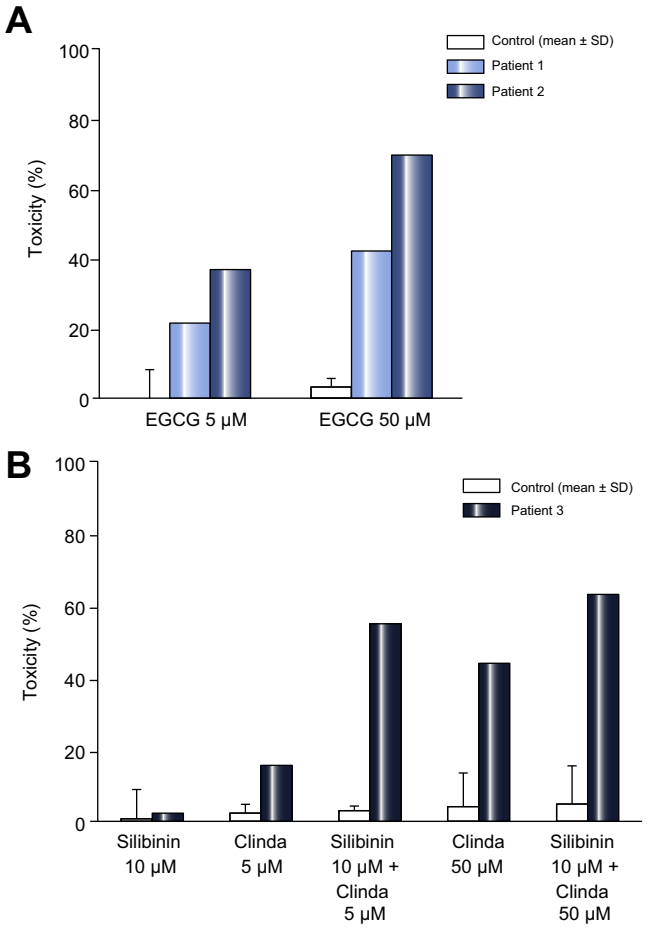

Fig. 1. MH cell test results of the three patients. (A) Control (mean toxicity and standard deviation of subjects without drug-induced liver injury) in white bars. Patient bars represent means of a triplicate measurement. Patients 1 (light blue bars) and 2 (blue bars) show toxicity of EGCG. (B) Patient 3 (dark blue bars) shows an effect of clindamycin and an increase of clindamycin toxicity by combination with silymarin. EGCG, epigallo-catechin-gallate; MH, monocyte-derived hepatocyte-like.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.03.033.

References

[1] Alferink LJM, Fittipaldi J, Kiefte-de Jong JC, Taimr P, Hansen BE, Metselaar HJ, et al. Coffee and herbal tea consumption is associated with lower liver stiffness in the general population: the Rotterdam study. J Hepatol 2017;67:339–348.
[2] Philips CA, Augustine C. Herbal tea consumption and the liver – All is not what it seems! J Hepatol 2018;68:612–613.
[3] Benesic A, Leitl A, Gerbes AL. Monocyte-derived hepatocyte-like cells for causality assessment of idiosyncratic drug-induced liver injury. Gut 2016;65:1555–1563.
[4] Kullak-Ublick GA, Andrade RJ, Merz M, End P, Benesic A, Gerbes AL, et al. Drug-induced liver injury: recent advances in diagnosis and risk assessment. Gut 2017;66:1154–1164.
[5] Benesic A, Rahm NL, Ernst S, Gerbes AL. Human monocyte-derived cells with individual hepatocyte characteristics: a novel tool for personalized in vitro studies. Lab Invest 2012;92:926–936.
[6] Benesic A, Rotter I, Dragoi D, Weber S, Buchholtz M-L, Gerbes AL. Development and validation of a test to identify drugs that cause idiosyncratic drug-induced liver injury. Clin Gastroenterol Hepatol 2018. https://doi.org/10.1016/j.cgh.2018.04.049, PII: S1542-3565(18)30454-3.
[7] Alferink LJM, Fittipaldi J, Kiefte-de Jong JC. Reply to: "Herbal tea consumption and the liver – All is not what is seems!". J Hepatol 2018;68:613–614.
[8] Navarro VJ, Khan I, Bjoernsson E, Seef LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. Hepatology 2017;65:363–373.
[9] Medina-Caliz I, Garcia-Cortes M, Gonzalez-Jimenez A, Cabello MR, Robles-Diaz M, Sanabria-Cabrera J, et al. Herbal and dietary supplement-induced liver injuries in the Spanish DILI registry. Clin Gastroenterol Hepatol 2018, [pii: S1542-3565(18)30010-7].
[10] Slim M, Stephens C, Robles-Díaz M, Medina-Caliz I, Grove JI, Ortega-Alonso A, et al. Pro-euro-dili registry: a collaborative effort to enhance the understanding of dili. J Hepatol 2016;64:S293–S294.

Andreas Benesic[1,2,*]
Alexander L. Gerbes[1]
[1]*Liver Centre Munich, Department of Medicine II, University Hospital, LMU Munich, Germany*
[2]*MetaHeps GmbH, Martinsried, Germany*
*Corresponding author. Address: Department of Medicine II, Liver Centre Munich, University Hospital LMU Munich, Germany.
Tel.: +49 89 44007 3130; fax: +49 89 44007 6000.
E-mail address: andreas.benesic@med.uni-muenchen.de

Immune-related hepatitis with immunotherapy: Are corticosteroids always needed?

To the Editor:

We read with interest the recent report of liver damage caused by monoclonal immune checkpoint inhibitors published by De Martin *et al.*[1]

Checkpoint inhibitors such as anti-programmed cell death 1 (PD-1) (pembrolizumab, nivolumab), anti-PD ligand 1 (PD-L1) (avelumab, durvalumab and atezolizumab) and anti-cytotoxic T-lymphocyte antigen 4 (CTLA4) (ipilimumab) antibodies have revolutionized cancer treatment especially in melanoma,[2–5] by the restoration of functional T cell responses, yielding tumor destruction by the immune system and improved clinical outcomes.

These drugs have a distinct toxicity profile with immune-related side effects including liver toxicities. De Martin *et al.*[1]

Keywords: Immune-related hepatitis; Immune checkpoint inhibitors; Anti-CTLA4; Anti-PD-1; Immune-related adverse events.

reported clinical, biological and histological immune-related grade ≥3 hepatitis characteristics in 16 patients treated with anti-PD-1/PD-L1 and anti-CTLA4 monoclonal antibodies, in monotherapy or in combination, for various cancers. Management of these hepatoxicities particularly caught our attention. In this cohort, six patients (38%) did not receive any corticosteroid therapy and experienced a spontaneous improvement in liver tests. No ≥grade 3 hepatitis was observed after reintroduction of immunotherapy in two patients. The authors discussed the need for a patient-oriented management, which contrasts with current guidelines, and could eventually avoid useless systemic corticosteroid therapy. Spontaneous resolution of immune-related hepatitis was also reported for six patients.[7]

We would like to report our experience on this important topic, as we had the opportunity to perform a retrospective analysis of all immune-related hepatitis that occurred in our center from October 2010 to May 2015. Among 128 patients treated for advanced melanoma with immune checkpoint inhibitors, 10 (7.8%) patients experienced immune-related hepatitis (Table S1). Median age was 55 years (range 36–80). There was no history of alcohol consumption, but one patient presented with resolved viral C hepatitis and two had pre-existing hepatic steatosis. Six patients were treated with anti-CTLA4, three patients with anti-PD-1 and one with the combination of anti-CTLA4 and anti-PD-1. One, seven and two patients experienced grade 2, grade 3 and grade 4 aminotransferase increase, respectively. Median time from the first infusion of immunotherapy to immune-related hepatitis onset was 9.9 weeks (range 2.9–19.7): 9.9 weeks (6.1–14.7) for anti-CTLA4, 14.1 weeks (9.4–19.7) for anti-PD-1 and 2.9 weeks for the combination. No patient experienced liver failure or toxicity-related death. Median peak aminotransferase level was 416 IU/L (range 155–1,735). Total bilirubin level increase was observed for four patients, but was only above 50 μmol/L in three patients. Median total bilirubin level was 76 μmol/L (range 4–160). The prothrombin time was normal for all patients. No patient presented autoantibody positivity except one: anti-mitochondrial antibody was positive at 1/1,600 with an aspect of primary biliary cholangitis at liver biopsy.

Liver biopsy was performed in three patients and identified features of primary biliary cholangitis in one patient, and granulomatous hepatitis associated with a moderate and polymorphous inflammatory infiltrate, without interface hepatitis in the other two patients. For all patients, immunotherapy was discontinued because of the hepatic events. Ipilimumab was resumed in one patient, and another checkpoint inhibitor (from ipilimumab to nivolumab) was introduced in four patients without immune-related hepatitis relapse.

Regarding immune-related hepatitis management, only half (five) of our patients received steroids:

- Two patients were included in clinical trial and managed according to the trials recommendations
- One patient received steroids for concomitant severe colitis
- One patient was already on steroids for cerebral metastasis
- One patient with concomitant diagnosis of primary biliary cholangitis was treated with ursodeoxycholic acid and low dose steroids (0.3 mg/kg/day)

Hepatitis resolved in all five patients, and none needed a second-line treatment for the hepatic event. The other five patients, in accordance with the hepatologist's recommendation, did not receive any steroids but were monitored for clinical and biological evolution.

Interestingly, resolution of the adverse events was observed in all cases, with a median time of 4.7 weeks (range 2.0–20.6) for patients who received no corticosteroid treatment or no steroid dose increase (including a patient with cerebral metastasis) (n = 6) *vs.* 8.6 weeks (4.3–55.1) in patients who received corticosteroids (n = 4). No significant difference was observed due to the small number of patients.

Currently, immune-related hepatitis management recommendations[8–10] are based on a colitis model and recommend a high dose of steroids (from 1 to 2 mg/kg/d) for grade 3–4 or persistent grade 2 hepatitis (more than 1–2 weeks). If no response to corticosteroids is obtained within 2–3 days, mycophenolate should be considered. Use of steroids is logical based on the mechanisms of immune-related colitis, highly reminiscent of idiopathic intestinal inflammatory disease. However, corticosteroids might not be necessary for all toxicity-related to immune checkpoint inhibitors. Accordingly, the management of immune-related hepatitis appears heterogeneous, from abstention to corticosteroids or immunosuppressive drugs.[8–10]

The administration of corticosteroids is highly debatable in cases of drug-induced liver injury. Indeed, corticosteroids could induce severe adverse events and decrease the efficacy of immunotherapy. Based on these results, we agree with the authors' conclusion[6] that management of immune-related hepatitis should be reconsidered, especially the indication for corticosteroids in this setting. Further controlled studies are needed to assess new management strategies for immune-related hepatitis.

Financial support
This research did not receive any specific grant from any funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

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

Authors' contributions
M.-L.G., B.B., C.Z., C.L. and M.B. had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors made substantial contributions to the conception and design, the acquisition of data or analysis and the interpretation of data; contributed to drafting the article or revising it critically for important intellectual content; gave their final approval of the version to be published.

Acknowledgment
We thank all the authors for their contribution.

Supplementary data
Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.03.034.

References

[1] De Martin E, Michot J-M, 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] Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.
[3] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–723.
[4] Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320–330.
[5] Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab *vs.* ipilimumab in advanced melanoma. N Engl J Med 2015;372. https://doi.org/10.1056/NEJMoa1503093.
[6] Zhang X, Ran Y, Wang K, Zhu Y, Li J. Incidence and risk of hepatic toxicities with PD-1 inhibitors in cancer patients: A meta-analysis. Drug Des Devel Ther 2016;10:3153–3161.
[7] Bernardo SG, Moskalenko M, Pan M, Shah S, Sidhu HK, Sicular S, et al. Elevated rates of transaminitis during ipilimumab therapy for metastatic melanoma. Melanoma Res 2013;23:47–54.
[8] Haanen JBAG, 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.
[9] Puzanov I, Diab A, Abdallah K, Iii COB, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immuno Ther Cancer 2017:1–28.
[10] Information IS, Full US, Information P, Information IS. Immune-mediated adverse reactions management guide OPDIVO® is approved in 8 tumor types n.d.:62–5.

Marie-Léa Gauci[1,2]
Barouyr Baroudjian[1,2]
Charlotte Zeboulon[1,2]
Cécile Pages[1,2]
Nicolas Poté[3,4]
Olivier Roux[5]
Mohamed Bouattour[6,*,†]
Céleste Lebbé[1,2,†], and the PATIO group
[1]*AP-HP, Département de Dermatologie Hôpital Saint-Louis, Paris, France*
[2]*INSERM U976, Université Paris Diderot-Paris VII, Sorbonne Paris Cité, France*
[3]*AP-HP, Département d'Anatomopathologie, Hôpital Beaujon Clichy, France*
[4]*INSERM UMR 1149, Université Paris Diderot-Paris VII, Sorbonne Paris Cité, France*
[5]*AP-HP, Département d'Hépatologie et Réanimation Hépatique, Hôpital Beaujon, Clichy, France*
[6]*AP-HP, Département d'Oncologie Digestive, Hôpital, Beaujon Clichy, France*
*Corresponding author. Address: AP-HP, Département d'Oncologie Digestive, Hôpital Beaujon, 100 Boulevard du Général Leclerc, 92110 Clichy, France. Tel.: +33 1 40 87 55 53.
E-mail address: mohamed.bouattour@aphp.fr

† Co last authors

Reply to: "Immune-related hepatitis with immunotherapy: Are corticosteroids always needed?"

To the Editor:

We thank Gauci and colleagues for their interest in our paper "Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors"[1].

The authors reported their experience on diagnosis and management of 10 patients who developed immune-mediated hepatitis during treatment with immune checkpoint inhibitors for advanced melanoma. The management of hepatic immune-related adverse events (IRAEs) is currently based on the administration of corticosteroids, however their use should not be systematic but needs several considerations.

The authors highlighted the heterogeneity of the hepatotoxicity induced by immune checkpoint inhibitors for clinical and biological aspects: the age of patients affected ranged from 36 to 80 years, the alterations of liver tests were mild to marked with total bilirubin ranging from 4 to 160 µmol/L and peak aminotransferases ranging from 155 to 1.735 IU/L, and mostly the interval time between immunotherapy administration and hepatitis onset varied from 2.9 to 19.7 weeks. The interval time in their cohort was shorter in patients who received anti-cytotoxic T-lymphocyte antigen 4 (CTLA4) monoclonal antibodies (mAbs) compared to patients who received anti-programmed cell death protein 1 (PD1) mAbs, in agreement with our findings the diagnosis of immune-mediated hepatitis requires the exclusion of all causes of acute hepatitis, if necessary through liver histology.

We believe that liver biopsy is helpful to manage patients with immune-mediated hepatitis. Indeed, liver histology enables to rule out differential diagnoses. In Gauci *et al.*'s report, a liver biopsy was only performed in three patients, among whom one disclosed histological lesions of primary biliary cholangitis. Danlos FX *et al.*[2] recently published data showing that patients with autoimmune or inflammatory diseases treated with anti-PD1 mAbs have a significantly increased risk of developing IRAEs. Nevertheless, no patients with autoimmune liver disease were reported in their series and the risk of immune checkpoint inhibitors in this setting remains largely unknown. The increase of liver tests, even mild, before the introduction of immunotherapy needs to be accurately explored.

Gauci *et al.* confirmed that the administration of corticosteroids is not mandatory in all patients with immune-related hepatitis, as half of their patients improved spontaneously. We acknowledge that these data challenge the current recommendations and, in line with our results, highlight the need for patient–tailored management based on specialized hepatology and the assessment of liver histological lesions. As we reported the severity of liver injuries should guide the decision of corticosteroid introduction.