Table 1. Treatment indications in treatment-naïve and treatment-experienced patients (as defined in the recommendations) infected with HCV genotype 3 with compensated cirrhosis according to the availability of HCV resistance testing, as per the 2018 EASL Recommendations on Treatment of Hepatitis C [6].

Patients infected with HCV genotype 3 with compensated cirrhosis				
Availability/ performance of HCV NS5A resistance testing	**Results of HCV NS5A resistance testing***	**Sofosbuvir/velpatasvir-based regimen**		**Glecaprevir/pibrentasvir-based regimen**
		Sofosbuvir/velpatasvir/ voxilaprevir available: apply 2018 EASL recommendations	**Sofosbuvir/velpatasvir/ voxilaprevir not available: apply 2016 EASL recommendations**	**Glecaprevir/pibrentasvir available: apply 2018 EASL recommendations**
Not available/not performed	–	Sofosbuvir/velpatasvir/ voxilaprevir for 12 weeks	Sofosbuvir/velpatasvir plus ribavirin for 12 weeks	Glecaprevir/pibrentasvir for 12 weeks in treatment-naïve or 16 weeks in treatment-experienced patients°
Available and performed	Presence of the Y93H RAS at baseline	Sofosbuvir/velpatasvir/ voxilaprevir for 12 weeks	Sofosbuvir/velpatasvir plus ribavirin for 12 weeks	Glecaprevir/pibrentasvir for 12 weeks in treatment-naïve or 16 weeks in treatment-experienced patients°
	No Y93H RAS at baseline	Sofosbuvir/velpatasvir for 12 weeks	Sofosbuvir/velpatasvir for 12 weeks	Glecaprevir/pibrentasvir for 12 weeks in treatment-naïve or 16 weeks in treatment-experienced patients°

EASL, European Association for the Study of the Liver; RAS, resistance-associated substitution.
* The presence of the NS5A RAS Y93H at baseline is by population sequencing or >15% by deep sequencing.
° Data with 12 weeks of treatment with glecaprevir and pibrentasvir in treatment-experienced patients with cirrhosis are needed.

and most universal treatment indications. EASL acknowledges the depth of detail in the 2018 recommendations: numerous tables and layers of evidence were provided.[6] To clarify, 3 regimens are recommended in the guidelines for the treatment of patients infected with genotype 3: sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, or glecaprevir/pibrentasvir. The indications for genotype 3-infected patients with compensated cirrhosis are summarized in Table 1.

References

[1] Gottwein JM, Pham LV, Mikkelsen LS, Ghanem L, Ramirez S, Scheel TKH, et al. Efficacy of NS5A inhibitors against hepatitis C virus genotypes 1–7 and escape variants. Gastroenterology 2018;154:1435–1448.
[2] Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko S, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med 2015;373:2608–2617.
[3] European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2016. J Hepatol 2017;66:153–194.
[4] Esteban R, Pineda JA, Calleja JL, Casado M, Rodriguez M, Turnes J, et al. Efficacy of sofosbuvir and velpatasvir, with and without ribavirin, in patients with hepatitis C virus genotype 3 infection and cirrhosis. Gastroenterology 2018;155:1120–1127.
[5] Jacobson IM, Lawitz E, Gane EJ, Willems BE, Ruane PJ, Nahass RG, et al. Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials. Gastroenterology 2017;153:113–122.
[6] European Association for the Study of the Liver. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018.. J Hepatol 2018;69:461–511.
[7] Jacobson IM. Does ribavirin still have a role in sofosbuvir and velpatasvir therapy for patients with HCV genotype 3 infection and cirrhosis? Gastroenterology 2018;155:969–971.
[8] von Felden J, Vermehren J, Ingiliz P, Mauss S, Lutz T, Simon KG, et al. High efficacy of sofosbuvir/velpatasvir and impact of baseline resistance-associated substitutions in hepatitis C genotype 3 infection. Aliment Pharmacol Ther 2018;47:1288–1295.

European Association for the Study of the Liver *
*Corresponding author. Address: European Association for the Study of the Liver (EASL), The EASL Building – Home of Hepatology, 7 rue Daubin, CH 1203 Geneva, Switzerland. Tel.: +41 (0) 228070360; fax: +41 (0) 223280724.

Acute liver failure due to immune-mediated hepatitis successfully managed with plasma exchange: New settings call for new treatment strategies?

To the Editor:

We read with great interest the recent article by De Martin *et al.* characterizing the liver injury induced by cancer immunotherapy. Their experience in immune-mediated hepatitis related to checkpoint inhibitors included 16 histologically proven cases after anti-PD-1/PD-L1 or anti-CTLA-4 therapy; in 38%, hepatitis resolved without steroid therapy.[1] However, as illustrated by the case recently reported by Bhave *et al.*, immune-mediated hepatitis can be severe and lead to acute liver failure (ALF), with a poor prognosis despite treatment with high steroid doses plus mycophenolate mofetil (MMF).[2] The oncological context of

Keywords: Immune-mediated hepatitis; Acute liver failure; Plasma exchange; Immunotherapy.

these drugs rules out assessment for liver transplantation in cases associated with ALF. Therefore, new strategies should be explored in this setting. We would be like to add our experience in this line, involving a patient who developed ALF following immunotherapy and survived after receiving combined therapy with immunosuppressant drugs plus plasma exchange.

A 76-year-old woman was admitted to hospital for jaundice. Her medical records included a wild-type BRAF vulvar melanoma, initially treated by surgery with subsequent metastatic relapse (lymph node involvement). In May 2017, she was recruited for a first-line clinical trial including nivolumab (anti-PD1) and a dioxygenase1 inhibitor. After the first dose of nivolumab, she showed grade 2 hepatitis (aspartate aminotransferase [AST] 140 IU/ml [10–35] and alanine aminotransferase [ALT] 138 IU/ml [7–35] with normal bilirubin, gamma glutamyltransferase and alkaline phosphatase) and arthralgia, managed with steroids at a dose of 1 mg/kg/day. The analytical abnormalities normalized and doses were subsequently decreased, without complications. However, after 5 courses of this regimen, she developed progressive disease. Therefore, immunotherapy was changed to ipilimumab (anti-CTLA-4) at a dose of 3 mg/kg every 3 weeks. Twenty days after the second infusion of ipilimumab and with previously normal liver function, she consulted for jaundice. Laboratory findings showed AST at 4,470 IU/ml, ALT 2,530 IU/ml, total bilirubin 7.8 mg/dl (0.3–1.2) (conjugated 5.4), and a prothrombin time (PT) of 30%. The viral hepatitis panel was negative and serum copper and ceruloplasmin were within normal levels. Abdominal ultrasound study showed a normal liver. Moreover, a recent PET (before starting ipilimumab) had shown no melanoma-associated liver involvement. Steroids at 2 mg/kg/day were initiated, and 48 hours later MMF (1.5 g/day) was added, as bilirubin levels had risen to 10.5 mg/dl and PT had decreased to 24%. To confirm the diagnosis of immune-related hepatitis, a transjugular liver biopsy was scheduled, but could not be performed, because the patient developed grade 2 hepatic encephalopathy. As she had metastatic cancer, which made liver transplantation fully contraindicated, and currently there are no clinical recommendations or consensus regarding management of immune-related hepatitis beyond the steroids and MMF combination,[3] alternative supportive options for ALF were assessed.

Plasma exchange (PE) is the treatment of choice for some immune-mediated diseases such as Guillain-Barré syndrome or thrombotic thrombocytopenic purpura because of its proven capacity to increase T reg cells.[4] In addition, PE could accelerate removal of ipilimumab because this molecule has some ideal target characteristics, such as high molecular weight (148,000 Da) and a low volume of distribution (0.1 L/kg). Furthermore, a recent prospective, multicenter study in patients with ALF reported that PE can improve survival by attenuating innate immune activation.[5] Based on these data, PE was initiated a few hours after the onset of hepatic encephalopathy, along with the regular medical measures. PE consisted of a course of 5 treatments with 1,500 ml of 5% albumin plus 4 units of plasma as replacement fluid, carried out every other day. PE was started on the same day as the onset of overt hepatic encephalopathy, and from that time on the patient experienced a gradual clinical and analytical improvement (Fig. 1). Two weeks after starting PE she was discharged on treatment with MMF and prednisone at a dose of 20 mg/dl. At that time clotting was within normal range, bilirubin was 2 mg/dl, AST 49 IU/ml, and ALT 123 IU/ml. One month later, liver function tests were within normal values.

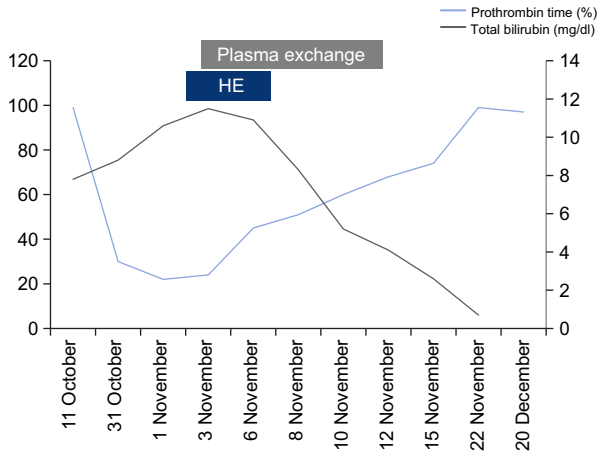

Fig. 1. Clinical and analytical follow-up of acute liver failure secondary to immune-mediated hepatitis related to ipilimumab. Blood tests performed before the second infusion of ipilimumab (11 October) showed completely normal liver function. Twenty days later, the patient consulted for jaundice. At that time she was conscious and aware, but the analyses showed severe acute hepatitis with coagulopathy, aspartate aminotransferase >4,000 IU/ml and total bilirubin at 8 mg/dl. Despite high doses of steroids (2 mg/kg/day) and mycophenolate mofetil (1.5 mg/day), bilirubin level continued to increase and coagulopathy worsened. Three days after admission, the patient developed hepatic encephalopathy. Plasma exchange was initiated and performed every other day, with progressive clinical and analytical improvement. In the boxes: Duration of HE (hepatic encephalopathy) and plasma exchange therapy.

Our case raises 2 important issues. First, although patients with a history of mild immune-mediated hepatitis can be re-treated without complications,[1,3] they can also present with more severe forms of acute hepatitis. Second, although further evidence is needed to fully understand the role and benefit of PE in the management of severe immune-mediated hepatitis, our limited experience suggests that PE may be a feasible treatment option for ipilimumab-induced ALF.

Financial support

The authors have no support or funding to report.

Conflict of interest

The authors have no personal interests related to this manuscript

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

Authors' contributions

Mar Riveiro-Barciela (MRB) and Eva Muñoz-Couselo (EMC) designed the manuscript; MRB, EMC, Jesús Fernandez-Sojo (JFS) and Nely Diaz Mejia (NDM) drafted the manuscript. Rafael Parra-López (RPL) and María Buti (MB) performed a critical revision of the manuscript. English language support was provided by Celine Cavallo. All authors approved the final version of the article.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.10.020.

References

[1] De Martin E, Michot JM, Papouin B, Champiat S, Mateus C, Lambotte O, et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol 2018;68:1181–1190.
[2] Bhave P, Buckle A, Sandhu S, Sood S. Mortality due to immunotherapy related hepatitis. J Hepatol 2018;69:976–978.
[3] Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28: iv119–iv142.
[4] Reeves HM, Winters JL. The mechanisms of action of plasma exchange. Br J Haematol 2014;164:342–351.
[5] Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: An open randomised controlled trial. J Hepatol 2016;64:69–78.

Mar Riveiro-Barciela[1,2,*]
Eva Muñoz-Couselo[3]
Jesús Fernandez-Sojo[4]
Nely Diaz-Mejia[3]
Rafael Parra-López[4]
María Buti[1,2]

[1]*Liver Unit, Internal Medicine Department, Vall d'Hebron Hospital, Barcelona, Spain*
[2]*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain*
[3]*Oncology Department, Vall d'Hebron Institut of Oncology (VHIO), Vall d'Hebron Hospital, Barcelona, Spain*
[4]*Blood Bank, Banc de Sang i Teixits, Vall d'Hebron Hospital, Barcelona, Spain*

*Corresponding author. Address: Liver Unit, Internal Medicine Department, Vall d'Hebron Hospital, Psg Vall d'Hebron, 119-129 Barcelona, Spain. Tel.: +34 932746240.
E-mail address: mar.riveiro@gmail.com

Reply to: "Acute liver failure due to immune-mediated hepatitis successfully managed with plasma exchange: New settings call for new treatment strategies?"

To the Editor:

We thank Riveiro-Barciela *et al.* for their interest in our paper "Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors".[1] They reported the case of a patient who developed grade 2 hepatitis under first line treatment with nivolumab (anti-PD-1) and dioxygenasel inhibitor for a metastatic melanoma. The hepatitis improved with corticosteroid therapy. Because of tumor progression a second line treatment with ipilimumab (anti-CTLA4) was administered. She developed fulminant hepatitis induced by ipilimumab and she was treated with corticosteroids and mycophenolate mofetil, since no improvement was seen she underwent plasma exchange with hepatitis resolution.

Retreatment of a patient who developed acute hepatitis induced by immune checkpoint inhibitors is a crucial issue. Compared to other drug-induced liver disease, in which the drug re-administration is not possible, the re-challenge with immune checkpoint inhibitors is feasible as it is not always associated with acute hepatitis recurrence. The choice of the monoclonal antibody and the time of therapy re-introduction are relevant points and there are no data in the literature that can help in taking the decision.

In our experience 2 patients who developed acute hepatitis on ipilimumab were previously exposed to nivolumab.[1] We hypothesized that the activation of the immune system by a first treatment might have enhanced the immune response to the second line therapy and induced the immune related adverse event (irAE). While ipilimumab front-line followed by nivolumab is well tolerated, the nivolumab front-line followed by ipilimumab has been associated with severe adverse events.[2] In the clinical case the patient was first exposed to the anti-PD-1 and secondly to the anti-CTLA4. Considering our experience and the data reported in the literature, we think that retreatment with ipilimumab might be avoided.

Of course the re-challenge with immunotherapy can be associated with hepatitis recurrence but also with the development of another irAE. We followed a 64-year-old woman who was treated with the combination of nivolumab and ipilimumab for a metastatic melanoma. After the first injection she developed an acute hepatitis characterized by aspartate aminotransferase 2,048 IU/L, alanine aminotransferase 2,122 IU/L and total bilirubin 87 μmol/L. Immunotherapy was discontinued. The liver biopsy showed sub-acute hepatitis with lobular inflammatory infiltration made by lymphocytes and eosinophils associated with a cholangiolitis. She was treated with corticosteroids 1 mg/kg/day and her liver tests normalized. Three months later she presented with tumor progression. After multidisciplinary discussion the patient was retreated with pembrolizumab (anti-PD-1) and concomitant corticosteroids prophylaxis (20 mg/day). After 8 courses of immunotherapy she had no hepatitis but presented with diarrhea and was diagnosed with immune-related colitis. The immunotherapy was stopped and the corticosteroid dose was increased to 40 mg/day and then to 60 mg/day. The diarrhea improved but it recurred after corticosteroid discontinuation. The patient was treated with anti-TNFα. The corticosteroid-dependent colitis responded to anti-TNFα therapy.

Fatal events induced by immune checkpoint inhibitors remain a rare complication of cancer immunotherapy. A recent published paper based on Vigilyze-Vigibase, the World Health Organization pharmacovigilance database, identified 613 (2%) fatal irAEs among 31,059 individuals who received cancer immunotherapy. Overall they noted an increase of fatal toxic effects over time. Fulminant hepatitis related death was reported in 124 (0.4%) patients, 31 on ipilimumab, 74 on anti-PD-1/PD-L1 and 19 on combination therapy. The study authors also reported on a multicenter analysis, which included 7 academic centers. The incidence of fatal irAEs was 0.6%. Of 3,545