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Reply: Comment on "Emergence of severe spondyloarthropathy-related entheseal pathology following successful vedolizumab therapy for inflammatory bowel disease"

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SIR,

We read with great interest the letter by Alivernini et al in response to our paper on vedolizumab (VDZ) induced severe SpA related entheseal pathology[1,2]. We note their agreement with our study demonstrating severe SpA and enthesitis following VDZ treatment for inflammatory bowel disease (IBD), including either VDZ initiation or withdrawal of prior TNFi as potential triggers of this complication[1]. We would like to congratulate Alivernini and colleagues for the provision of novel data on the incidence of SpA under vedolizumab therapy which is surprisingly high at nearly 5%[1]. This is surprising since this complication was completely unreported in large phase III studies of vedolizumab in IBD.

All their cases fulfilled ASAS criteria, were HLA-B27 negative, failed at least one previous TNFi, and had well controlled IBD[1]. Interestingly, SpA was observed in 8/187 (4.8%) cases post-VDZ treatment for IBD which is higher than the previous reported SpA prevalence in other VDZ treated IBD cohorts[1,3]. In comparison, the disease severity of their cases appears lower with a median CRP of 15.9 compared to a much higher mean CRP of 56.7 mg/L in our study[1,2].

The synovial biopsy conducted in two cases of knee synovitis by Alivernini et al is also novel and afforded the first opportunity for immunohistochemistry evaluation of VDZ associated SpA. Synovial infiltration with CD68+ macrophages, CD138+ and CD20+ indicating B lineage cells and CD3+ a pan-T-cell marker was reported. It is known that macrophages are linked to the destruction of synovial tissue through the T-cell mediated release of pro-inflammatory cytokines[4]. The authors do not report on VDZ relevant protein expression including anti- $\alpha 4\beta 7$ integrin or MADCAM-1, its corresponding receptor but point to literature that reported such $\alpha 4\beta 7$ expression from synovial lymphocytes previously in SpA. However, previous studies failed to demonstrate MADCAM-1 expression in inflammatory

synovitis[5]. Salmi et al previously reported on adhesion molecules on HEVs in inflamed synovium identifying that intercellular adhesion molecule-1 (ICAM-1/CD54) and vascular adhesion protein-1 (VAP-1) were prominently expressed in synovial HEVs, and all other adhesion molecules were present at much lower levels with complete absence of mucosal addressin (MADCAM-1)[5]. Studies have suggested $\alpha4\beta1$ on lymphocytes binds VCAM-1 preferentially at the $\alpha4$ subunit and is linked to chronic established synovitis whereas ICAM-1, overexpressed in tissue from early synovitis, is pivotal in activation and cell binding into inflamed synovial tissue[6,7]. Reports of adherence of immunoblasts (activated lymphocytes) to high endothelial venules (HEVs) in rheumatoid arthritis (RA) synovium showed only partial inhibition by monoclonal antibody (mAb) to $\alpha4\beta1$ (25%) and very little inhibition (5%) by mAb to $\alpha4\beta7$ suggesting no functional significance of $\alpha4\beta7$ in RA synovitis[8]. The rate of lymphocyte migration into synovium was found to be determined by expression of ICAM-1 on HEVs in RA[9]. In contrast to the specificity of MADCAM-1, selectively present in gut mucosal lymphoid organ HEVs, the role of ICAM-1 and VAP-1 in synovial HEVs are more likely to contribute to the influx of circulating immune cells during $\alpha4\beta7$ blockade[2]. However, possible differences in adhesion molecule pathways between RA and SpA synovitis may exist[10]. We wonder if the authors plan to stain for these relevant adhesion molecules and ligands in their samples?

Definitive data on the presence of adhesion molecules at spinal and peripheral joint entheses is lacking, but increased $\alpha4\beta7$ expressing type 3 innate lymphoid cells (ILC3s) were reported in a small study in the gut and non-entheseal iliac crest bone marrow of patients with ankylosing spondylitis (AS)[11]. The same study reported MADCAM-1 in iliac crest bone marrow aspirates from a small number of cases where, in our opinion, the immunohistochemistry staining showed non-specific or stromal staining in addition to marrow venule staining[11].

Interestingly, just as no reports of arthritis occurred in clinical trials for VDZ in IBD, neither have there been any reports of arthritis with natalizumab, a humanised mAb that binds α4β1 and α4β7 integrin, which was trialled successfully in Crohn's disease (CD) and multiple sclerosis (MS), but increased reports of progressive multifocal leukoencephalopathy, have been a limitation[12]. The synovial blockade of the lymphocyte α4β1-synovial VCAM-1 interaction might be expected to lessen this paradoxical arthritis development, since unlike MADCAM-1, VCAM-1 synovial expression has been shown. We wonder if Alivernini et al have any cohort data on natalizumab to address this topic since α4β1 and its receptor may be expressed in the synovium. Treatment with natalizumab in one patient with both AS and multiple sclerosis was reported suggesting α4β1 and α4β7 inhibition may be effective for co-treatment of both diseases[13]. Nevertheless, the evidence for synovitis supports an underlying MADCAM-1 independent process for lymphocyte infiltration into the synovium via other mechanisms including an inflammatory effect from adjacent entheses. We feel that the underlying complex pathogenetic link between IBD and SpA in the context of VDZ associated SpA is not yet fully understood and further research would be required to confirm such mechanisms.

Disclosure statement

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