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Efficacy of 8 weeks elbasvir/grazoprevir regimen for naïve-genotype 1b, HCV infected patients with or without glucose abnormalities: Results of the EGG18 study

Vincenza Calvaruso[a,*], Salvatore Petta[a], Donatella Ferraro[b], Claudia La Mantia[a], Gerlando Gibilaro[a], Giada Reina[a], Velia Chiara Di Maio[c], Anna Licata[d], Francesca Ceccherini-Silberstein[c], Vito Di Marco[a], Antonio Craxì[a]

[a] *GI & Liver Unit, Department of Health Promotion Sciences Maternal and Infantile Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Piazza delle Cliniche n.2, Palermo 90127, Italy*
[b] *Virology Unit, Department of Health Promotion Sciences Maternal and Infantile Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Italy*
[c] *Department of Experimental Medicine, University of Rome Tor Vergata, Rome, Italy*
[d] *Internal Medicine Unit, Department of Health Promotion Sciences Maternal and Infantile Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Italy*

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ABSTRACT

Background and aim: Direct Acting Antivirals(DAAs) achieve the highest rate of sustained viral response(SVR) in patients with genotype-1b(G1b) Hepatitis C virus(HCV) infection. Reducing treatment duration can simplify the management and improve adherence of therapy.
Patients and methods: The study evaluates the efficacy of 8 weeks of elbasvir/grazoprevir regimen in 75 treatment-naïve(TN), G1b patients with mild-moderate fibrosis(Liver Stiffness by Fibroscan® <9.0 kPa). Viral load(VL) has been evaluated by Roche TaqMan RT-PCR(LLOQ<15 IU/ml).
Results: Mean age was 61.0 ± 14.2 years, 44% were male, mean LS by Fibroscan® was 6.1 ± 1.8 kPa. Twenty-eight patients(37.3%) had an HOMA>2.5. Two patients were excluded from analysis(one dropped out and the other one had diagnosed genotype 2c at genotyping by sequencing performed after relapse).
At 8 weeks(EOT), 71 out of 73 patients(97.3%) had undetectable HCV-RNA, while in two cases HCV-RNA was detectable but with VL<15 IU/ml. Both of them achieved SVR. Two G1b patients relapsed at 12 weeks of follow-up, both with baseline VL>800,000 IU/ml and HOMA score 1.3 and 3.8 respectively. Both had undetectable HCV VL at 4th week and at the EOT. Modified intention-to-treat SVR12 for G1b patients was 71/73(97.3%).
Conclusion: In naïve, genotype-1b HCV-infected patients with mild/moderate liver fibrosis, short course of 8 weeks of EBR/GZR appears to achieve high efficacy regardless of features of insulin resistance.

1. Introduction

In the past decade, novel direct acting antivirals (DAAs) have revolutionized the treatment of chronic HCV infection by yielding rates of over 90% sustained virologic response (SVR) in both treatment-naive and experienced patients [1].

Achievement of the World Health Organization (WHO) global target for HCV elimination by 2030 depends on access to low-cost and simplified assessment of stage of liver disease as well as access to effective and simple DAA treatment [2,3].

Genotype 1 was the most common, affecting 44% of patients and subtype 1b is the most common HCV genotype worldwide, accounting for the largest proportion of infections in Europe, Russia, Latin America and Asia [4] which are the countries with low resource and that, more than others countries, need to reduce the costs of antiviral treatment.

The combination of grazoprevir and elbasvir can achieve a very high level of sustained virologic response twelve weeks after the end of the treatment (SVR12) [5-7].

Zeuzem et al. [7] have shown that this combination given for 12 weeks has also a very high efficiency in a large cohort of naive ot experienced patients from 30 different countries. SVR12 rate was 97% and it was independent of age, sex, gender, ethnicity,

* Corresponding author.
E-mail address: vincenza.calvaruso@unipa.it (V. Calvaruso).

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treatment history, viral load, IL28 genotype and cirrhosis. However, they found that NS5A RAS was associated with failure.

In order to achieve a further simplification of antiviral treatment, improve adherence and reduce drug exposure and costs, Abergel et al. [8] conducted a multicenter study reducing treatment duration of grazoprevir/elbasvir at 8 weeks in treatment-naïve patients, with non-severe fibrosis. They enrolled 112 GT1b naive patients with mild fibrosis and by modified intention-to-treat analysis SVR12 was achieved in 109/112 (97%).

The main aims of this Italian phase III study were to: (i) evaluate the efficacy of grazoprevir and elbasvir fixed-dose combination for eight weeks in treatment-naïve, HCV GT1b-Infected patients, with non-severe fibrosis as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR 12); and (ii) evaluate the safety and tolerability of grazoprevir and elbasvir treatment by a clinical evaluation of adverse experiences based on vital signs, physical examinations and standard laboratory tests.

Secondary aims were: to evalutate the clinical variables associated with low response and in particularly the role of insulin resistance.

- to determine the presence of resistance to EBR/GZR before and after cessation of treatment by sequencing the HCV NS3 (considering positions associated with resistance to GZR in genotype 1b: 56, 155, 156, 168) and the NS5A region (considering positions associated with resistance to EBR in genotype 1b: 28, 31 and 93) with homemade protocols by using Sanger method [9-11].

Genotypic resistance testing was evaluated at baseline and at relapse only for patients not achieving SVR12.

2. Patients and methods

2.1. Study design

EGG-18 was a phase III monocenter open-label study initiated on september 2018, at Gastronterology and Hepatology Unit of University of Palermo in Italy. The study was approved by the ethical committee (Comitato Etico Palermo 1) on March 23, 2018 and met the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provides written informed consent. The EudraCT Number is 2017–003,710–58. Treatment naïve adults with a chronic HCVGT1b infection, non-severe fibrosis and detectable and quantificable plasma HCV RNA at screening were eligible for inclusion. Non severe fibrosis ($F < 2$) was defined according to non-invasive test: Fibroscan® lower than 9.0 kPa at screening or between screening and Day one. Exclusion criteria included hepatic decompensation, liver disease of non-HCV etiology, infection with HCV non-GT1b, active hepatitis B or human immunodeficiency virus, and significant laboratory abnormalities or presence of other clinically significant disease. Patients were also excluded if they had previously been treated for chronic HCV infection. The study consisted of eight weeks of treatment with fixed dose grazoprevir (100 mg – second generation protease inhibitor) in combination with elbasvir (50 mg – NS5A inhibitor). Patients were followed until 12 weeks after end of treatment (EOT).

Blood samples for HCV RNA level determination were collected within one month before baseline, repeated ad baseline, weeks four, eight (end of therapy-EOT) and weeks 12 of follow-up. HCV RNA was measured using local laboratories tests. The method used was Real time PCR Cobas TaqMan (Roche) (lower limit of quantification: 15 UI/mL) [12]. Patients were selected according a genotyping performed within the previous three months before therapy.

Seventy-five patients were enrolled, laboratory (hematology, biochemistry) tests were done in local laboratories. Vital signs and physical examination were performed regularly during treatment and follow-up. Adverse events were monitored throughout the study and up to 12 weeks after planned EOT.

Table 1
Clinical and laboratory features of 75 patients with mild chronic hepatitis from HCV Genotype 1b treated with grazoprevir/elbasvir.

	75 patients
Age (years)	61.0 ± 14.2
Gender – M (%)	33 (44)
AST (U/L)	37.5 ± 27.3
ALT (U/L)	51.0 ± 39.9
GGT (U/L)	36.3 ± 28.8
PLT (x 109)	235.7 ± 55.4
Bilirubin (mg/dl)	0.5 ± 0.5
Albumin (g/dl)	4.3 ± 0.4
INR	1.0 ± 0.2
APRI score	0.5 ± 0.4
FIB 4 score	1.2 ± 0.7
HOMA score > 2.5 (%)	28 (37.3)
TE Liver (kPA)	6.1 ± 1.8
Diabetes (%)	5 (6.7)
HCV RNA > 800.000 IU/ml (%)	48 (64)
HCV RNA > 1.500.000 IU/ml (%)	30 (40)

2.2. Statistical analysis

Data were analyzed with the SPSS statistical package (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Data for continuous variables are presented as mean and SD or as median and range, and data for categorical variables as frequency and percentage. Differences between continuous data were analyzed by Student t-test, and Yate's continuity correction to c2 was used for dichotomous or categorical variables.

Univariate and multivariate logistic regression analysis were used to identify baseline variables, such as age, sex, HCV viral load, diagnosis of diabetes, HOMA score, bilirubin, albumin, INR, platelets values associated with SVR.

Variables with a threshold value of <0.10 at univariate analysis were included in the multivariate model, and variables in the final model with a P value of <0.05 were considered statistically significant. The results are expressed as odd ratio (HR) and their 95% confidence intervals (CI).

2.3. Role of the funding source

The study was supported in part by a research grant from Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp & Dohme Corp."

Vironet C foundation granted the RAS evaluation.

3. Results

As shown in Table 1, the mean age of the 75 participants was 61.0 years (SD, 14.2), and 33 (44%) were male. All patients were naive for previous antiviral therapy and had a diagnosis of mild chronic hepatitis. The mean liver stiffness value was 6.1 kPa (SD 1.8). Forty-eight patients (64%) had a baseline HCV RNA higher than 800.000 IU/ml.

Only 5 patients (6.7%) had a diagnosis of diabetes but HOMA score was higher than 2.5 in 28 (37.3%) of patients. Only 5 patients had a diagnosis of arterial hypertension (6.7%) and only 1 patient had a chronic kidney disease (Stage 5 eGFR < 15 mL/min/1.73 m2). This female patient completed 12 weeks of EBR/GZR therapy and achieved SVR.

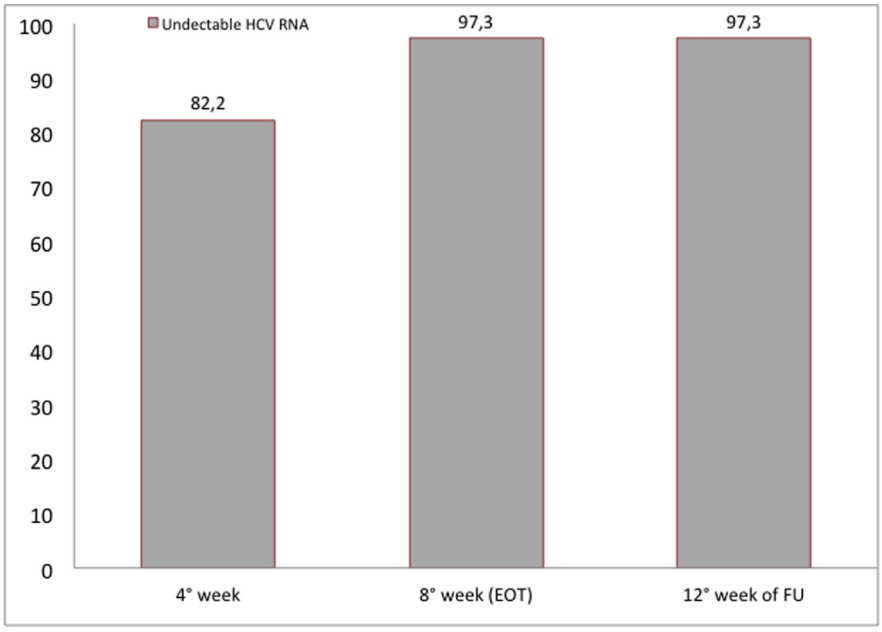

Fig. 1. Viral outcomes rate in patients with mild chronic hepatitis from HCV Genotype 1b treated with elbasvir/grazoprevir for 8 weeks (Per Protocol analysis).

3.1. EBR/GRZ therapy efficacy

Seventy-one patients achieved SVR 12 on 74 patients who completed the 8 regimen treatment and follow up. One patient dropped out one week after starting therapy for poor compliance unrelated to an adverse event. One among the three patients who experienced an HCV relapse at 12° weeks of follow up was infected with a genotype 2c although he was previously classified as GT1b and therefore was excluded from the analysis.

As shown in Fig. 1, SVR was achieved by 97.3% patients on EBR/GRZ therapy.

At 4° and at 8° weeks of therapy (EOT), 60/73 patients (82.2%) and 71/73 (97.3%) had an undetectable HCV viral load (Fig. 1). Indeed two patients had a detectable but not quantifiable HCV RNA at the EOT. Both of them achieved SVR at 12° week of follow up.

Two patients, one male of 85 years old and one female of 56 years old, relapsed after 12 weeks of follow up, both had a baseline viral load higher than 800,000 IU/ml (3,660,000; 1,190,000 respectively). The male patients had an HOMA score of 1.3 and LS of 5.7 kPa. The female patient had insuline resistance as indicated by an HOMA score of 3.8 and her LS was 6.1 kPa. In both of them HCV viral load was undetectable at 4th week and at the end of therapy. Both were adherent to the study drug. Characteristics of these patients are presented in Table 2.

Table 2
Characteristics of patients who relapsed after a treatment with grazoprevir-elbasvir for eight weeks.

	Patient 1	Patient 2
Gender	M	F
Age	85	56
BMI	25	29
Baseline ALT	2 x N	4 x N
Baseline GGT	1 x n	1.5 x N
HBcAb	yes	no
Baseline HCV RNA	3,660,000	1,190,000
NS3 RAS at baseline	None	N.A.
NS5A RAS at baseline	N.A.	N.A.
Liver stiffness by Fibroscan	5,7	6,1
Diabetes	no	no
HCV RNA at failure	916,000	261,000
NS3 RAS at failure	N.A.	T54S
NS5A RAS at failure	N.A.	L328M+Y93H
NS5B RAS at failure	N.A.	L159F+C316N

3.2. RAS (resistance associated substitutions) evaluation in patients who failed EBR/GRZ treatment

HCV resistance testing at failure was available for 1 out of 2 genotype 1b relapsed patients. This female patient showed no RAS (resistance associated substitutions) in NS3 and the NS5A RAS pattern L328M+Y93H. Unfortunately, a baseline sample was not available for the resistance testing and therefore was not possible evaluate if one or both these NS5A RASs could be naturally present before treatment.

The third patient who failed therapy, previously classified as GT1b, was diagnosed as GT2c after a relapse both on baseline and follow up samples. He showed the F28C polymorphism in NS5A (already present in baseline sample), while no RASs were detected in NS3.

All patients were retreated with sofosbuvir-voxilaprevir-velpatasvir for 12 weeks. The first G1b patient achieved SVR12, the other one and the G2c patient are not yet completed the 12°weeks of follow up.

3.3. Clinical predictors of viral response

We looked for effect of the insulin resistance calculated by HOMA score as predictor of viral failure but neither HOMA score than other clinical variables analysed were significantly associated with viral response according to logistic regression analysis. (Table 3).

3.4. Tolerability of elbasvir/grazoprevir therapy

Adverse events of any grade were reported only in 4 patients (5.3%) during EBR/GZR therapy, in three cases mild headache and

Table 3
Evaluation of potential predictors of viral response by logistic regression analysis.

Variable	Univariate logistic regression analysis	
	OR CI95%	p value
Age	0.93 (0.83 – 1.04)	0.21
Gender	2.73 (0.24 – 31.55)	0.42
Baseline HCV RNA	0.99 (0.98 – 1.03)	0.77
HCV RNA > 800.000 IU/ml	–	0.99
HCV RNA > 1.500.000 IU/ml	2.93 (0.25 –33.87)	0.39
Liver stiffness by Fibroscan	0.66 (0.27 – 1.62)	0.36
HOMA score	1.38 (0.51 – 3.73)	0.52

fatigue were reported and one patients experienced mild itching which appears almost at the end of the therapy.

Nonetheless, no subject withdraw from EBZ/GZR therapy because of the symptoms. The unique patient who stopped antiviral therapy within the first week in our study, did not report any symptoms.

4. Discussion

The challenge for HCV elimination programs which is one of the main objectives of WHO by 2030, is the improvement of the linkage to care and the simplification of antiviral therapy by shortening therapy and reduction of clinic visits.

With this study we clearly confirm that eight weeks of treatment with Grazoprevir and Elbasvir has a very high efficacy in naive patients with genotype 1b infection and mild fibrosis. SVR12 was obtained in 97.3% of the patients by modified intention to treat analysis. These results are very similar to the SVR12 obtained in patients treated with grazoprevir and elbasvir for eight weeks in the Abergel study [8] and also to the SVR12 obtained with the recommended regimen of the same combination for 12 weeks [1,7].

Moreover, the SVR12 rate is similar to the one obtained by the regimen of 8 weeks of glecaprevir and pibrentasvir combination [13] which obtained an SVR 12 rate of 98% in non cirrhotic patients with genotype 1 even if SVR rate of patients with genotype 1b has not been reported.

The very high SVR rate to antiviral treatment hampers the possibility to predict of treatment failure. For the first time to our knowledge, in our study we wanted to assess, the potential role of insulin resistance on the efficacy of the grazoprevir/elbasvir combination used for 8 weeks in a setting of mild fibrosis. We did not found a relationship between HOMA score and viral response. Also the baseline viral load was not related with SVR in our study. By contrast, Huang et al. in EGALITE study [14] founded that high viral load > 1.5 million IU/mL was related with low SVR rate and in the STREAGER phase III study [8] patients with baseline viral load higher than 1.5 milion IU/ml had a lower rate of SVR 12.

Another potential predictor could be the presence of baseline RASs, particularly Y93H in NS5A. Indeed, all patients with virologic relapse in Abergel study [8] had an NS5A Y93H RAS, before and after treatment. Also in the Egalite study the presence of Y93H before treatment was associated with a lower SVR [14].

Unfortunately, in our study baseline presence of NS5A RASs was not evaluated.

Resistance test was available at failure for 2 out 3 relapsers. In particular, one was found to be infected with a GT2c, so in this case the “misclassification” was probably the main reason of the virologic failure. The other patient, showed at failure the NS5A RAS Y93H in association with L28M. The Y93H alone confers high level of resistance to elbasvir (fold change=67) while L28M alone confers only a low level of resistance (fold change=3.3). No data are available regarding the effect of the pattern on elbasvir efficacy but could be presumably greater than that given by Y93H alone. The natural frequencies of these RASs in GT1b Italian patients is around 10% for Y93H and 3.4% for L28M [15] so we can’t exclude that at least one of them could be already present at baseline before starting treatment, and may have contributed to the therapeutic failure.

Interestingly, this patient had at failure also in NS3 the polymorphism T54S associated with low level resistance to asunaprevir, boceprevir and telaprevir [16] and in the NS5B other 2 frequent polymorphisms associated in GT1b with low level-resistance to dasabuvir and sofosbuvir (L159F and C316N) [16].

Our experience further confirmed that the grazoprevir-elbasvir combination has a very low frequency of side effects and of drug to drug interactions (DDI) [17]. No patients reported SAE and dropped out due to side effects. As well as other combinations the regimen is very simple and account for 1 pills a day. All these features would allow the reducing of clinical visits, patients could started therapy after the lab evaluation with virological profile and the liver stiffness and can repeat the viral load at 12° week of follow up to confirm the SVR.

It’is still necessary perform a genotype before to start the treatment, however the cost of the genotype is very affordable and can be broadly performed also in lower income countries. On the other hand, the price of grazoprevir/elbasvir for 8 weeks could be very competitive compared to other combinations.

In conclusion, we can confirm that in naïve, genotype 1b HCV infected patients with mild or moderate liver fibrosis, short course of 8 weeks of EBR/GZR appears to achieve high efficacy regardless of features of insulin resistance and that this simple regimen achieves an optimal SVR rate in this setting maintaining an excellent safety profile.

Declaration of Competing Interest

VC: Travel Grant, Speaking, and Participation to Advisory Boards for: AbbVie, Gilead Sciences and Intercept. Grant and research support: MSD

SP: Travel Grant, Speaking, and Participation to Advisory Boards for: AbbVie, Gilead Sciences and Intercept.

VDM received research support from Abbvie, Gilead, Intercept and Merck/MSD and served on the advisory boards of Abbvie, Gilead and MSD/Merck.

FCS: Research grants, travel grant, lecturing fees, advisory boards, scientific consultancy for Abbvie, Gilead Sciences, Janssen, MSD, ViiV

AC: Research grants, lecturing fees, advisory boards, scientific consultancy for Abbvie, Gilead Sciences, BMS, MSD, Intercept.

The other authors have no disclosures to declare.

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