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Characteristics of Inflammatory Bowel Diseases in Patients with Concurrent Immune-Mediated Inflammatory Diseases

Reviewer #1:
Specific Comments to Authors: The focus of the present review is to describe the characteristics of inflammatory bowel disease in patients with concurrent immune-mediated inflammatory diseases. Awareness of IMIDs in IBD is important and their co-existence is documented in many published papers For what reason a review is of relevance. The manuscript is in general well disposed and well written. The english is excellent. I have a few points to be adressed: 1. In the abstract and in the introduction it is noted that concurrent IMIDs could influence the IBD phenotype. This is correct but the opposite could also be the case in that the IBD phenotype could influence the type of IMIDs and the course of these

> **Response:** Thank you for this comment. We agree that IBD could influence the type and outcomes of IMIDs. From our literature review, we found a recent meta-analysis assessing this important topic. We cited this study in the introduction (Attauabi et al. Inflamm Bowel Dis 2022). To avoid confusion, this review primarily focuses on IBD phenotype and clinical outcomes in patients with concurrent IMIDs.

2. The common pathogenetic pathways in IBD and concurrent IMIDs is exemplifield by the three IMIDs asthma, psoriasis and rheumatoid arthritis. Even though these three IMIDs are among the most common co-existing with IBD there could be multiple other examples. Actually coeliac disease ought to be mentioned. It could be considered to add a table showing some of the more important IMIDs seen in IBD. Likewise it could be considered to give a more broad description af common pathogenetic pathways in IBD and IMIDs rather than devide the description in separate sections for only three.

> **Response:** We appreciate this constructive comment. We changed the outline of this review. The main body was separated into two sections as follows: IMIDs WITH HIGH PREVALENCE AMONG IBD and IMIDs AFFECTING IBD PHENOTYPES AND OUTCOMES. We added the sub-section of *Celiac disease and IBD* into the latter section to introduce Celiac disease and IBD. Figure 1 was also edited accordingly. Hence, each section reviews three IMIDs (6 IMIDs in total) which are often complicated with patients with IBD or affect IBD phenotypes and outcomes. We created Table 1 to summarize the characteristics and outcomes of IBD in patients with concurrent IMIDs.

3. In a global perspective Takayasu´s arteritis is a rather rare disease and in many parts of the world there will be only very few patients suffering from this disease and IBD. For that reason the section describing this disease seems to be a little too long. In contrast the section on IBD and PSC is highly relevant.

> **Response:** We appreciate this comment. There are a few IMIDs affecting IBD phenotypes. To the best of our knowledge, only PSC and Takayasu's arteritis (TAK) are IMIDs which can develop unique IBD phenotypes. TAK may be a rare disease worldwide but can be a good example to emphasize an importance to understand immunological mechanisms of the concurrence of IMIDs and IBD as recent investigations revealed that tofacitinib can be effective both IBD and TAK.

4. Regarding IBD and PSC it is stated that these patients may have a more benign course of IBD. I think this can be debated since there is a high risk of colorectal cancer in these patients. This should be noted clearly even though I agree that the course of IBD as such in these cases could be mild.

> **Response:** Thank you for the comment. We added the following sentences in the sub-section of *PSC and IBD*: The mechanism regarding the discordance between endoscopic disease activity and clinical outcomes in PSC-IBD patients remains

unclear. A retrospective study revealed that the cumulative incidences of immunosuppressant use, and colonic or ileal surgical resection were lower in PSC-IBD patients than in IBD patients without PSC. However, this study also found that a greater proportion of PSC-IBD patients used 5-aminosalicylates, suggesting that PSC-IBD patients may be more likely to use 5-aminosalicylates to reduce their risk of colorectal cancer or dysplasia, and their use can be associated with mild disease activity [46-48]. Meanwhile, another case-controlled study showed that PSC-UC patients had a milder disease course than patients with UC alone, although the number of patients taking 5-aminosalicylates or sulfasalazine was the same [49]. Hence, further studies are needed to understand if the unique disease phenotype of PSC-IBD can be explained by differences in pathogenesis or medical therapies between PSC-IBD patients and patients with IBD alone.

Reviewer #2:

Specific Comments to Authors: Thank you for nice reviewing, You should add more references about Th17 driven IBD pathology in 2th paragraph of introduction text(https://journals.sagepub.com/doi/full/10.1177/2058739220942626 , https://journals.sagepub.com/doi/full/10.1177/20587384211059677)

Response: Thank you for this important comment. In the introduction, we added the following sentences to explain Th17-driven IBD pathology: APCs including dendritic cells and macrophages play an important role to initiate and modulate T cell-mediated immune responses. Th1 cells are induced by interleukin (IL)-12 and secrete interferon-γ, tumor necrosis factor (TNF)-α, and IL-12 [7] (Figure 1). Interferon-γ induces TNF-α release from activated macrophages, resulting in the differentiation of stromal cells into myofibroblasts and the production of matrix metalloproteinases which function to degrade tissue [8]. While abnormal Th1 responses are involved in the intestinal inflammation of CD, Th2 cell-mediated inflammation is thought to be central the pathogenesis of UC [8]. Th17 cells are characterized by a distinct subset of $CD4^+$ T cells promoting the expression of IL-17 and maintained by IL-23 [9, 10] (Figure 1). Th17 cells and their cytokines are crucial mediators in the inflammatory pathways for both UC and CD [11].

Reviewer #3:

Specific Comments to Authors: The authors have undertaken an extensive review on IBD in patients with associated immune-mediated inflammatory disorders. Although other papers on this topic have been already published, this review is easy to read and extensively describes the characteristics of IBD in this specific set of complicated patients. A table summarizing the characteristics of IBD for each IMID and the possible shared therapies would be helpful for the reader

Response: Thank you for this suggestion. We created Table 1 to summarize characteristics and clinical outcomes of IBD in patients with concurrent IMIDs. To summarize possible shared therapies in Table 1, we added the following sentences to explain which medications can be effective for both RA and IBD: Clinical trials of patients with RA demonstrated that ustekinumab was not effective, whereas TNF inhibitors, IL-6 inhibitors, and Janus kinase (JAK) inhibitors such as tofacitinib significantly improved disease activity of RA compared with placebo [31]. Therefore, among medications approved for RA and IBD, TNF inhibitors and JAK inhibitors can be effective for both IMIDs. Given that JAKs bind to cytokine receptors and transmit various extracellular cytokine signals including IL-6, IL-12, IL-23, and interferons, JAK inhibitors are therefore expected to be effective for various IMIDs [28, 32] (Table 1).