

Utilization and effectiveness of elbasvir/grazoprevir and adoption of resistance-associated substitutions testing in real-world treatment of hepatitis C virus genotype 1A infection: results from the German Hepatitis C-Registry

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Background For treatment of genotype 1a (GT1a) infection with elbasvir/grazoprevir, the German guidelines recommend a differentiated approach depending on baseline viral load (BVL). For low BVL $\leq 800\,000$ IU/mL, treatment with 12 weeks elbasvir/grazoprevir should be considered, whereas for high BVL $> 800\,000$ IU/mL, this regimen is only recommended in nonstructural protein 5A (NS5A) resistance-associated substitutions (RAS) absence. With present NS5A RAS or when RAS-testing is not available, 16 weeks elbasvir/grazoprevir + ribavirin is preferred. Here, we investigated the adherence to these recommendations and the effectiveness of elbasvir/grazoprevir in a large German Hepatitis C-Registry GT1a cohort.

Methods From September 2016 until July 2018, 195 GT1a-infected patients were treated with elbasvir/grazoprevir \pm ribavirin for 12–16 weeks. The primary outcome was per protocol SVR12 or SVR24.

Results Mean age was 50 years, 89% were male, 19% had cirrhosis, 72% were treatment-naïve. Forty-five percent had low BVL $\leq 800\,000$ IU/mL, 55% high BVL $> 800\,000$ IU/mL, of whom 49 vs. 42% were baseline RAS-tested. Four patients with high (7.7%) and two with low BVL (5%) had NS5A RAS of whom 50% received elbasvir/grazoprevir + ribavirin, respectively. Ninety-four percent of patients with low and 65% with high BVL received elbasvir/grazoprevir without ribavirin. Thirty-five percent of patients with high BVL received ribavirin, mostly without prior RAS-testing. Per protocol sustained virologic response (SVR) by low vs. high BVL was 98.8 and 95.1%. All patients with NS5A RAS achieved SVR.

Conclusions In German, real-world most patients received elbasvir/grazoprevir without ribavirin. Ribavirin was mainly added in GT1a patients $> 800\,000$ IU/mL, who were not NS5A RAS tested. SVR rates were consistently high and comparable to clinical trial results. *Eur J Gastroenterol Hepatol* 33: 415–423

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Introduction

Chronic hepatitis C infection affects globally an estimated 71 million people. Left untreated the risk of liver-related mortality by developing cirrhosis and hepatocellular carcinoma

increases significantly [1–3]. In Germany, approximately 0.3% of the population is infected with hepatitis C virus (HCV) [3,4]. However, some studies show much higher prevalence in special populations including injecting drug-use (37–75%) and people in prison (8.6–17%) [4–11].

Successful treatment reduces the risk of HCV-related complications and death from liver disease [1]. Moreover, since the approval of all-oral direct-acting antiviral (DAA) regimens a tremendous improvement of efficacy, safety and tolerability was shown in comparison to the historical standard of care with interferon and ribavirin [1].

However, a small proportion of patients experience viral rebound. A reason for that could be the error-prone HCV RNA polymerase. During replication, a genetically highly diverse quasispecies population is produced [12]. Some variations in the genomic regions of nonstructural protein 3 (NS3), nonstructural protein 5A (NS5A), and/or nonstructural protein 5B (NS5B) can be associated with resistance to specific inhibitor classes [12–14].

Especially in genotype 1a (GT1a) and GT3 patients, baseline resistance-associated amino-acid substitutions (RAS) within the NS5A gene have been shown to be associated with reduced sustained virologic response (SVR) rates [13,15–19].

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Hence, to prevent virologic failure, testing of treatment naïve patients for baseline RAS can be considered [20,21]. Other strategies include the extension of treatment duration, addition of ribavirin or considering an alternative NS5A-inhibitor with a different resistance profile [15,18,22,23].

In 2016 the once-daily, fixed-dose combination of elbasvir, an NS5A inhibitor, and grazoprevir, an NS3 inhibitor, was approved for the treatment of chronic HCV genotype (GT) 1 and 4 infections in adults [24,25]. Elbasvir/grazoprevir has demonstrated high rates of SVR and a favorable tolerability profile in clinical trials [26–30]. Additionally, high efficacy and safety were shown in special patient populations including persons under opiate substitution therapy, people with advanced chronic kidney disease (CKD) and people with inherited blood disorders [31–33].

Within the clinical study program, the observation was made that NS5A baseline resistances may play a role for patients with GT1a and high baseline viral load (BVL). Consequently, the European label recommends a differentiated approach for elbasvir/grazoprevir therapy in GT1a patients with the consideration of RAS testing [20]. In alignment with the label, the German Guidelines recommend the following approach for the treatment of GT1a patients with elbasvir/grazoprevir: for patients with low BVL $\leq 800\,000$ IU/mL treatment with 12 weeks elbasvir/grazoprevir is suggested, as is for patients with high BVL $> 800\,000$ IU/mL who were tested negative for NS5A RAS. By contrast, for patients with high BVL $> 800\,000$ IU/mL who have NS5A RAS present or have not been tested for NS5A RAS 16 weeks of therapy plus the addition of ribavirin is recommended.

The aim of this study was to investigate the adherence to these guidelines in routine clinical practice and the effectiveness of elbasvir/grazoprevir regimens in GT1a patients selected for treatment in a nationwide real-world HCV cohort.

Methods

Study cohort and treatment

Data were derived from the German Hepatitis C-Registry (DHC-R), a project of the German Liver Foundation, managed by Leberstiftungs-GmbH Germany in cooperation with the association of German gastroenterologists in private practice (bng). The aim of the DHC-R is the investigation of novel HCV treatment strategies in German routine clinical practice. All patients had to provide written informed consent.

For the present study, inclusion criteria were as follows (1) treatment of chronic hepatitis C GT1a infection with elbasvir/grazoprevir \pm ribavirin for 12–16 weeks and (2) completion of follow-up visit 12 or 24 weeks after end of antiviral treatment or documented early treatment discontinuation. Enrolled patients were treated from September 2016 until July 2018 in 130 medical practices and hospital outpatient departments. HCV treatment (ribavirin use, duration of treatment) were at the discretion of the physician and were guided by product recommendations at the time of treatment.

Exclusion criteria in the context of antiviral treatment for this study were pregnant women (patient or female partner of male patient), breast-feeding women or women

of childbearing potential not using reliable contraception, patients who have been treated in the past or present for HCV in phases I–IV clinical trials, patients whose HCV treatment was being documented in another noninterventional study and patients with contraindications for HCV treatment (according to the summary of product characteristics).

All routine parameters, including comorbidities and regular outpatient medications, were recorded by a web-based system at baseline, during treatment and after the end of treatment. Data quality was analyzed by monthly plausibility checks and on-site monitoring.

The DHC-R is conducted in accordance with the ethical guidelines of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice and was approved by the Ethics Committees of Aertzekammer Westfalen-Lippe (reference number 2014-395-f-S).

Baseline and treatment-related patient parameters

All routine parameters were recorded at baseline, during treatment (weeks 4, 8, 12 and 16) and at weeks 12 or 24 after end of treatment. These included laboratory measurements, HCV genotyping (only at baseline) and HCV RNA levels, comorbidities and regular outpatient medications. Data on demographics were recorded at baseline. Liver cirrhosis (transient elastography, liver biopsy and/or clinical diagnosis) was documented at the initial and final examination. Missing values were ignored, and extra visits were documented. Data are shown for the intention-to-treat (ITT) population.

Outcomes

Effectiveness was assessed by SVR 12 or 24 weeks after termination of HCV treatment (SVR12 or SVR24, defined as HCV RNA ≤ 25 IU/mL at weeks 12 or 24 posttreatment). All HCV RNA measurements were made using highly sensitive quantitative reverse transcription-PCR assays. The per protocol effectiveness analysis included patients who completed follow-up 12–24 weeks after end of treatment. The following patients from the ITT population were excluded: noncompliant patients and patients who were lost to follow-up. Noncompliance (incomplete or irregular treatment) was evaluated by physicians' point of view. Virologic failures comprised patients with a qualitative positive HCV RNA count > 25 IU/mL due to non-response or relapse after end of treatment. Reinfections, defined as detectable HCV RNA > 25 IU/mL after cure at 12 months follow-up, were counted as therapy success.

Resistance testing

Resistance testing was recorded before HCV treatment. NS5A RAS considered were M28T/V/L, Q30E/R/H, L31F/M/V/H, H54Y, Q54N/H, H58P/D, P58S and Y93C/H/N.

Statistics

The present study includes data through 15 July 2018. Descriptive statistics were used for quantitative variables (number, mean and median) and categorical variables (relative frequencies). For comparison of quantitative and categorical variables, a Fisher's exact test (two-sided) was

performed. A *P*-value <0.05 was considered statistically significant. All authors had access to study data and have reviewed and approved the final article.

Results

Hepatitis C virus study population

During the evaluation period, 195 patients with chronic HCV GT1a infection received elbasvir/grazoprevir-based treatment, 88 patients (45%) with low BVL of ≤800 000 IU/mL and 107 patients (55%) with high BVL of >800 000 IU/mL.

Patient demographics and clinical characteristics at baseline of all 195 patients are summarized in Table 1. Overall, the mean age was 49.9 years (SD=11.9) and 69% (134/195) of the patients were male. The majority were native German (75.9%, *n*=148) and HCV treatment naïve (71.8%, *n*=140). Previous regimen of treatment-experienced patients comprised IFN-based dual therapy (80.5%, *n*=128), triple therapy (8.2%, *n*=13), DAA therapy (6.9%, *n*=11) and others (4.4%, *n*=7). Clinically, patients showed a mean BMI of 25.3 kg/m² (SD=4.8), 64.7% (121/187) had elevated alanine aminotransferase (ALT) and 61.1% (113/185) elevated gamma GT. The fibrosis stage (F0–F4)

was reported in 51% (100/195) of patients. On average, 22% (43/195) had F0–F1, 4.6% (9/195) had F2 and 5.6% (11/195) had F3. On average, 19% (37/195) of the treated patients had liver cirrhosis (F4). Patients with BVL ≤800 000 IU/mL and patients with BVL >800 000 IU/mL showed comparable characteristics (Table 1).

Comorbidities in hepatitis C virus genotype 1a-infected patients

A high proportion of patients suffered from comorbidities (93.8%, *n*=183). The most prevalent are depicted in Table 2. Drug addiction and substitution therapy were most commonly reported, in 41.1% (82/195) and 25.1% (49/195) of patients, respectively. About 23.6% (46/195) of the patients had cardiovascular disease, especially arterial hypertension (20%, *n*=39), and psychiatric disorders (16.4%, *n*=32), mainly depression (13.3%, *n*=26). Less prevalent were coinfection with HIV (10.8%, *n*=21), metabolic disorders (7.7%, *n*=15) including diabetes mellitus (6.7%, *n*=13), renal dysfunction (7.2%, *n*=14) with a requirement for hemodialysis (4.6%, *n*=9) and alcohol misuse (5.1%, *n*=10). Coinfection with HBV occurred in 3.1% (6/195). All six patients were hepatitis B surface antigen positive.

Table 1 Patient and disease characteristics at baseline

Baseline characteristics	Genotype 1A		
	All (N=195)	≤800 K IU/mL (N=88)	>800 K IU/mL (N=107)
Age (years) – mean ± SD	49.9 ± 11.9	48.9 ± 11.7	50.9 ± 12.1
<50 years, <i>n</i> (%)	96 (49.2)	45 (51.1)	51 (47.7)
50–70 years, <i>n</i> (%)	90 (46.2)	41 (46.6)	49 (45.8)
>70 years, <i>n</i> (%)	9 (4.6)	2 (2.3)	7 (6.5)
Gender – <i>n</i> (%)			
Female	61 (31.3)	26 (29.5)	35 (32.7)
Male	134 (68.7)	62 (70.5)	72 (67.3)
Native country – <i>n</i> (%)			
Germany	148 (75.9)	70 (79.5)	78 (72.9)
Other	47 (24.1)	18 (20.5)	29 (27.1)
BMI (kg/m ²) – mean ± SD	25.3 ± 4.8	25.7 ± 5.2	25.0 ± 4.5
ALT elevated (U/L) – <i>n</i> (%) ^a	121 (64.7)	57 (65.5)	64 (64.0)
Gamma GT elevated (U/L) – <i>n</i> (%) ^b	113 (61.1)	50 (57.5)	63 (64.3)
Liver cirrhosis – <i>n</i> (%)	37 (19.0)	19 (21.6)	18 (16.8)
Treatment status – <i>n</i> (%)			
Treatment-naïve	140 (71.8)	65 (73.9)	75 (70.1)
Pretreated	55 (28.2)	23 (26.1)	32 (29.9)

ALT, alanine aminotransferase.

^aALT: available in 187 (total), 87 patients with BVL ≤800 000 IU/mL, 107 patients with BVL >800 000 IU/mL

^bGamma GT: available in 185 (total), 87 patients with BVL ≤800 000 IU/mL, 98 patients with BVL >800 000 IU/mL.

Table 2 Frequency of the most important comorbidities in genotype 1a-infected patients according to baseline viral load

Comorbidities	All (N=195)	≤800 K IU/mL (N=88)	>800 K IU/mL (N=107)
All comorbidities – <i>n</i> (%)	183 (93.8)	85 (96.6)	98 (91.6)
Drug addiction	82 (42.1)	37 (42.0)	45 (42.1)
Opioid substitution	49 (25.1)	23 (26.1)	26 (24.3)
Cardiovascular disease	46 (23.6)	19 (21.6)	27 (25.2)
Arterial hypertension	39 (20.0)	18 (20.5)	21 (19.6)
Psychiatric disorders	32 (16.4)	11 (12.5)	21 (19.6)
Depression	26 (13.3)	10 (11.4)	16 (15.0)
Coinfection with HIV	21 (10.8)	10 (11.4)	11 (10.3)
Metabolic disorders	15 (7.7)	4 (4.5)	11 (10.3)
Diabetes mellitus	13 (6.7)	4 (4.5)	9 (8.4)
Renal dysfunction	14 (7.2)	4 (4.5)	10 (9.3)
Hemodialysis	9 (4.6)	2 (2.3)	7 (6.5)
Alcohol misuse	10 (5.1)	5 (5.7)	5 (4.7)
Coinfection with HBV	6 (3.1)	4 (4.5)	2 (1.9)
HBsAg positive	6 (3.1)	4 (4.5)	2 (1.9)

The frequency of comorbidities per patient was 4.9 (964/195) and compared between patients with high BVL (5.1 542/107) and patients with low BVL (4.7 416/88). There was a nonsignificant trend towards higher prevalence of renal dysfunction (4.5%, $n=4$ vs. 9.3%, $n=10$) ($P=0.268$), metabolic (4.5%, $n=4$ vs. 10.3%, $n=11$) ($P=0.179$) and psychiatric disorders (12.5%, $n=11$ vs. 19.6%, $n=21$) ($P=0.244$) in patients with high BVL.

Baseline resistance testing

For GT1a patients with BVL >800 000 IU/mL, the German guidelines recommend resistance guided therapy. In this cohort, NS5A RASs testing at baseline was conducted in 52 of 107 GT1a patients (49%) with BVL >800 000 IU/mL (Fig. 1). Although not recommended by the guidelines, NS5A RAS were also tested in a comparable frequency in GT1a patients with low BVL \leq 800 000 IU/mL (42%) (Fig. 1).

Four therapeutically relevant RASs (M28T/V/L, $n=3$; Y93C/H/N, $n=1$) were detected in 4 of 52 (7.7%) patients with BVL >800 000 IU/mL.

Additionally, two therapeutically relevant RASs (M28T/V/L, $n=1$; Y93C/H/N, $n=1$) were present in 2 of 37 (5.4%) patients with BVL \leq 800 000 IU/mL.

In all patients who were tested positive for NS5A RAS, only single mutations were detected.

Treatment regimen

The utilization of elbasvir/grazoprevir-based therapy for the treatment of GT1a patients in the German real-world is summarized in Fig. 2. Overall, 78.5% (153/195) of patients were treated with elbasvir/grazoprevir and 21.5% (42/195) with elbasvir/grazoprevir + ribavirin.

Most GT1a patients with BVL \leq 800 000 IU/mL were treated with elbasvir/grazoprevir without ribavirin (94.3%, 83/88). However, five patients (5.7%) received elbasvir/grazoprevir plus ribavirin (against guideline recommendation). Two patients were tested positive for NS5A RAS (although resistance testing is not required in this population), one was treated with elbasvir/grazoprevir and the other with elbasvir/grazoprevir + ribavirin.

34.6% (37/107) of GT1a patients with BVL >800 000 IU/mL received elbasvir/grazoprevir with ribavirin. The majority (83.8%, 31/37) of these patients had not been tested for NS5A RAS. Of the six patients who had been tested for NS5A RAS, two received elbasvir/grazoprevir + ribavirin due to the presence of NS5A RAS and four received elbasvir/GZR + ribavirin despite a negative NS5A RAS test result.

Of the 70 (65.4%) GT1a patients with BVL >800 000 IU/mL who did not receive ribavirin, 34% (24/70) had not been tested for NS5A RAS (against guideline recommendation), while 66% (46/70) had been tested. Forty-four patients (95.7%) were treated without ribavirin as no NS5A RAS had been detected and two patients (4.3%) were treated without ribavirin despite the presence of NS5A RAS (against guideline recommendation).

Virologic response

Per protocol SVR rates were available from 188 patients after exclusion of 7 patients (4%) because of lost to

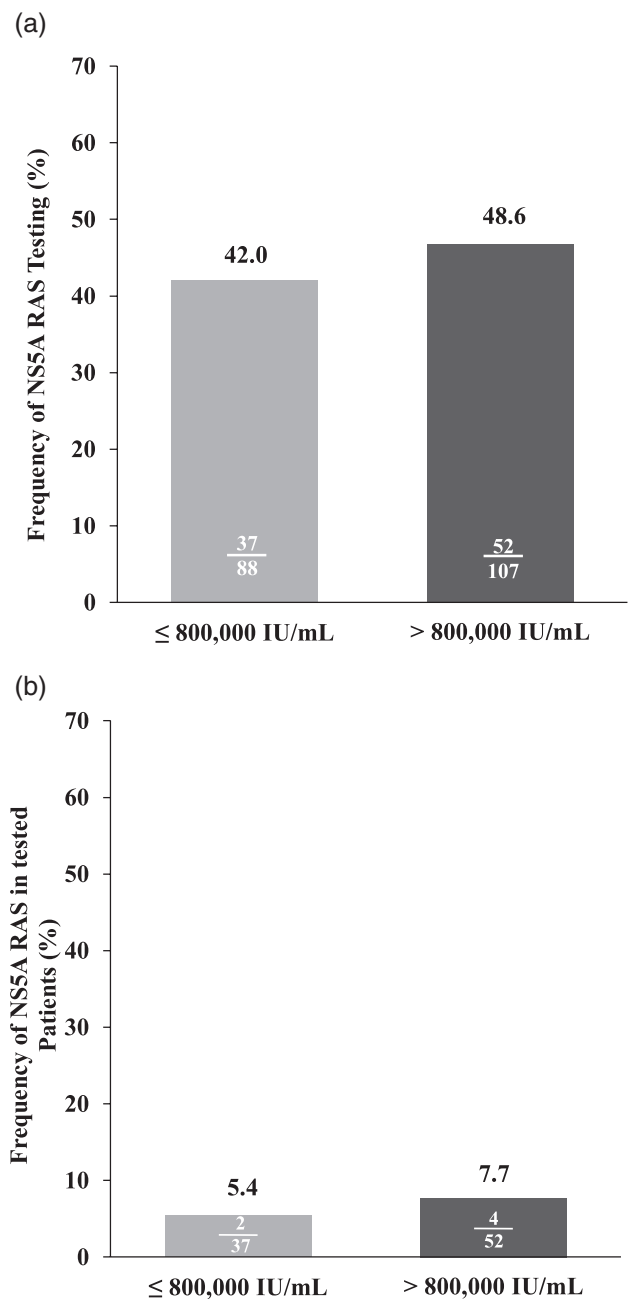


Fig. 1 Frequency of (a) NS5A RAS testing by low and high baseline viral load and (b) NS5A RAS in tested patients by low and high baseline viral load. NS5A, nonstructural protein 5A.

follow-up or noncompliance. One reinfection occurred which was counted as therapy success in the per protocol analysis. The intent-to-treat SVR rate for patients with low BVL was 96.6% (85/88) and the per protocol SVR rate was 98.8% (85/86) (Fig. 3). The majority of the successfully treated patients (98.8%, 79/80) received elbasvir/grazoprevir for 12 weeks while five patients were treated with elbasvir/grazoprevir plus ribavirin, two for 12 weeks and three for 16 weeks. One patient was treated with elbasvir/grazoprevir for 12 weeks and did not achieve SVR. This patient had not been tested for NS5A RAS.

For patients with high BVL, the intent-to-treat SVR rate was 89.7% (96/107) and the overall per protocol SVR rate was 95.1% (97/102). Of the successfully treated patients,

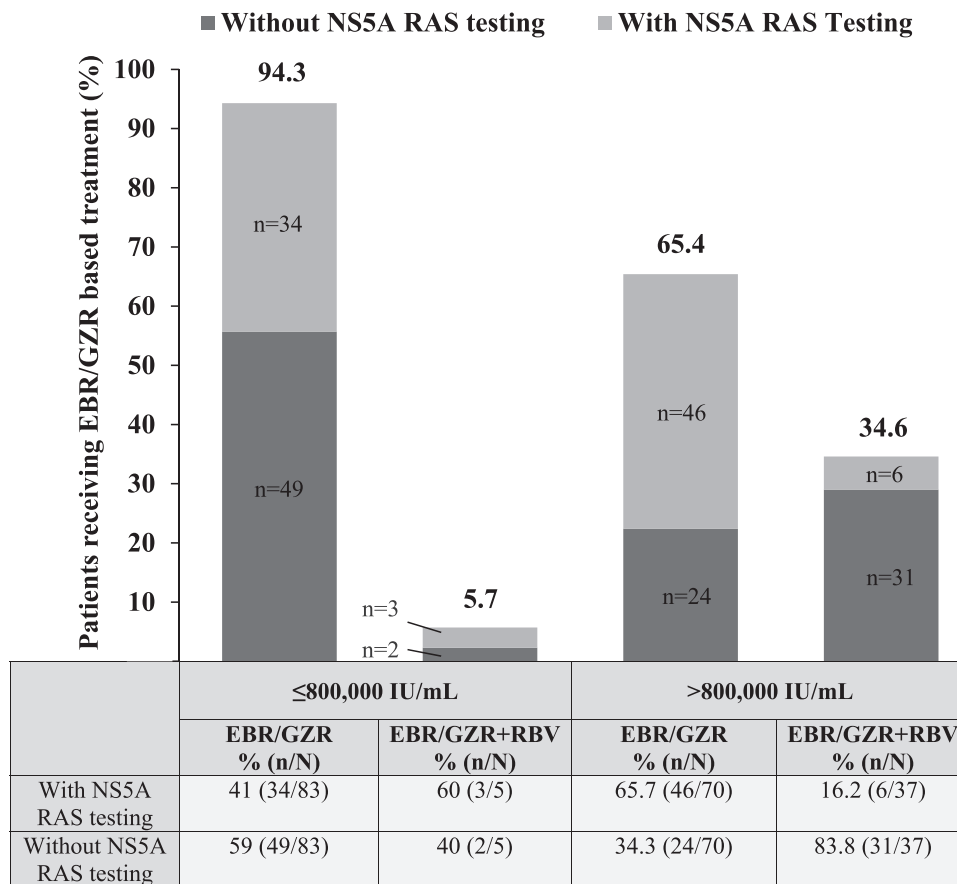


Fig. 2 Elbasvir/grazoprevir-based treatment regimens of GT1a infection. GT1a, genotype 1a.

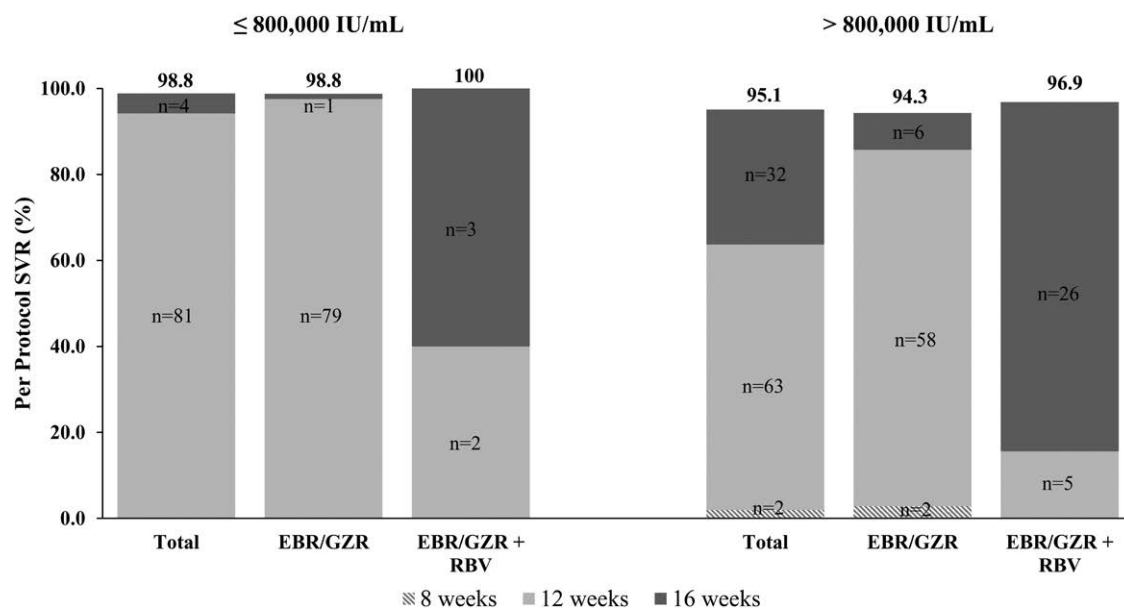


Fig. 3 Per protocol SVR rates in GT1a patients according to baseline viral load. GT1a, genotype 1a; SVR, sustained virologic response.

66 (68.0%) received elbasvir/grazoprevir, 58 for 12 weeks (87.9%), 6 for 16 weeks (9.1%) and 2 for 8 weeks (3.0%). Thirty-one patients (32.0%) were treated with elbasvir/grazoprevir plus ribavirin, 26 (83.9%) for 16 weeks and 5 (16.1%) for only 12 weeks. Four patients who received elbasvir/grazoprevir for 12 weeks as well as one patient who was treated with elbasvir/grazoprevir plus ribavirin for 16 weeks did not achieve SVR.

Per protocol SVR rates for patients with high BVL by RAS status and treatment regimen are summarized in Fig. 4. All four patients with therapeutically relevant NS5A RASs achieved SVR, two patients had been treated with elbasvir/grazoprevir for 12 weeks and two patients with elbasvir/grazoprevir+ribavirin for 16 weeks. Two out of 48 patients with a negative NS5A RAS test result failed elbasvir/grazoprevir therapy for 12 weeks due to

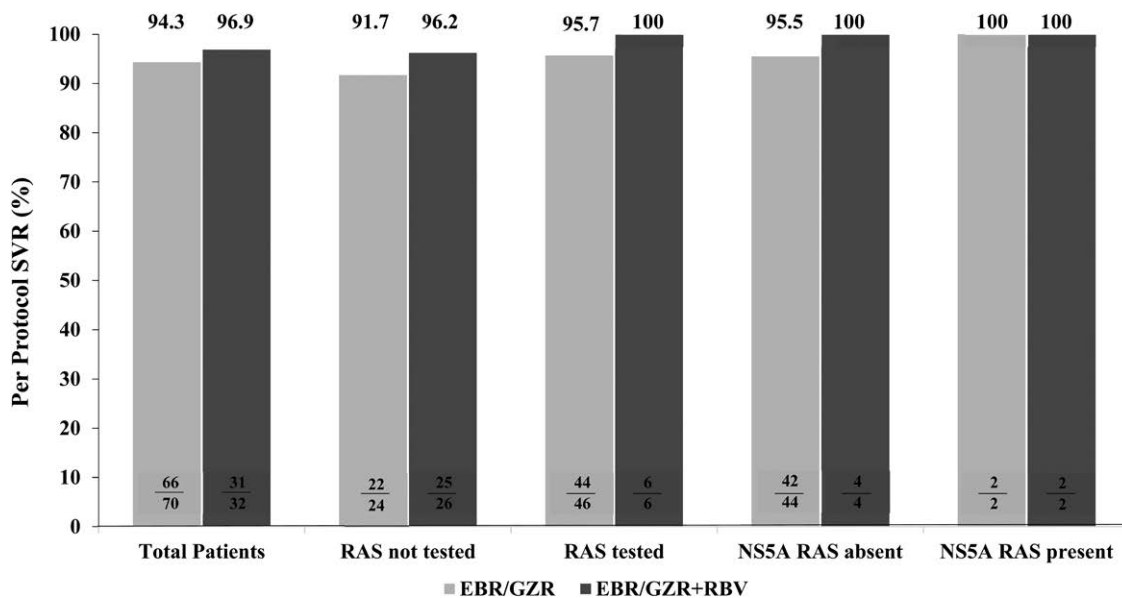


Fig. 4 Per protocol SVR rates in GT1a patients with high BVL according to RAS status and treatment. BVL, baseline viral load; GT1a, genotype 1A; RAS, resistance-associated substitutions; SVR, sustained virologic response.

relapse. Of 50 patients who had not been tested for NS5A RASs, three patients did not achieve SVR: two patients had received elbasvir/grazoprevir for 12 weeks (against guideline recommendations) and failed due to either non-response or relapse and one patient had been treated with elbasvir/grazoprevir+ribavirin for 16 weeks and had a relapse. Overall, per protocol SVR rates were consistently high and above 95% in patients with low BVL and high BVL.

Treatment failures

Analyzing the patient profiles of the six patients who did not achieve SVR revealed the following characteristics (Table 3): two patients were above 70 years and the remaining four between 50 and 70 years, five of six were female, 50% showed BMI above 30. Four patients were treatment-naïve, one had shown a relapse after therapy with PegIFN alfa-2a/ribavirin and was treated with elbasvir/grazoprevir for 12 weeks in the absence of NS5A RAS, another had failed pre-therapy with ledipasvir/sofosbuvir and was treated with elbasvir/grazoprevir+ribavirin for 16 weeks without prior NS5A RAS testing (despite the lack of data for patients with prior second-generation DAA therapy as stated by the label). Two patients had a history of drug use or were under substitution therapy. In line with a higher age ranging from 55 until 85, all six patients were either under treatment for hypertension or were diagnosed with cardiovascular disease.

Five out of six patients had high BVL, of which only two patients were tested for baseline RAS. As the result showed the absence of NS5A RAS both were treated with elbasvir/grazoprevir for 12 weeks. Only one patient not tested for RAS was treated with elbasvir/grazoprevir+ribavirin for 16 weeks, the remaining two received elbasvir/grazoprevir for 12 weeks (against label recommendation). In summary, three out of six failures were either treated against label recommendations regarding regimen choice and schedule or were treated in situations where data are lacking, that

is, retreatment of DAA failures. All patients had advanced age. Cirrhosis was not a negative predictor.

Discussion

Elbasvir/grazoprevir ± ribavirin has been approved by the European Medicines Agency for the treatment of chronic HCV GT1 and four infections. In Germany, GT1 is the predominant genotype whereas GT4 is relatively rare. Regarding GT1 subtypes, a significant increase in the prevalence of HCV GT1a with a concurrent decrease in HCV GT1b could be observed in recent years. This may be caused by the fact that the historic cohort of GT1b patients, that had been infected primarily via contaminated blood products, has largely been treated [34]. Underserved populations such as people who inject drugs and prisoners remain, leading to a shift of the genotype distribution towards GT1a (and GT3), which are the most prevalent genotypes in these populations [6].

This study, therefore, evaluated the real-life effectiveness as well as the level of adherence to German treatment guidelines for elbasvir/grazoprevir-based therapy of HCV GT1a infection in routine clinical practice in a large cohort of the DHC-R. Based on disparate recommendations for patients with low vs. high BVL, baseline characteristics, comorbidity profile, baseline resistance testing, regimen utilization and treatment outcomes were described for both viral strata separately and compared to assess differences and commonalities between these groups.

The results demonstrate comparable characteristics and comorbidities of GT1a patients with high and low BVL. In addition, the data on treatment history (72% therapy naïve) and liver disease progression (19% cirrhosis) are comparable to results for GT1a patients from other previously published international studies including veteran affairs (VA) cohort (82% therapy naïve; 31% cirrhosis), TRIO health network (80% therapy naïve; 30% cirrhosis) and Z-Profile cohort (19% cirrhosis) [35–37]. The mean age of GT1a infected patients in this study was slightly younger compared to

Table 3 Characterization of patients with virologic treatment failures

Gender	Age	BMI	Treatment status	Comorbidities	Comedications	Baseline viral load	RAS testing	Treatment regimen	Cirrhosis
1 Female	>70 years	BMI <30	Relapse after pretreatment with LDV/SOF	Hypertension	Ramipril, pantoprazole	>800 000 IU/mL	No prior NS5A RAS testing	Elbasvir/grazoprevir + ribavirin for 16 weeks	No cirrhosis
2 Female	>70 years	BMI ≥30	Therapy – naïve	Hypertension	Valsartan, metoprolol	>800 000 IU/mL	No prior NS5A RAS testing	Elbasvir/grazoprevir for 12 weeks	No cirrhosis
3 Female	50–70 years	BMI ≥30	Therapy- naïve	Opioid substitution	Candesartan, opiopramol, zopiclone, tilidine	>800 000 IU/mL	No prior NS5A RAS testing	Elbasvir/grazoprevir for 12 weeks	No cirrhosis
4 Female	50–70 years	BMI ≥30	Therapy – naïve	Cardio-vascular disease	Letrozole	>800 000 IU/mL	NS5A RAS absent	Elbasvir/grazoprevir for 12 weeks	No cirrhosis
5 Male	50–70 years	BMI <30	Relapse after pretreatment with PegIFN alfa-2a/ribavirin	Hypertension, depression, history of drug abuse	Doxepin, ramipril	>800 000 IU/mL	NS5A RAS absent	Elbasvir/grazoprevir for 12 weeks	No cirrhosis
6 Female	50–70 years	BMI <30	Therapy- naïve	Hypertension	Amlodipine, DHEA	≤800 000 IU/mL	No prior NS5A RAS testing	Elbasvir/grazoprevir for 12 weeks	No cirrhosis

DHEA, dehydroepiandrosterone; LDV, ledipasvir; NS5A, nonstructural protein 5A; RAS, resistance-associated substitutions; SOF, sofosbuvir.

other cohorts (50 years compared to 55 years, 59 years and 64 years in Z-Profile, TRIO and VA, respectively) [35–37].

With regards to comorbidities, nearly half of the GT1a-infected patients (41%) reported drug addiction and 25% substitution therapy. Thirteen percent of patients suffered from depression, 24% from cardiovascular disease and 20% from hypertension. Within the VA cohort history of drug use was similar (54%); however, a higher proportion of patients reported depression (57%) [35]. By contrast, in Z-Profile only 16% of patients used drugs within the last 12 months before treatment initiation and 17% suffered from depression [37]. For patients in TRIO hypertension was more prevalent (54%) [36].

Large differences could be observed in the frequency of renal disease and diabetes between the cohorts. VA and TRIO showed high rates of CKD stage 4/5 (17 and 32%, calculated, respectively) and diabetes (53 and 30%), whereas renal dysfunction as well as diabetes were reported for only 7% of GT1a patients in the DHC-R [35,36].

The recommendations for resistance testing vary in different countries [21,38]. The German guidelines suggest treatment with elbasvir/grazoprevir for 12 weeks in patients with low BVL ≤800 000 IU/mL and for 16 weeks with the addition of ribavirin in patients with high BVL >800 000 IU/mL who have NS5A RAS present or have not been tested for NS5A RAS.

Within the DHC-R resistance testing was performed in 49% of GT1a patients with high BVL >800 000 IU/mL and in 42% of GT1a patients with low BVL ≤800 000 IU/mL. By comparison, the US cohort (TRIO) showed a higher percentage (69%) of RAS testing in GT1a patients, while in the Canadian cohort Z-Profile resistances were assessed in only 12% of patients reflecting the different country guidelines/labels [36,37]. In the German real-world cohort, the rate of baseline NS5A RAS was low. Similar to clinical trials (7%, 55/825), prevalence of baseline substitutions within the NS5A gene occurred in 7.7% of GT1a patients with high BVL >800 000 IU/mL and in 5.4% of GT1a patients with low BVL ≤800 000 IU/mL. The presence of baseline NS5A RAS in GT1a patients according to high or low BVL has so far not been evaluated in other cohorts. Prevalence of GT1a RAS mutations varies in different countries. Some cohorts from the USA, Spain and Scotland reported presence of NS5A RAS in 12–19% of GT1a patients [36,39,40]. Here, the prevalence of NS5A RAS in GT1a in total was only 6.7%. Additionally, the analysis revealed only single mutations, in contrast to other publications [39,40]. In the present cohort, the presence of baseline NS5A RAS did not seem to impair treatment response if treated according to label as all patients with proven NS5A RAS achieved SVR12 (100%).

With regard to treatment regimens being used in German real-world practice the majority (94%) of patients with GT1a infection and BVL ≤800 000 IU/mL received elbasvir/grazoprevir for 12 weeks without ribavirin. Following the German guidelines, the addition of ribavirin was mainly restricted to GT1a-infected patients with high BVL >800 000 IU/mL who have NS5A RAS present or had not been tested for NS5A RAS. 92% of patients with negative RAS test results received elbasvir/grazoprevir without ribavirin, in only 4 patients ribavirin was added without necessity.

Against label and guideline recommendations, 24 GT1a patients with high BVL >800 000 IU/mL lacking RAS test received elbasvir/grazoprevir without ribavirin. Of those, 18 patients were treated with elbasvir/grazoprevir for 12 weeks, 4 received a longer duration treatment of 16 weeks and 2 received a shorter duration treatment of 8 weeks. Two patients experienced virologic failure; however, 22 achieved SVR12. Overall, recommendations in the guidelines were mostly followed.

In this real-world setting, treatment with elbasvir/grazoprevir ± ribavirin yielded high SVR rates of 98.8% in GT1a patients with BVL ≤800 000 IU/mL and 95.1% in GT1a patients with BVL >800 000 IU/mL. Worth mentioning in this context is the high efficacy in this cohort despite a comorbidity rate over 90%. Additionally, treatment of patients younger than 50 years resulted in high SVR rates of 100% independent of BVL or ribavirin addition.

By comparison, the VA cohort included 2436 patients treated with elbasvir/grazoprevir ± ribavirin showing an ITT SVR12 rate in GT1a patients of 93.4% (788/844). Unfortunately, the per protocol SVR data for GT1a were not published (all GT ITT: 95.6%; all GT per protocol: 97%). Of note, the VA cohort is a unique cohort that markedly differs from other cohorts in that patients were generally older, predominately male (97%), and had a much higher prevalence of comorbidities [35]. The analysis of real-world data from the TRIO network of 470 patients receiving elbasvir/grazoprevir-based regimens reported a per protocol SVR12 rate in GT1a patients of 99% (259/262) [36]. Other real-world studies of elbasvir/grazoprevir-based regimens have shown modified ITT SVR12 rates of 97.7% in GT1a patients [41]. Altogether, our results add to the accumulating real-world evidence confirming the effectiveness of elbasvir/grazoprevir-based regimens in GT1a-infected patients in daily clinical practice.

Despite smaller patient numbers in this study compared to others, the strength of this cohort is the low number of missing data. Of 195 patients, only 7 (4%) did not have SVR12 results, due to lost-to-follow-up or noncompliance, compared to 18% (VA) and 10% (TRIO) of missing data in other studies [35,36].

There are certain limitations of real-world data collections: Resistance testing, laboratory data, comorbidities as well as reasons for treatment discontinuations may have been under-reported at the time of analysis. Also, a misclassification bias regarding diagnoses and assessment of comorbidities may exist. Further on, sample sizes were low for some subgroups (i.e. elbasvir/grazoprevir+ribavirin for 16 weeks, patients with proven NS5A RAS) and larger study populations are needed to determine more robust results. Since this analysis focuses only on GT1a patients undergoing elbasvir/grazoprevir-based treatment, the patient population does not entirely reflect the current German landscape.

Compared to former IFN-based treatment the tolerability of all-oral DAA regimens regimes has improved dramatically [42]. In general, within the DHC-R discontinuation rates due to adverse events were low [34], which is in alignment with has been observed for elbasvir/grazoprevir in the clinical study program [20,26–31].

In conclusion, this analysis of data from the German real-world registry provides evidence that in daily clinical practice, elbasvir/grazoprevir ± ribavirin regimens are effective treatment options for patients with chronic HCV GT1a infection. In German routine clinical practice, most patients received elbasvir/grazoprevir without ribavirin. The addition of ribavirin was mainly restricted to GT1a patients with high BVL >800 000 IU/mL that was not tested for NS5A RAS or had NS5A RAS present as recommended by German guidelines. Nearly half of GT1a-infected patients with high BVL were tested for NS5A RAS at baseline. Therapeutically relevant NS5A RASs were detected in only 7.7% of patients. Treatment with elbasvir/grazoprevir ± ribavirin achieved consistently high rates of SVR12 that were comparable to those observed in randomized controlled trials.

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Conflicts of interest

H.H.: sponsored lectures (National or International): MSD Sharp & Dohme GmbH

A.S., consultant: AbbVie and ViiV; Sponsored lectures (National or International): AbbVie, Gilead, Janssen and MSD. M.C.: sponsored lectures (National or International): AbbVie, Falk Foundation e.V., Gilead, MSD, Siemens Healthcare; Advisory board: AbbVie, MSD, Spring Bank Pharma. H.K.: Grants: Abbvie, BMS, Gilead, Janssen, MSD; Sponsored lectures (National or International): AbbVie, BMS, Gilead, Janssen, MSD; Advisory board: AbbVie, BMS, Gilead, Hexal, Janssen and MSD. R.H.: sponsored lectures (National or International) Abbvie, Falk and MSD. C.J.: None declared. K.-G.S.: sponsored lectures (National or International): AbbVie, FALK, Gilead, MSD; Advisory Committee or Review Panel: AbbVie and MSD. V.G.: employee: MSD Sharp & Dohme GmbH. K.M.: employee: MSD Sharp & Dohme GmbH. V.W.: employee: MSD Sharp & Dohme GmbH. S.Z.: grants: AbbVie, Gilead, Janssen; consultant: AbbVie, Gilead, Janssen; sponsored lectures (National or International): AbbVie, Gilead and Merck/MSD.

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