JHEP|Reports

Reply to: "Unlocking hope: HCV re-treatment strategy for patients with active hepatocellular carcinoma"

To the Editor:

We thank Shah *et al.*[1] for their interest in our study and for presenting additional data on rescue treatment with glecaprevir/pibrentasvir and sofosbuvir with or without ribavirin (G/P+SOF±RBV) in patients with chronic hepatitis C failing re-treatment with voxilaprevir/velpatasvir/sofosbuvir (VOX/VEL/SOF).

So far, only case reports have been published on re-treatment in patients with failure on VOX/VEL/SOF rescue therapy. Thus, data on G/P+SOF±RBV and other treatment regimens as third-line therapy are still scarce.[2–4] In a phase II trial, which evaluated the use of G/P+SOF±RBV as second-line therapy in patients with prior G/P failure, the sustained virologic response (SVR) rate was high (95%), demonstrating the high effectiveness of this regimen.[5] Accordingly, EASL as well as AASLD guidelines recommend treatment with the G/P+SOF±RBV combination not only as third-line therapy after failing the triple combination with VOX/VEL/SOF but also as second-line treatment option in difficult-to-treat patients.[6,7]

In line with data reported by Shah *et al.*, we also observed excellent SVR rates in difficult-to-treat patients receiving G/P+SOF±RBV as third-line rescue treatment. We are pleased to now be able to present an update on the outcome of patients failing re-treatment with VOX/VEL/SOF in our study including an extended analysis of patients receiving G/P+SOF±RBV as rescue treatment. In our published work, 11 patients were retreated after failure on VOX/VEL/SOF±RBV, 10 of whom had an available follow-up 12 weeks after the end of treatment. We have now identified four further patients who were retreated after failing VOX/VEL/SOF therapy. Three patients were retreated with G/P+SOF over 12 to 24 weeks: one of these patients was lost-to-follow-up (LTFU) after the end of treatment, the other two patients achieved SVR12. Both of these patients carried difficult-to-treat cofactors: one patient suffered from Child-Pugh A cirrhosis, the other patient had multiple (≥3) failures on prior HCV therapies. In addition, one further patient with treatment failure to VEL/SOF and VOX/VEL/SOF in the first- and second-line was retreated with G/P over 12 weeks and achieved an SVR12. The overall updated PP-SVR rate on rescue therapy now is 92.9% (n = 13/14). Of the 13 patients who received G/P+SOF±RBV for 12-24 weeks and had an available follow-up 12 weeks after the end of treatment, the updated PP-SVR rate is 100% (n = 13/13; Fig. 1).

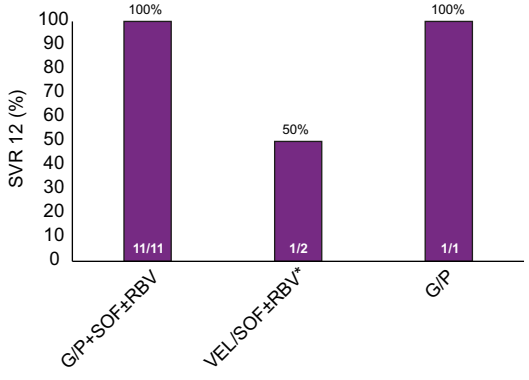

Fig. 1. Efficacy of third-line rescue treatment after VOX/VEL/SOF failure. Overall SVR: 93% (n = 14 patients with final treatment outcome). *n = 1 patient with post-treatment relapse. G/P, glecaprevir/pibrentasvir; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; VOX, voxilaprevir.

The study conducted by Shah *et al.* investigated three patients with a VOX/VEL/SOF treatment failure, all of whom were retreated with G/P+SOF±RBV and achieved an SVR12. All of these patients carried several difficult-to-treat cofactors such as Child-Pugh A cirrhosis, HCV genotype 3a and HCC. Accordingly, our data demonstrate that G/P+SOF is effective and safe in patients with difficult-to-treat cofactors, including HCC (n = 5), cirrhosis (n = 8) and genotype 3 (n = 9), and treatment failure on VOX/VEL/SOF. One potential reason for this observation may be that pibrentasvir has a higher barrier to resistance than all other approved NS5A inhibitors *in vitro*. Thus, the triple combination could offer an interesting alternative for retreating patients with difficult-to-treat cofactors. These observations could be confirmed by a further analysis that included a subgroup of our cohort: in this study, a total of 13 patients received rescue therapy with G/P+SOF over 12-24 weeks and had an available follow-up 23 weeks after the end of treatment.[3] Except for one patient who experienced a post-treatment relapse, all other 12 patients achieved an SVR12 (PP-SVR: 92.3%).

All these results imply that G/P+SOF may be a more effective retreatment option than VOX/VEL/SOF. However, due to the limited number of cases, it cannot currently be proven whether G/P+SOF is actually more effective than VOX/VEL/SOF. Furthermore, our data demonstrate that VOX/VEL/SOF is also highly effective in difficult-to-treat subgroups, especially when ribavirin is added. In our published study cohort, subgroups of patients with GT3, cirrhosis and HCC benefited from the addition of RBV, with considerably higher SVR rates compared to those without RBV (100% *vs.* 90%, 93% *vs.* 91%, 90% *vs.* 84%, respectively). However, the effects of RBV were not found to be significant in these difficult-to-treat subgroups, probably due to the small number of cases.

We can therefore conclude that, based on our data and the data from Shah *et al.*, G/P+SOF is an effective third-line therapy for patients with difficult-to-treat cofactors failing treatment with VOX/VEL/SOF. However, whether G/P+SOF±RBV is a more effective alternative second-line therapy in difficult-to-treat subgroups such as those with HCC, cirrhosis or genotype 3 infection cannot be proven based on the current data Thus, further studies are warranted to clarify this issue.

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Conflict of interest

PD Dr. C. Graf: travel support from Gilead and speaking fees from Abbvie outside the submitted work. PD Dr. J. Dietz: research support from Gilead outside the submitted work. Prof. Dr. C. Sarrazin: Speaking and/or consulting fees: AbbVie, BMS, Gilead, Merck/MSD. Research support: Abbvie, Gilead.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Data collection was performed by JD. Analysis and interpretation of data was performed by CG, JD and CS. Draft of the manuscript was written by CG. CS and JD provided critical revision of the manuscript.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101197.

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