Dr Liang-Sheng Mag

President and Editor-In-Chief

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Dear Dr Liang-Sheng Mag

Please find enclosed the revised version of our manuscript entitled "AUTOIMMUNE-LIKE HEPATITIS DURING MASITINIB THERAPY IN AN AMYOTROPHIC LATERAL SCLEROSIS PATIENT" (Ref. EPS No 17710)

In response to Reviewer 1's comments:

- **As regards query # 1.** Treatment with prednisone in combination with azathioprine was chosen, as this combination was associated with fewer side effects than conventional corticosteroid regimen alone, and reduces exacerbations when corticosteroids are discontinued. It is a standard regime recommended by most Consensus Guidelines and Recommendations on managing DILI with autoimmune features [Gleseon et al, 2011, Czaja 2013, de Lemos et al, 2014, Moura, et al 2014].

  This paragraph in the revised manuscript now reads: "After that, the patient started taking oral prednisone 60 mg daily and oral azathioprine 50 mg daily. Treatment with prednisone in combination with azathioprine was chosen, as this combination has been associated with fewer side effects than conventional corticosteroid regimen alone, and reduces exacerbations after discontinuation of immunosuppressive drugs, according to most Consensus Guidelines and Recommendations on managing DILI with autoimmune features [Gleeson et al, 2011; Czaja 2013; de Lemos et al, 2014, Casal-Moura, et al 2014]."

- **As regards query # 2.** The pathogenesis of drug-induced autoimmune hepatitis is complex and not fully understood. At present, limited information is available about the mechanisms by which masitinib and other TK inhibitors induce immune-mediated hepatotoxicity, although a hypersensitivity mechanism has been suggested for imatinib. It has been established that reactive metabolites (RM) form during the TK metabolism. These RM in genetically susceptible individuals (within the HLA region on the short arm of chromosome 6, especially those encoding DRB1 alleles) lead to alterations of neighboring host proteins or macromolecules, mainly peptides, and give rise to neoantigens, which are recognized as foreign by the host immune system and able to activate an immune response [de Lemos et al. 2014; Liberal et al. 2013; Teo et al 2015].

  This paragraph in the discussion section now reads: "Our patient had an acute icteric hepatitis with elevated transaminases (>10ULN) and bilirubin (>5ULN), which can be considered a grade IV hepatotoxicity. Six months after beginning masitinib treatment,

she developed a marked elevation of ALT; the drug was discontinued but transaminase levels and bilirubin continued rising for 9 weeks. After immunosuppressive therapy, the patient improved and a biochemical remission was observed. Grade 3 and 4 liver adverse events, as in our case, have previously been reported with other tyrosine kinase inhibitor drugs. After a literature review, we found at least 16 cases of severe Drug-Induced Liver Injury (DILI) secondary to other members of the TK inhibitors family, predominantly with erlotinib [Ramanarayanan et al. 2007; Lai et al. 2011; Leise et al. 2014], but never with masitinib. Interestingly, in four of the cases associated with imatinib, clinical features, time course, histological pattern in the liver biopsy, and a good response to corticosteroids were consistent with an autoimmune DILI [Dahullin-Venier et al, 2006; Al Sobhi et al 2007; Charier et al. 2009; Aliberti et al. 2009; de Lemos et al. 2014; Casal Moura et al. 2014].

The exact hepatotoxicity mechanisms of tyrosine kinase inhibitors are still unknown, and the pathogenesis of most drug-induced autoimmune hepatitis are complex and not fully understood. At present, limited information is available about the mechanisms by which masitinib and other TK inhibitors induce immune-mediated hepatotoxicity, although a hypersensitivity mechanism has been suggested for imatinib. It has been established that reactive metabolites (RM) are formed during the TK metabolism. These RM in genetically susceptible individuals (within the HLA region on the short arm of chromosome 6, especially those encoding DRB1 alleles) lead to alterations of neighboring host proteins or macromolecules, mainly peptides, and give rise to neoantigens, which are recognized as foreign by the host immune system and able to activate an immune response [de Lemos et al 2014; Liberal et al. 2013; Teo et al. 2015]."

- **As regards query # 3.** In accordance with the reviewer's proposal, we have removed the word "TOXIC" from the title. As a consequence, the final title is now AUTOIMMUNE-LIKE HEPATITIS DURING MASITINIB THERAPY IN AN AMYOTROPHIC LATERAL SCLEROSIS PATIENT

- **As a consequence, the following references have been added:**

Al Sobhi E, Zahrani Z, Zevallos E, Zuraiki A. Imatinib-induced immune hepatitis: case report and literature review. Hematology. 2007 Feb;12(1):49-53.

Casal Moura M, Liberal R, Cardoso H, Horta E Vale AM, Macedo G. Management of autoimmune hepatitis: Focus on pharmacologic treatments beyond corticosteroids. World J Hepatol. 2014 Jun 27;6(6):410-8.

Charier F, Chagneau-Derrode C, Levillain P, Guilhot F, Silvain C. [Glivec induced autoimmune hepatitis]. Gastroenterol Clin Biol. 2009 Oct-Nov;33(10-11):982-4

Czaja AJ. Review article: the management of autoimmune hepatitis beyond consensus guidelines. Aliment Pharmacol Ther. 2013 Aug;38(4):343-64.

deLemos AS, Foureau DM, Jacobs C, Ahrens W, Russo MW, Bonkovsky HL. Drug-induced liver injury with autoimmune features. Semin Liver Dis. 2014 May;34(2):194-204

Dhalluin-Venier V, Besson C, Dimet S, Thirot-Bibault A, Tchernia G, Buffet C. Imatinib mesylate-induced acute hepatitis with autoimmune features. Eur J Gastroenterol Hepatol. 2006 Nov;18(11):1235-7.

Dubreuil P, Letard S, Ciufolini M, Gros L, Humbert M, Castéran N, Borge L, Hajem B, Lermet A, Sippl W, Voisset E, Arock M, Auclair C, Leventhal PS, Mansfield CD, Moussy A, Hermine O. Masitinib (AB1010), a potent and selective tyrosine kinase inhibitor targeting KIT. PLoS One. 2009 Sep 30;4(9):e7258.

Gleeson D, Heneghan MA; British Society of Gastroenterology. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut. 2011 Dec;60(12):1611-29.

Liberal R, Grant CR, Mieli-Vergani G, Vergani D. Autoimmune hepatitis: a comprehensive review. J Autoimmun. 2013 Mar;41:126-39

Teo YL, Ho HK, Chan A. Formation of reactive metabolites and management of tyrosine kinase inhibitor-induced hepatotoxicity: a literature review. Expert Opin Drug Metab Toxicol. 2015 Feb;11(2):231-42

We thank the reviewers for the insightful comments, which have improved the manuscript.
We hope we have addressed the concerns of the reviewers.

Thank you in advance for reconsidering our manuscript.

Sincerely,

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