

Response Letter

Dear Editor,

On behalf of my co-authors, I would like to thank the editorial staff and reviewers for their thoughtful comments regarding our work entitled “Inflammatory bowel diseases and Spondyloarthropathies. From pathogenesis to treatment”. We appreciate the opportunity to address reviewers’ comments, and we believe the suggested changes have added value to our manuscript. Please find our responses to the queries below. We have uploaded our revised manuscript (changes are highlighted with yellow color).

We hope that the issues raised by the reviewers have been now answered and our manuscript will be appropriate for publication in “World Journal of Gastroenterology”.

Authors’ replies

Editor’s suggestions were all incorporated. Namely: Running title, post codes, ORCID numbers, authors’ contributions and corresponding author’s details have been added, “conflict of interest” and “funding” were filled in. All Format changes (e.g font size, line spacing, figure format etc) have been made. References were checked

Reviewer 1, code: 03476292

Interesting article, I have no comments.

Authors’ reply: We would like to thank the reviewer for finding our article interesting.

Reviewer 2, code: 01587889

Fragoulis et al. present an interesting discussion on the possible pathophysiology of spondylarthropathies associated with inflammatory bowel disease (IBD) involving the so-called "gut-synovial axis" hypothesis, which implicates environmental and host factors. Many of them act as triggers leading to initiation of inflammation in genetically predisposed individuals SpA, PsA, peripheral SpA, enteropathic arthritis, reactive arthritis, undifferentiated spondyloarthropathy and axSpA have many extra-articular manifestations the most common of which is bowel involvement. Obviously various therapeutic modalities are available with monoclonal antibodies against TNF, Interleukin-23 and Interleukin-17, being the most effective intervention. Both gastroenterologists and rheumatologists should be alerted to identify the co-existence of these conditions and ideally follow-up these patients in combined clinics. This is a fairly good review.

Authors' reply: We would like to thank the reviewer for his comments, which agree to what is presented in the manuscript.

Reviewer 3, code: 00049331

The Authors aimed to review the pathogenesis and treatment in the Spondyloarthropathies and inflammatory bowel disease. In this review, both clinically silent and overt IBD in Spondyloarthropathies were revealed. This is a useful paper, however I have some comments. In the first paragraph, definition of Spondyloarthropathies should be begin with general terminology as a "Spondyloarthropathies is a type of arthritis that attacks the spine (axial) and/or the joints of the arms and legs (peripheral)", than it can proceed with different forms of inflammatory arthritis.

Authors' reply: We thank the reviewer for this comment. A new sentence ("SpA affects mainly the spine, but symptomatology from the peripheral joints as well as from entheses and other tissues might occur") has been added in the first paragraph to give a brief definition of Spondyloarthropathies as suggested.

In the subtitle section of “Spondyloarthropathies occurring in patients with Inflammatory Bowel Diseases” I would suggest to add a paper regarding peripheral arthritis in patients with IBD (Yuksel I et al., Peripheral arthritis in the course of inflammatory bowel diseases. Dig Dis Sci. 2011;56:183-7). This review is acceptable for publication after arrangement according to recommendations.

Authors’ reply: We totally agree with this suggestion. This reference has been added in several places through-out the text. Also, a couple of sentences were added (“Furthermore, Yüksel et al, examining the characteristics of peripheral arthritis in patients with IBD, they found that erythema nodosum and pyoderma gangrenosum were more commonly observed in IBD patients who also had peripheral arthritis, compared to those without”) to highlight some of the findings of this study. Thank you.

Reviewer 4, code: 00073640

The title/subject is interesting and topical, the manuscript is well structured and well written. However, to improve the manuscript I suggest the following: - Abstract does not reflect the manuscript appropriately - first half of the abstract is just classification of spondyloarthropathies, which is then repeated in the Core tip and in the Introduction section – in the abstract and Core tip this part should be properly shortened – instead more information from other sections of the review should be included in the abstract - Please explain what is the aim of this review article - In the introduction section information about the purpose of the manuscript should be provided

Authors’ reply: Thank you for this comment. We acknowledge that definitions of Spondyloarthropathies were disproportionally represented in the abstract and core tip. Following reviewer’s advice, we significantly reduced the length of that. As suggested, we added more information from the main manuscript, mainly pertaining to the association between inflammatory bowel disease and spondyloarthropathies. Also, a paragraph has been added in the introduction section, page 7, describing the purpose of the manuscript.

- In the text there are many long sentences which are difficult to understand and should be properly re-form- For instance: - Page 4 "In a large population, control-matched study, including 4101 patients with AS, Stolwijk et al [6] found that at the time of AS diagnosis, the cumulative incidence was 4%, while in a French large, prospective study for early inflammatory back pain, IBD occurred in 7.2% of patients with newly diagnosed AS [9]. - In a multi-centre AS study with a long follow-up, no differences were recorded between patients who had a history of IBD at baseline and those who did not [8], while development of IBD was associated with disease activity and spinal pain scores at baseline and worse physical function and patient well-being, at the time of IBD diagnosis [8]. - Interestingly, in a sub-analysis of the GIANT cohort, it was shown that in patients with axSpA, SPARCC (Spondyloarthritis Research Consortium of Canada) scores which is a tool to measure MRI-defined sacroiliitis were higher in patients with chronic gut inflammation, as assessed by ileocolonoscopy compared to those without gut lesions [12]. - Page 6: Comparing CD patients with and without AS, in a small single centre study, Liu et al did not observe any differences between these two groups [29]. Of note, it was found that CD disease activity, measured by Crohn's disease activity index, paralleled AS disease activity and functional disability, assessed by BASDAI and Bath AS functional index – BASFI, possibly implying a tight connection in the pathogenetic mechanisms of these conditions.

Authors' reply: We would like to thank the reviewer for his comments and suggestions. The above- mentioned sentences have all been re-formed so that they are more easily understandable. Also, during the proof-reading of the manuscript, we identified similar problems in other sentences as well (e.g page 13, lines 4-5, page 14, lines 2-3, page 19, lines 3-5. These are now fixed following the reviewer's suggestion.

There are also sentences in which there is probably something missing: Page 10: Further studies detected in the inflamed joints of these patients *Yersinia enterocolitica*, *Salmonella enteritidis* and *typhimurium*, *Yersinia* and *Shigella* related antigens which may be translocated by monocytes [25, 77, 78]. Page 11: The latter seems to regulate IgA induction in the lamina propria and therefore to the intestinal microbiota composition [91, 92].

Authors' reply: We would like to thank the reviewer for identifying these sentences. These are now rephrased to make sense.