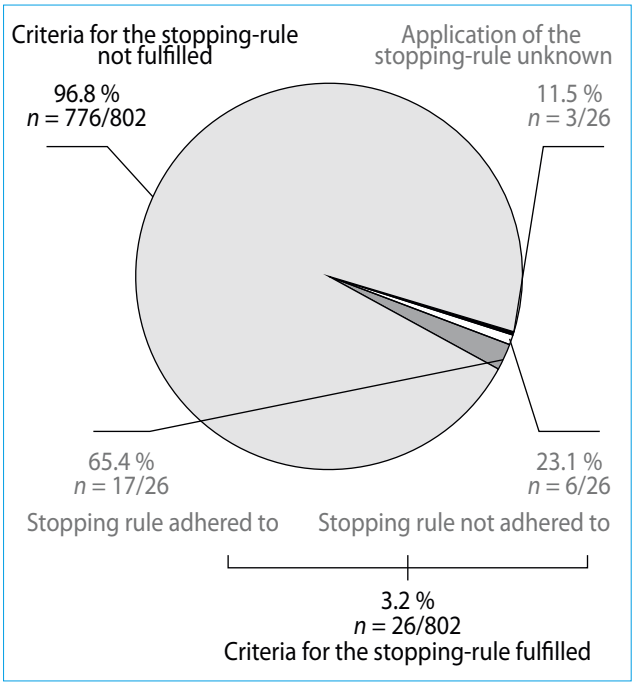

Fig. 1. Adherence to the stopping rule

Рис. 1. Приверженность правилу прекращения терапии

Shortening of therapy (Response-Guided Therapy, RGT)

275 patients (34.3 %) were eligible for shortening the duration of therapy. For 133 of these patients (48.4 %) this rule was followed (two-sided 95 % confidence interval [42.3 %; 54.4 %]). In 95 of the applicable patients (34.5 %) the therapy was not shortened, and for 47 patients (17.1 %) this remained unknown. The duration of treatment in the 95 patients, whose therapy was not shortened contrary to the stopping rule, was in mean 40.0 weeks. 66.3 % of these patients achieved an SVR, one patient (1.1 %) did not achieve an SVR and in 32.6 % of the patients the virological response remained unknown at the 24-week follow-up (fig. 2).

With respect to the RGT, the following difference was shown between the previously treated and previously untreated patients: A shortening of the therapy was applicable more frequently for previously untreated patients (54.8 %) than for previously treated patients (24.2 %). The rule was followed in 60.4 % of the applicable untreated patients, but only in 34.1 % of the pre-treated patients. In those cases, where the shortening of therapy duration was not realized despite meeting the criteria 51.4 % of the previously untreated and 75.0 % of the pre-treated patients achieved an SVR.

Results on therapy outcome

Virological Response (SVR)

Undetectable HCV-RNA for 24 weeks after the end of treatment (SVR24) was used as a surrogate endpoint for curing of the HCV infection. This was

Table 1. Baseline parameters
Таблица 1. Базовые параметры

	Previously untreated patients Пациенты, не проходившие лечение ранее (*N* = 272)	Previously treated patients Пациенты, проходившие лечение ранее (*N* = 520)
Gender (Male / Female) Пол (Муж./Жен.)	59.9/40.1 %	63.7/36.3 %
Age (years*) Возраст (в годах*)	45.1 ± 10.9	51.3 ± 10.0
Duration of infection (years*) Продолжительность заболевания (в годах*)	6.7 ± 8.3	10.9 ± 7.4
HCV Subtype 1a (%) Подтип вируса гепатита С 1а (%)	40.4 %	35.4 %
1b (%) 1б (%)	46.3	52.1
1a and 1b (%) 1а и 1б (%)	0	1.0
unknown не определен	13.2	11.5
Fibrosis of the liver (%) Фиброз печени (%)	23.9	34.8
Cirrhosis of the liver (%) Цирроз печени (%)	8.5	18.3
Co-infection: Коинфекция:		
HIV (%) ВИЧ (%)	6.6	9.8
Hepatitis B (%) Гепатит В (%)	0.7	0.8
Most common transmission pathway: Наиболее распространенные пути передачи:		
Blood-based products (%) Препараты на основе крови (%)	9.6	16.7
I.v. drugs (%) Внутривенное введение лекарственных препаратов (%)	31.6	18.5
Previous therapy: Предыдущая терапия:		
Relapse (%) Рецидив (%)		38.5
Non-Response (%) Резистентность (%)		38.3
Breakthrough (%) Прорыв (%)		6.7
Comorbidity (%) Коморбидность (%)	59.6	68.7

* Mean value ± standard deviation; the mean values are based on all patients.
* Среднее значение ± стандартное отклонение; средние значения даны для всех пациентов.

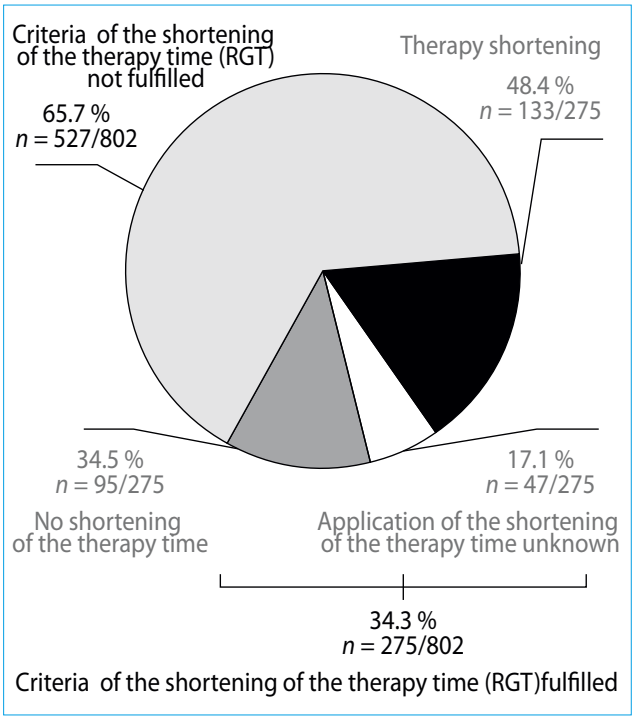

Fig. 2. Adherence to the therapy shortening (RGT)

Рис. 2. Применение сокращенного плана лечения

achieved by 454 of the 802 patients (56.6 %) (ITT analysis). The SVR rate was higher for patients with relapse after a previous HCV treatment (68.0 %) and lower for patients with a previous null-response (31.1 %). In treatment-naïve patients the SVR rate was 58.1 % (fig. 3).

In the 24-week follow-up, 130 of the 802 patients (16.2 %) could no longer be contacted (Lost-to-follow-up) and in 49 patients (6.1 %) HCV-RNA levels were not documented. If these patients were excluded from the analysis (per protocol analysis), SVR24 was reached by 72.9 % of all patients.

Based on a multiple logistic regression analysis, predictive factors for a treatment success were exploratively investigated. The following variables were negatively associated with a therapy success (fig. 4): Cirrhosis at baseline (OR: 0.500), shortening of treatment duration (RGT) not applicable, i.e. no rapid virologic response (OR: 0.266), discontinuation due to side effects (OR: 0.376) and non-compliance (medication intake with a fat-containing meal); OR: 0.483).

Tolerability

90.8 % of the patients with TVR-based therapy presented with anaemia during the observation period. In 49.5 % of these patients this was accompanied by at least one haemoglobin value of ≤ 10 g/dl and in 21.3 % a value of <8.5 g/dl. The SVR24 in patients with anaemia was 57.5 %, for 21.5 % of the patients the response is unknown.

A total of 69.5 % of the patients achieved the regular end of treatment without premature termination. A discontinuation of the therapy due to adverse events was documented for 8.9 % of the patients.

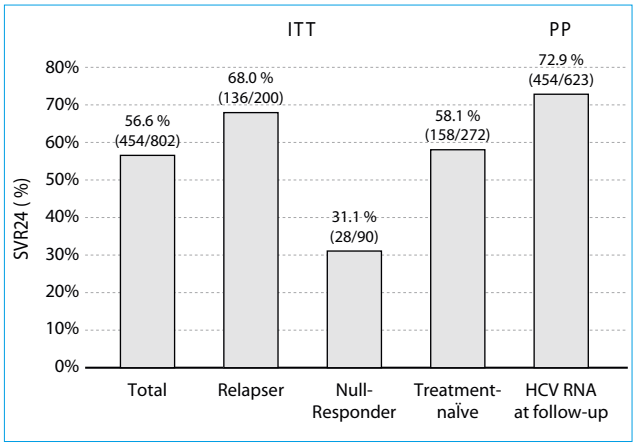

Fig. 3. Sustained Virological Response 24 weeks after end of treatment (SVR24)

Рис. 3. Устойчивый вирусологический ответ на 24-й неделе после окончания лечения

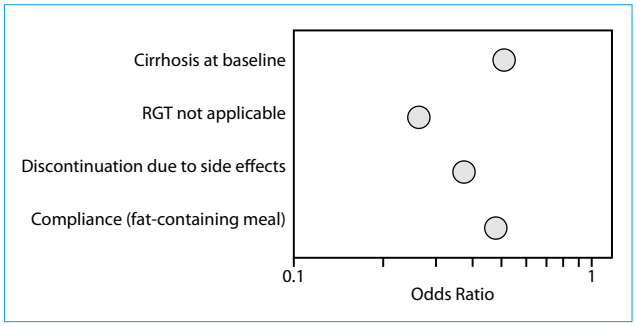

Fig. 4. Odds ratio values of the multiple logistic regression analysis

Рис. 4. Оценка факторов успешного исхода терапии с использованием анализа множественной логистической регрессии

During the treatment, a total of 4,650 non-serious adverse events (AEs) were reported in 774 of the 802 patients (96.5 %). In accordance with MedDRA (Version 14.1) these non-serious AEs were most frequently grouped in the system organ classes (SOC) "general disorders and administration site conditions" (65.3 % of the patients), "skin and subcutaneous tissue disorders" (60.5 %) and "gastrointestinal disorders" (57.7 %). 3443 of the 4650 events (74.0 %) were regarded by the physicians at least as possibly related to TVR.

A skin rash was observed in 288 of the 802 patients (35.9 %). In 14 cases (1.8 %) of pre-treated patients and 4 cases (0.5 %) of therapy-naïve patients this adverse event presented as serious. However, a change of the TVR dosage or a TVR discontinuation was only realized in 29 patients. Anaemia was observed in 727 of the 802 patients (90.6 %) (see above). A change of TVR dosage or discontinuation was only reported for 8 patients.

In 137 of the 802 patients (17.1 %), a total of 234 serious adverse events (SAEs) were documented. 113 of the 234 SAEs (48.3 %) were reported as at least possibly related to TVR by the physician. The outcome of 169 of the 234 SAEs (72.2 %) were reported as being resolved by the end of the study. The outcome of 23 SAEs (9.8 %) was reported as resolved with consequences.

During the observation period 6 patients died (0.7 %), for whom a total of 10 SAEs were reported. In 5 of the 6 patients, no association with the treatment was apparent, or it was doubtful or not stated. One case of gastroenteritis, sepsis and multi-organ failure was assumed to be treatment associated.

Treatment costs

Averaged for all patients the total therapy costs per patient were €43,026 (±€12,873 SD) for previously untreated patients and €44,071 (±€15,311) for pre-treated patients. In addition, the costs associated with the follow-up period were €668 (±€2,116) per patient for previously untreated and €921 (±€2,868) for previously treated patients.

As Table 2 shows, the TVR-based therapy accounts for the major portion of the HCV-related costs. The costs for laboratory tests, consultations with other physicians, hospitalizations and further HCV-related concomitant medications played a subordinate role.

From an economic perspective, per-patient costs from the societal perspective during treatment were estimated at 4,054€ (±€8,044). Apart from occupational disability (€8.25) and incapacity to earn an income (€66.87), these costs mainly consist of costs for short-term sick-leaves (3,979€/4,054€ (98 %).

In the subgroup of 169 patients with therapy failure (i.e. patients failed to achieve SVR24) the total costs for the therapy period were €38,606 (±€14,178.93) per patient and thereby lower than the average costs in the entire group.

For the 17 patients with application of the stopping-rule due to lack of treatment response the total costs for the therapy period were €19,880 (±€7,470) per patient and for the 133 patients eligible for the shortening of the therapy (RGT) the costs were €42,364 (±€8,150) per patient.

From the perspective of the health insurance providers the follow-up period caused further costs of €668 (±€2,116) for pre-treated patients and €921 (±€2,868) for treatment naïve patients. From an overall economic perspective, further costs of €1,239 (±€3,884) arose during the follow-up period, mainly due to short-term sick-leaves (€1,173 respectively €1,239).

Use of resources

On average, every patient visited the study centre 14.6 ± 10.1 times during the treatment duration, which roughly corresponds to two visits per month.

Table 2. HCV-related therapy costs per patient [€] (NHI perspective)

Таблица 2. Стоимость лечения вируса гепатита С из расчета на одного пациента (евро) (по данным Национального индекса здоровья NHI)

	Previously untreated patients Пациенты, не проходившие лечение ранее (*N* = 272)	Previously treated patients Пациенты, проходившие лечение ранее (*N* = 520)
Visits to the study centre Посещения исследовательского центра	328.79 ± 213.55	325.35 ± 182.98
Diagnostics Диагностика	800.90 ± 219.93	818.25 ± 225.10
Laboratory Лабораторные исследования	26.72 ± 15.22	27.51 ± 13.86
Visits to other physicians Посещения других врачей	21.98 ± 61.99	25.13 ± 57.45
Sick leaves Денежное пособие по болезни	1,483.17 ± 4,017.30	2,117.30 ± 5,545.78
Telaprevir-based treatment Лечение на основе Телапревира	40,038.51 ± 11,840.63	40,251.03 ± 13,041.13
HCV-related concomitant medication Лечение сопутствующими препаратами	12.40 ± 181.91	4.69 ± 48.01
Hospitalisations Госпитализация	313.46 ± 1,086.93	501.71 ± 1,564.80
Total costs (€) Общая стоимость (€)	43,025.92 ± 12,872.55	44,070.97 ± 15,310.81

Mean value ± standard deviation (SD); the mean values are based on all patients.
Среднее значение ± среднее отклонение; средние значения рассчитаны с учетом всех пациентов.

For most patients, diagnostic and laboratory tests were conducted regularly. 34.8 % (n = 279/802) of the patients also consulted other physicians. 11.1 % (n = 89/802) of the patients were admitted to hospital due to the HCV disease during the observation period, whereas 35.8 % (n = 287/802) of the patients reported HCV-related sick leaves.

The HCV-related consumption of resources during the therapy for pre-treated and treatment naïve patients is represented in Table 3.

A follow-up examination was conducted on average 26.1 ± 5.8 weeks after the end of treatment. During the follow-up period, every patient visited the study centre on average 2.6 ± 2.4 times. Diagnostic tests were performed for 25.9 % (n = 208/802) and laboratory tests for 80.2 % (n = 643/802) of the patients. 7.5 % (n = 60/802) of the patients reported visiting other physicians. Hospital admissions due to the HCV disease occurred rarely (3.2 %; n = 26/802) and HCV-related cases of sick leave were reported by 17.5 % (n = 140/802) of the patients.

Discussion

Prior to the introduction of the protease inhibitors, the dual combination of pegylated interferon and ribavirin with SVR rates of 40–50 % was the standard treatment for patients with chronic Genotype 1 hepatitis C for roughly 10 years [4]. In the registration trials the triple combination with the ad-

Table 3. The HCV-related consumption of resources

Таблица 3. Расходы, связанные с лечением вируса гепатита С

	Treatment naïve patients Пациенты, не проходившие лечение ранее (наивные) (N = 272)	Pre-treated patients Пациенты, проходившие лечение ранее (N = 520)
Visits to the study centre per patient* Посещения исследовательского центра, на одного пациента*	14.8 ± 11.1	14.6 ± 9.5
Telaprevir intake (weeks)* Прием Телапревира (кол-во недель)*	11.8 ± 2.8	11.2 ± 2.8
Ribavirin intake (weeks)* Прием Рибавирина (кол-во недель)*	29.5 ± 12.7	32.4 ± 15.7
Peg-Interferon application (weeks)* Прием Пегинтерферона (кол-во недель)*	28.5 ± 12.1	32.2 ± 15.5
Concomitant medication against HCV Сопутствующее лечение против вируса гепатита С	3.3 %	3.7 %
Diagnostics Диагностика	73.5 %	75.2 %
Laboratory tests Лабораторные тесты	100.0 %	99.8 %
Visits to other physicians Посещения других врачей	28.3 %	38.3 %
Hospitalisations Госпитализация	9.2 %	12.3 %
Hospital days per patient* Количество дней, проведенных в стационаре на одного пациента*	1.8 ± 17.1	1.3 ± 5.1
Sick leave Денежное пособие по болезни	39.0 %	34.0 %
Days of sick leave per patient* Количество дней отпуска по болезни на одного пациента*	39.3 ± 84.3	47.6 ± 105.7
Incapacity to work Нетрудоспособность	0.4 %	1.2 %
Occupational disability Утрата профессиональной трудоспособности	1.1 %	1.2 %
Further measures Иные затраты	5.2 %	4.6 %

* Mean values ± standard deviation; the mean values are based on all patients.

* Среднее значение ± среднее отклонение; средние значения рассчитаны с учетом всех пациентов.

ditional protease inhibitor telaprevir (TVR) over 12 weeks resulted in significantly higher SVR rates of up to 75 % for treatment naïve patients and about 64 % for pre-treated patients. The latter group was composed of 83 % SVR for relapsers, 59 % for partial-responders and 29 % for null responders [11].

The current data were based on a non-interventional, prospective study. As no study-specific instructions are present, in contrast to clinical trials, a large portion of data is not available as the patients dropped out during treatment and data surveys were no longer done. According to an ITT analysis 454 of the 802 patients (56.6 %) achieved a SVR. For treatment naïve patients the SVR rate was 58.1 %.

24 weeks after the end of treatment 130 of the 802 patients (16.2 %) were lost-to-follow-up and for 49 patients (6.1 %) no HCV-RNA levels were documented for the follow-up examination. If these patients are excluded from the calculation of the virological response (per protocol analysis) the SVR24 was achieved by 72.9 % of all patients.

Overall, these real-world data reflect the virological response that was determined in the clinical trials. However, at a slightly lower level. A possible explanation is the loss of patients during the daily collection of data, because of a lack of close monitoring. But further, this may also reflect the importance of keeping the patients motivated during the therapy and observational period. This may be somewhat easier when carried out within the scope of a clinical trial, and be carried out with more commitment than it is possible under routine real-world conditions.

Klass et al. (2012) described a trend towards more difficult to treat HCV patients based on epidemiological data in relation to chronic hepatitis C in Germany published by Hueppe et al. (2008) [12, 2]. The presented data are in line with this as 14.8 % of the patients in this study already had a liver cirrhosis and 30.7 % a fibrosis at baseline.

The tolerability of the TVR-based triple therapy was consistent with the expectations. The discontinuation rate of 8.9 % (71/802 patients) due to side-effects presented to be lower than the 15 % reported by Zeuzem et al. (2011) [11]. Attention was given to the occurrence of rashes and anaemia over the course of the therapy. The appearance of a rash was observed in 35.9 % (288/802) of the patients, of which 18 cases (2.2 %) this adverse event was rated serious. However, discontinuation or change of TVR dose took place in only 29 patients (7.7 %). Anaemia was observed in nearly all patients (90.6 %), a change of the TVR treatment was, however, only documented for 8 (1.0 %) patients.

The consideration of the application of the stopping-rule within this observational study shows various aspects. Only 3.2 % of the patients fulfilled the requirements for the application of the stopping-rule. In 65 % of these patients the treatment was stopped, in 23 % it was not stopped and for 12 % this remained unknown. Concerning the frequency of occurrence, the stopping-rule is of rather minor importance in everyday clinical routine. Whether the non-application with 35 % of the eligible patients was an intentional decision made against the rule, or was rather an oversight of the possibility cannot be answered based on the available data. However, it must be noted that out of 9 patients without the stop, one patient achieved an SVR24. From an economic perspective, the application of the stopping-rule is able to show a distinct cost reduction: whereas the average costs for patients with therapy failure were €38,606 per patient, the costs for the application of the stopping-rule were nearly halved with an average of €19,880 per patient.

The possibility of a shortening of the treatment duration (RGT) was present in275/802 (34.3 %) of the patients and was utilised for 133/275 (48.4 %) of these. It presented more frequently for treatment naïve (54.8 %) than for pre-treated (24.2 %) patients. The significance of the RGT appears more based on early indications for a successful therapy and therefore to relieve stress on patients. From an economic perspective, in the case of the patients whose treatment was shortened there were no decisive cost savings compared to the average treatment costs across all patients.

The data presented from the TEPS study describe the application of the protease inhibitor TVR that was introduced into routine clinical practice in 2011. Compared to the previously applied dual standard therapy with peg-interferon and ribavirin, the new TVR-based triple therapy in HCV-Genotype 1 patients represented a therapeutic breakthrough. With improved therapeutic response and manageable tolerability, it also offered the possibility of a RGT and a shortening of treatment duration for many patients.

From today's perspective, further Direct Acting Antivirals (DAAs) have become additionally available as therapeutic options, which have led to a further improvement of the response rates and above all also the possibility for oral intake. In consequence, a wide range of therapeutic options is available for the treatment of the chronic Hepatitis C, which offer promising and more tolerable treatment options, also in difficult to treat conditions — e.g. advanced disease, liver cirrhosis and co-infections. At the same time the demands on treating physicians are increasing when it comes to choosing the right treatment option, convincing the patients about the necessity of adherence and also undertaking the recommended decisions over the course of the treatment. The real-world data of this study show that these recommendations were not always followed with respect to the rules available at the time of the data survey. To what extent an individual reason for tailoring the individual therapy and hereby intentionally not applying the rules cannot be clarified based on the available data. In at least one case, however, a rule was not applied for the benefit of the patient and an SVR was nevertheless achieved.

The further development of new guidelines and implementation of clinical trial data in real-world settings of the treatment of chronic Hepatitis C is therefore both, an opportunity as well as a challenge for all those involved. Today, a good basis for overcoming these challenges is offered by the German Hepatitis C register (Deutsches Hepatitis C Register, DHC-R), which gathers prospective, non-interventional information on the use of many available HCV treatments in Germany on behalf of the German Liver Foundation (Deutsche Leberstiftung).

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Received: 27.09.2018 Accepted: 26.11.2018
Поступила: 27.09.2018 Принята: 26.11.2018

Редакционный комментарий

В свое время препарат Телапревир стал первым препаратом с прямым противовирусным действием, который расширил возможности лечения пациентов с гепатитом С. Проведение терапии стало возможным пациентам с циррозом печени, с отсутствием ответа на предшествующее лечение, с рецидивом после лечения, пациентам с тяжелыми сопутствующими заболеваниями. Включение препарата в схемы противовирусного лечения стало революционным решением, которое привело к увеличению продолжительности жизни пациентов, что, в свою очередь, изменило структуру заболеваний печени среди находящихся в листе ожидания трансплантации пациентов. Так, по данным НИИ скорой помощи им. Н.В. Склифосовского (Москва, Российская Федерация) в 2018 г. снизилась доля пациентов с вирусным HCV-индуцированным циррозом печени, которым была проведена трансплантация печени. Аналогичная тенденция наблюдается во всем мире (см., например, [Belli L.S., Perricone G., Adam R., Cortesi P.A., et al. Impact of DAAs on Liver Transplantation: Major Effects on the Evolution of Indications and Results. An ELITA Study Based on the ELTR Registry. J. Hepatol. 2018;69(4):810–817). Телапревир стал платформой для создания новых безопасных и высокоэффективных препаратов в лечении пациентов с гепатитом С. Учитывая важную историческую значимость препарата Телапревир, редакция посчитала нужным и интересным публикацию результаты собственного опыта применения препарата в клинической практике в Германии.

Редакционная коллегия «Российского журнала гастроэнтерологии, гепатологии, колопроктологии»

Editorial comment

At the time, Telaprevir was the first drug exhibiting a direct antiviral effect. This expanded the possibilities of treating patients with hepatitis C. As a result, it became possible to treat patients suffering from liver cirrhosis, as well as those with no response to previous treatment, a relapse after treatment or severe co-morbidities. The inclusion of this drug into antiviral treatment regimens was a revolutionary decision, which led to an increase in the life expectancy of patients and a subsequent change in the structure of liver diseases among patients on the waiting list for transplantation. Thus, according to the N.V. Sklifosovsky Research Institute of Emergency Medicine (Moscow, Russian Federation), in 2018, the number of patients with HCV-induced liver cirrhosis who had underwent liver transplantation decreased. A similar trend is currently observed all around the world (see, for example, [Belli L.S., Perricone G., Adam R., Cortesi P.A., et al. J. Hepatol. 2018; 69(4):810–817). Telaprevir has become a platform for creating new safe and highly effective drugs for treating patients with hepatitis C. Considering the historical significance of Telaprevir, the editors believe it necessary and expedient to publish the practical experience of using this drug in clinical practice in Germany.

Editorial Board of the Russian Journal of Gastroenterology, Hepatology, Coloproctology

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