Format for ANSWERING REVIEWERS

February 3, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6767-review.doc).

Title: An update on Inflammatory Bowel Disease in patients with Primary Sclerosing CholangitisA review of the literature

Author: Tsaitas c, Semertzidou A, Sinakos E

Name of Journal: *World Journal of Hepatology*

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The manuscript has been improved according to the suggestions of the editor and the reviewers.

1 Format has been updated regarding the references. In addition, a core tip has been added.

Core Tip

The combination of PSC and IBD has recently arisen as a challenging research field in the medical community. In this review, we present all the recent data and highlight the specific clinical and genetic traits that differentiate PSC-IBD from the two diseases in isolation. We have reviewed the literature with regards to the colorectal neoplastic susceptibility in this subset of patients and its underlying pathogenetic mechanisms. We have also emphasized on the technological advances that have provided novel diagnostic tools for a more accurate detection of dysplastic lesions. Finally, we present the current guidelines on patient follow-up as well as all available evidence as to whether UDCA should be used as chemoprevention against colorectal cancer.

2 Revision has been made according to the suggestions of the reviewer.

(1) Please describe the genetic susceptiblity of two kinds of disorders.

In response to this comment we have added the following in the section «The PSC-IBD interplay»: The genetic factors for PSC development are still poorly understood. There is an obvious geographic clustering with high prevalence in Northern countries compared to

Southern Europe and Asia. Furthermore, it has been shown that first- degree relatives of PSC patients have a disease prevalence of 0.7%, representing a nearly 100-fold increased risk of developing PSC compared to the general population [14]. In siblings the prevalence even reaches 1.5% [15]. Taken together, these epidemiologic data and heritability studies have revealed a strong genetic background for PSC. Genome-wide association studies have shed some light to the subcellular maze of PSC and its overlap with IBD. HLA and non-HLA haplotypes have been identified. The HLA-A1 allele [16], the HLA-C7 [17], the major histocompatibility complex class I chain-related A (MICA)*002 and 008/5.1 alleles [18-19] as well as the tumour necrosis factor alpha (TNFα) promoter -308 A allele [20] were identified as risk loci for PSC susceptibility. Data from five different European countries (UK, Italy, Norway, Spain and Sweden) demonstrated that PSC is positively associated with three different HLA class II haplotypes, the DRB1*03, DQA1*0501, DQB1*02 (which confers the highest relative risk for PSC development), the DRB1*15, DQA1*0102, DQB1*0602 and the DRB1*13, DQA1*0103, DQB1*0603 haplotypes [21]. However, non-HLA associations have also been confirmed. Of note, MMEL1 and TNFRS14 on chromosome 1p36 encoding a membrane metalloendopeptidase- like protein of unknown function and a receptor for cytokines and membrane-bound ligands respectively, have been identified as risk loci for PSC [22]. The risk of PSC has also been associated with the FUT2 gene encoding fucosyltransferase [22], which is an enzyme that regulates expression of the ABO blood group antigens on the surface of epithelial cells. To date, there is scarcity of molecular evidence regarding the shared susceptibility loci between PSC and IBD. A Scandinavian study comparing PSC patients with UC patients showed distinct HLA associations [23]. No significant differences were noted between PSC patients with concurrent UC and PSC patients without IBD. This study provides genetic evidence that UC in PSC patients follows a distinct course and demonstrates phenotypic uniquity compared with UC in isolation. More recently, REL, IL2 and CARD9 have been identified as genetic links between the two diseases [24].

(2) Please describe immuno-pathogenic links between two diseases.

We added the following paragraph after our response to the previous comment: «Taking into consideration its associations with HLA haplotypes, autoimmune diseases and the presence of

inflammatory bowel disease in the majority of PSC patients, immunopathogenetic mechanisms have been sought in PSC pathogenesis. In this regard, two theories have been proposed: the leaky gut hypothesis and the gut lymphocyte homing hypothesis. According to the leaky gut hypothesis, bacteria or bacterial products enter the portal-venous system due to the increased intestinal permeability resulting from inflammation and translocate to liver. Bacteria trigger the release of cytokines by Kupffer cells and macrophages in the liver and lead to periductal fibrosis [8]. The gut lymphocyte homing hypothesis, on the other hand, supports the notion that T lymphocytes primed in the inflamed gut may persist as long-lived memory cells, undergo enterohepatic circulation and trigger portal inflammation in PSC via aberrantly expressed adhesion molecules in liver and gut [25].»

3 In last sentence of Abstract, the authors mentioned the dose of UDCA at low doses (8-15 mg/dl) and high doses (15-30 mg/dl). Please check "mg/dl", it it correct?

UDCA doses were corrected as follows:
«UDCA at low doses (8-15 mg/kg/day) and high doses (15-30 mg/kg/day)»

4, Please describe how to differentially diagnose.

We added the following sentences in the Introduction. «The differential diagnosis of primary sclerosing cholangitis includes congenital diseases (eg. Caroli disease, choledochal cysts) and secondary cholangiopathy, as observed in patients with collagen vascular diseases (eg. systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis) and in those with infiltrative diseases (eg. mediastinal fibrosis, Riedel thyroiditis, eosinophilic cholangitis, histiocytosis X). Infectious causes from parasitic, fungal, viral, or bacterial infections or from recurrent cholangitis itself, especially in patients who are immunocompromised, can cause multifocal liver abscesses that lead to a PSC-like appearance of the bile duct.»

Thank you again for publishing our manuscript in the *World Journal of Hepatology*.

Sincerely yours,

Sinakos Emmanouil, M.D.