Anti-epileptic drugs and hepatitis C therapy: Real-world experience

To the Editor:
The latest update of the EASL recommendations for HCV treatment provides invaluable information to guide attempts at achieving the WHO goal of elimination. Direct-acting antivirals (DAAs) have significantly improved treatment of HCV infection, and almost all patients receiving these drugs achieve sustained virological response (SVR). However, there is still a niche of individuals with HCV who cannot be treated because of drug-drug interactions (DDIs), one of the few remaining impediments to DAA use. DDIs with antiseizure medication (ASM) are especially important, as clinical experience has shown that in some cases these drugs cannot be discontinued or replaced by others during HCV therapy.

Antiseizure drugs (e.g., phenytoin, carbamazepine, oxcarbazepine, phenobarbital, eslicarbazepine) are potent CYP/P-gp-inducing agents that can significantly reduce plasma DAA concentrations and increase the risk of treatment failure. Some ASMs are not only used as antiseizure agents but also as psychotropic drugs, often prescribed in patients with psychiatric and substance use disorders, recognized as difficult-to-treat populations. Patients who are receiving ASMs and cannot switch therapy remain problematic; hence, this situation is an obstacle to DAA therapy that must be improved.

To date, there is little real-life information evaluating these interactions. Seyen et al. presented a case series including 6 patients who remained on ASMs while being treated with daclatasvir and sofosbuvir, with an increase in the standard daclatasvir dose. The authors found that daclatasvir and sofosbuvir plasma concentrations were both decreased, to a degree dependent on the dosing strategy and concomitant ASMs. All patients achieved SVR. Another case series included 5 patients who achieved SVR after being treated with standard-dose DAAs while continuing ASMs.

This is a description of 5 patients with chronic HCV infection receiving ASMs who were treated with DAAs even though co-administration of these drugs is not recommended due to potential DDIs (Table 1). All patients achieved an end-of-treatment response and SVR12. No adverse events or required dose modifications were reported.

Patient 1 was a 40-year-old man on treatment with oxcarbazepine 300 mg BID for a psychotic and personality disorder. The attending psychiatrist deemed that treatment discontinuation was not feasible, as the patient's condition was extremely labile. Concomitant medications: clorazepate 50 mg daily, clozapine 60 mg daily, levetiracetam 500 mg BID, and zuclopenthixol 25 mg QID.

Patient 2 was a 39-year-old man on treatment with oxcarbazepine 600 mg TID for epilepsy. The neurologist attempted a switch from oxcarbazepine to levetiracetam to avoid interactions with DAAs, but 1 week later the patient experienced several complex seizures; hence, oxcarbazepine was re-started. No concomitant medications.

Patient 3 was a 54-year-old man on treatment with phenytoin 100 mg BID for epilepsy. Epilepsy control had been difficult until phenytoin was started, and although the neurologist was willing to change his medication, the patient refused. Concomitant medications: duloxetine 50 mg daily, abacavir 600 mg daily, lamivudine 300 mg daily, and clonazepam 0.5 mg daily.

Patient 4 was a 38-year-old man on treatment with oxcarbazepine 600 mg BID for a psychotic and personality disorder. Again, the attending psychiatrist considered that the patient's labile condition made oxcarbazepine discontinuation unfeasible. Concomitant medications: clonazepam 2 mg TID, paroxetine 20 mg daily, perphenazine 8 mg daily, and quetiapine 200 mg daily.

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, years</th>
<th>ASM Drug and daily dose</th>
<th>ASM indication</th>
<th>HCV GT</th>
<th>HCV RNA levels</th>
<th>HCV cirrhosis</th>
<th>HCV treatment</th>
<th>HCV RNA levels at week 4 of treatment</th>
<th>HCV RNA levels at end of treatment</th>
<th>HCV RNA levels 12 weeks after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>40</td>
<td>Oxcarbazepine 300 mg BID</td>
<td>Psychotropic</td>
<td>1b</td>
<td>10^6</td>
<td>No</td>
<td>GLE/PIB</td>
<td>10-4</td>
<td>Undetectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>39</td>
<td>Oxcarbazepine 600 mg TID</td>
<td>Epilepsy</td>
<td>1b</td>
<td>10^6</td>
<td>No</td>
<td>LPV/SOF</td>
<td>10-1</td>
<td>Undetectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>54</td>
<td>Phenytoin 100 mg BID</td>
<td>Epilepsy</td>
<td>4</td>
<td>10^6</td>
<td>Yes</td>
<td>SOF/VEL</td>
<td>n.a.</td>
<td>Undetectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>38</td>
<td>Oxcarbazepine 600 mg BID</td>
<td>Psychotropic</td>
<td>3</td>
<td>10^6</td>
<td>No</td>
<td>SOF/VEL</td>
<td>n.a.</td>
<td>Undetectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>43</td>
<td>Eslicarbazepine 400 mg TID</td>
<td>Epilepsy</td>
<td>3</td>
<td>10^6</td>
<td>No</td>
<td>GLE/PIB</td>
<td>8 weeks</td>
<td>Undetectable</td>
<td>Undetectable</td>
</tr>
</tbody>
</table>

ASM, antiseizure medication; GT, genotype; BID, twice daily; TID, thrice daily; GLE/PIB, glecaprevir/pibrentasvir; LPV/SOF, ledipasvir/sofosbuvir; SOF/VEL, sofosbuvir/velpatasvir.

Keywords: drug-drug interactions; direct-acting antivirals; hepatitis C virus; antiepileptic drugs.
Received 1 April 2021; received in revised form 25 April 2021; accepted 6 May 2021; available online 11 June 2021
https://doi.org/10.1016/j.jhep.2021.05.040
Patient 5 was a 43-year-old man on treatment with eslicarbazepine 400 mg TID for epilepsy. The neurologist switched eslicarbazepine to brivaracetam to avoid interactions with DAAs, but eslicarbazepine had to be re-started because of adverse events. Concomitant medications: topiramate 75 mg BID, sertindole 100 mg daily, clobazam 25 mg daily, enalapril 20 mg daily, and bisoprolol 5mg daily.

Recent data have shown that polypharmacy and DDIs remain a significant problem even with newer DAAs. One observational retrospective cohort study assessed co-medications and DDIs in 3,181 HCV patients treated with pangenotypic DAAs. With use of the Liverpool University tool, the authors classified DDIs into potential interaction (18.1%), weak interaction (4.8%), or contraindication (1.8%), in all cases related to cardiovascular or central nervous system drugs. They found that 4.2% of patients had to discontinue concomitant drugs during DAA treatment. DDIs force discontinuation of chronic treatments in a considerable percentage of HCV patients, and this is not always possible, especially in those receiving ASMs.

This report has the shortcoming that plasma DAA concentrations and HCV RNA levels were not serially analyzed during therapy, as these are real-life patients and such determinations are not routinely done in this clinical situation.

In conclusion, the cases reported here indicate promising outcomes for HCV treatment in patients receiving ASMs. DDIs, together with the known difficulties related to screening and linkage-to-care in some HCV-infected populations are the main obstacles we have yet to overcome to achieve the WHO HCV elimination goals. Further pharmacokinetic and real-world studies are needed to guide clinicians in HCV treatment for these challenging patients.

Financial support
The authors did not receive any financial support.

Conflict of interest
Cristina Marcos-Fosch has no personal or financial conflicts of interest. Joaquín Cabezas has no personal or financial conflicts of interest. Javier Crespo reports grants and research support from Gilead Sciences, AbbVie, MSD, Shionogi, and Intercept Pharmaceuticals (all outside the submitted study) and is a speaker for Gilead Sciences and AbbVie. No personal conflicts of interest. María Buti has received research grants from Gilead and has served as advisor for Gilead, Bristol-Myers Squibb, and Novartis. No personal conflicts of interest. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors’ contributions
All authors contributed substantially to this letter. Cristina Marcos-Fosch and Joaquin Cabezas contributed equally. Cristina Marcos-Fosch: acquisition of data, analysis and interpretation of data, drafting of the manuscript. Joaquín Cabezas: acquisition of data, analysis and interpretation of data, drafting of the manuscript. Javier Crespo: study concept and design, critical revision of the manuscript, study supervision. María Buti: study concept and design, critical revision of the manuscript, study supervision.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.05.040.

References

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Journal of Hepatology 2021 vol. 75: 984–1012
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