Real life data on elbasvir/grazoprevir efficacy, safety and drug-drug interaction profile in patients with chronic hepatitis C viral infection: a prospective analysis in the PITER cohort

M.G. Quaranta[1], S. Rosato[1], L. Ferrigno[1], D.C. Amoruso[2], M. Monti[3], P. Di Stefano[4], R. Filomia[5], F. Tamburini[6], G. Migliorino[7], A. Zanetto[8], E. Degasperi[9], L. Cavalletto[10], G. Brancaccio[11], P. Blanc[12], M. Cannizzaro[13], E. Castelli[14], G. Morsica[15], A. Licata[16], L.A. Kondili[1]
on behalf of PITER collaborating group

[1]Istituto Superiore di Sanità, Rome; [2]Gragnano Hospital, Naples; [3]University of Florence; [4]Pescara General Hospital; [5]University Hospital of Messina; [6]Policlinico Umberto I, Sapienza University of Rome; [7]San Gerardo Hospital, Monza; [8]University Hospital of Padua; [9]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano; [10]University of Padua; [11]Università della Campania Luigi Vanvitelli, Naples; [12]S.M. Annunziata Hospital, Florence; [13]Villa Sofia-Cervello Hospital, Palermo; [14]University Hospital of Padua; [15]IRCCS, Ospedale San Raffaele, Milan; [16]University of Palermo

BACKGROUND & AIM

In a previous real life study, based on data retrieved by the PITER cohort, it was reported that of HCV chronic infected patients, undergoing direct acting antiviral (DAA) therapy (sofosbuvir-based or paritaprevir/ritonavir, ombitasvir and dasabuvir) and taking comedications, 30% (with mild liver disease stage) and 44% (with moderate to severe liver disease stage), were at risk of potential drug-drug interactions (DDI). Following the recent introduction of Elbasvir/Grazoprevir (EBR/GZR) we aimed to evaluate the prospective profile of efficacy and safety combined with real life comedication profile used at the beginning, during and at the end of the DAA therapy in each of treated patient.

METHODS

The study was prospective in design and was conducted among patients attending 15 clinical centers involved in PITER (Italian Platform for the Study of Therapies for Viral Hepatitis). For the purpose of the present study, we retrieved all consecutive patients treated with EBR/GZR since its first use in Italy and who reached the 12-week post-treatment HCV RNA evaluation until June 2018. Each patient's data included complete prospective efficacy comedication profile from the beginning, during and at the time of the virological response at 12 weeks following the end of DAA therapy. Patients with severe liver disease (Child Pugh B and C) were excluded in that treatment with EBR/GZR is not indicated in these patients. Changes from baseline in transaminase and bilirubin levels as well as stiffness values were assessed at week 12 after treatment.

Statistical Analysis. Differences among the proportions were evaluated by chi-square or Fisher test, as appropriate, whereas the Student test was used for continuous variables. A P-value of less than 0.05 was considered as significant.
The crude odds ratios (OR) that link HCV treatment failure to potential risk factors (age, gender, Child-Pugh class, HCV RNA genotype, previous IFN-based treatment, presence of cirrhosis versus F3 fibrosis stage, the use of ribavirin and the comedications used) were calculated by univariate analysis.

Adjusted ORs were calculated by multiple logistic regression analysis to identify variables that were independently associated with failure. The reference category for OR estimates was that of the most favorable levels of exposure.

Assessment of comedications. Potential DDIs of drugs that were recorded in the comedication list of the eCRF of the treated patients, those that were added or removed by the list of comedications during the antiviral therapy were assessed and classified based on information available at www.hep-druginteractions.org.
Specifically, the potential DDIs for the EBR/GZR regimen and each drug used as comedication were assigned to four different risk categories:
Category 0: Classification not possible due to lack of information
Category 1: No clinical interaction possible
Category 2: May require dose adjustment/closer monitoring
Category 3: Co-administration not recommended or contraindicated
Consecutively, the profile of the comedications changed (added or removed) were evaluated according to the risk categories assigned in order to define if the changes were required due to a specific risk category. The reason for changes in the comedication profile was then evaluated considering also the clinicians notes for each change.

RESULTS

From January 2017 to December 2018, 365 patients with chronic HCV infection consecutively enrolled in the PITER platform of whom 298 (71.6%) with Gt 1b, 39 (10.7%) Gt 1a, and the remaining 28 (7.6%) Gt 4, underwent treatment with ELB/GZR with or without ribavirin. Demographic and clinical characteristics of the treated patients, according to the fibrosis stage, are reported in **Table 1**.

Fibrosis Stage	N	Age Mean (SD)	Gender M/F (%)	Ribavirin used N (%)	IFN experienced/ DAA experienced	NR/ total (%failure)	Stiffness in those who achieved SVR 12		
						Total evaluated 338 patients	Pre-treatment Mean (SD)	Post-treatment Mean (SD)	p
F0/F1	192	60 (12)	81/111 (42%/58%)	32 (17)	61 (32%)	6/185 (3.2%)	5.0 (0.9)	5.5 (2.1)	
F2	77	65 (11)	32/45 (42%/58%)	13 (17)	27 (35)	5/72 (6.9%)	7.6 (0.6)	6.6 (2.0)	<0.05
F3	42	66 (13)	21/21 (50%/50%)	5 (12)	12 (29)	4/34 (11.7%)	9.2 (2.4)	8.4 (3.6)	<0.05
F4 (Child A)	54	67 (13)	32/22 (59%/41%)	7 (13)	20 (37)	3/47 (6.4%)	16.1 (3.6)	10.3 (5.4)	<0.05
Total	365	65 (12)	153/187 (45%/55%)	57 (16)	120 (33)	17/338 (5%)	16.1 (3.6)	10.7 (5.6)	<0.05

Table 1.

According to the logistic regression analysis, female gender and previous IFN-based treatment were independent factors of failure (**Table 2**).

Variables	Crude OR	CI 95%	Adjusted OR	CI95%
Age	1	0.95-1.2	1	0.9-1
Gender (F/M)	3	0.97-1.02	4.1	1.2-14.1
Alcohol use (Yes/No)	1.1	0.4-2.9	0.7	0.2-2
Genotype 1b vs 1a	0.8	0.2-3.7	0.9	0.1-5.6
Genotype 4 vs 1a	1.7	0.4-8.1	1.4	0.2-8.1
Cirrhosis vs F1-F3 Fibrosis	1.9	0.3-4.6	1.4	0.1-5.4
Previous Interferon based treatment: Yes/No	2.5	0.9-6.4	3	1.1-8.8
Ribavirin use. Yes/No	0.8	0.1-6.6	0.6	0.1-7.4
Concomitant drug use:Yes/No	0.7	0.3-1.9	1	0.4-3.1

Table 2.

During the follow-up evaluation (mean follow up time 6.1; SD 4.6 months) significant decreases of ALT levels were observed between pre-treatment (mean ALT values: 55 SD: 36) and post-treatment (mean ALT values 24; SD 11) ($p<0.05$) in all but two patients who achieved SVR without differences in those younger and older than 65 years of age and gender. Significant decrease of stiffness values were observed in patients who achieved the SVR in each of fibrosis stage from F2 to F4 (**Table 1**).

Regarding the comorbidities (**Table 3**), of 365 patients evaluated 218 (60%) had at least one comorbidity The presence of comorbidities is similarly distributed in each fibrosis stage, whereas more than 3 comorbidities are more frequently presented in fibrosis stage 4 (15%) compared to the other fibrosis stages from F0 to F3 (9-10%) though not reaching significance level (p=0.6).
Regarding the comedications used (**Table 3**), 774 were (190 overall drugs used) used by 212 patients; 39 (72%) patients with F4/cirrhosis compared to 173 (60%) patients in the fibrosis stage F0-F3 (p=0.09) received comedications during the DAA therapy.
The use of 1-2 comedications was similarly distributed among F0-F3 fibrosis stages, whereas more than 3 comedications (up to 15) was more frequently observed in the F4/cirrhosis stage (48%) (p=0.03).
Of 190 drugs used, 28 (15%) were added as new drugs during the antiviral therapy.
Of them, none has been reported to have potential DDI, but Atorvastatin and Simvastatin added in 4 (1.9%) patients have been defined as "*Category 2: monitoring required" for* potential DDI. Eight drugs (3.7%) were interrupted and 10 (4.7%) were modified as dosage, none of changes related to a potential DDI.

Comorbidities	Total	F0-F1	F2	F3	F4/Child A cirrhosis
N. patients (%)	365	192	77	42	54
None	147 (40%)	82 (43%)	27 (35%)	20 (48%)	18 (33%)
1-2	182 (50%)	93 (48%)	43 (56%)	18 (43%)	28 (52%)
≥3	36 (10%)	17 (9%)	7 (9%)	4 (10%)	8 (15%)
Comedications* N patient (%)	343	187	67	35	54
None	131 (38%)	76 (41%)	26 (39%)	14 (40%)	15 (28%)
1-2	90 (26%)	51 (27%)	18 (27%)	8 (23%)	13 (24%)
≥3	122 (36%)	60 (33%)	23 (34%)	13 (37%)	26 (48%)

Table 3. *22 patients had no available information about comedications potentially used. The analysis of comedications used was performed for 343 patients

CONCLUSION

EBR/GZR demonstrated high cure rates and a very good safety profile. No drug-drug interactions were recorded in this real life cohort of treated patients with different comorbidities and comedications used.

ACKNOWLEDGEMENTS

Authors wish to thank PITER collaborating group and all the clinical centers (available at www.progettopiter.it) which are involved in the study on a voluntary basis and Giampaolo La Terza (Medisoft Informatic Services) for Database maintainance and implementation

REFERENCES

LA Kondili, S Vella and PITER Collaborating Group. PITER: An ongoing nationwide study on the real-life impact of direct acting antiviral based treatment for chronic hepatitis C in Italy. *Digestive and Liver Disease*. 2015; 47:741-743
LA Kondili et al. Real-life data on potential drug-drug interactions in patients with chronic Hepatitis C viral infection undergoing antiviral therapy with Interferon-free DAAs in the PITER Cohort Study. PLoS One. 2017; 12: e0172159. doi: 10.1371/journal.pone.0172159

CONTACT INFORMATION

Loreta Kondili: loreta.kondili@iss.it

Fibrosis Stage	N. of patients	Age Mean (SD)	Gender M/F (%)	Ribavirin used N (%)	Previous IFN experienced N (%)	NR/ total evaluated (% of failure)	Stiffness in those who achieved SVR 12*		
							Pre-treatment Mean (SD)	Post-treatment Mean (SD)	p
F0/F1	192 (52.6)	60 (12)	81/111 (42/58)	32 (17)	61 (32)	6/185 (3.2)	5.0 (0.9)	5.5 (2.1)	
F2	77 (21.1)	65 (11)	32/45 (42/58)	13 (17)	27 (35)	5/72 (6.9)	7.6 (0.6)	6.6 (2.0)	<0.05
F3	42 (11.5)	66 (13)	21/21 (50/50)	5 (12)	12 (29)	4/34 (11.7)	9.2 (2.4)	8.4 (3.6)	<0.05
F4 (Child A)	54 (14.8)	67 (13)	32/22 (59/41)	7 (13)	20 (37)	3/47 (6.4)	16.1 (3.6)	10.3 (5.4)	<0.05
Total	365	65 (12)	153/187 (45/55)	57 (16)	120 (33)	18/338 (5)	16.1 (3.6)	10.7 (5.6)	<0.05