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Editorial

Vedolizumab for inflammatory bowel disease: a two-edge sword in the gut-joint/enthesis axis

This editorial refers to Emergence of severe spondyloarthropathy-related entheseal pathology following successful vedolizumab therapy for inflammatory bowel disease, by Sayam Dubash *et al.*, on pages 963–8.

The approval of vedolizumab (VDZ) has enriched therapeutic options for IBD patients and provided new hope for patients who are refractory to TNF inhibitors (TNFis). VDZ is a monoclonal antibody that targets $\alpha4\beta7$ integrin and selectively prevents the infiltration of leucocytes into the gastrointestinal submucosa through interaction with the specific gut adressin MADCAM-1. While efficacy and safety has been proven for IBD, poor-quality data about the efficacy and safety of VDZ in IBD-associated SpA has been recorded in clinical trials [1] and real-world evidence is still being compiled. In contrast to TNFis, which have been demonstrated to control inflammation both in gut and skeletal manifestations, the presence of concomitant or quiescent SpA is emerging as a challenge for the management of these patients with VDZ, a gut-selective inhibitor.

Aside from some case reports, few preliminary prospective studies have focused on the effect of VDZ on IBD-associated SpA. Although some data indicate a potential benefit of VDZ in SpA manifestations, specifically in association with a successful gut response, limited sample sizes, insufficient follow-up or the lack of an accurate assessment and description of SpA disease prevent firm conclusions [2, 3]. Moreover, safety concerns have arisen in clinical practice in IBD patients, with or without associated SpA, related to the exacerbation or even *de novo* appearance of SpA features. Inefficacy of VDZ for SpA could explain some of the first descriptions of mild/moderate flares of arthritis and sacroiliitis [4, 5], simply reflecting the effect of TNFi withdrawal in a previously controlled or subclinical SpA disease. However, a more severe phenotype of paradoxical reactions is arising that strongly suggests that VDZ may have paradoxical effects in at least a subset of patients, leading to the development of SpA; this deserves new research to provide new insights into SpA pathogenesis.

In the current issue, Dubash *et al.* [6] present a case series of 11 patients with severe SpA-associated enthesitis/osteitis induced by VDZ exposition. The severity of the SpA manifestations was such that it led to VDZ discontinuation despite successful IBD control. Most of these cases occurred in subjects that had failed and consequently discontinued prior TNFi treatment. A potential risk effect of TNFi withdrawal in a previously undiagnosed, quiescent SpA cannot be ruled out. However, in accordance with previously reported data, a close relationship with VDZ exposition or rechallenge, the absence of any previous SpA features, a predominant HLA-B27-negative status and the occurrence in TNFi-naïve patients favour the hypothesis of a paradoxical VDZ-induced event.

This is a relevant emerging issue for rheumatologists in the practical setting, as risk factors have not yet been identified and the long-term outcome remains unknown. In this regard, the retrospective design of the study and the lack of information about the gut and skeletal outcomes of all patients exposed to VDZ precludes information about the real incidence of these adverse events and precipitating risk factors. Data from VDZ preauthorization and prospective studies are limited. Pooled safety data from six randomized controlled trials over an extended treatment period could not detect flares or new SpA onset and report non-significant differences in the exposure-adjusted incidence rate of 'arthralgia' on VDZ [11.2/100 patient-years (CI 10.1, 12.3) compared with placebo [19.3 (13.2, 25.4)] [1]. In an Italian multicentre prospective cohort, Macaluso *et al.* [7] report four SpA flares in 6 months of follow-up of 163 IBD patients and 3 flares in patients with no history of previous SpA, but limited additional profiles of the patients are provided. Those figures exceed the reported incidence of new SpA in IBD [8].

Therefore rheumatologists should be aware of VDZ-induced paradoxical reactions in IBD and contribute to their research, as this will provide important clues for pathogenic mechanisms of SpA and the rationale for the mechanisms of new targeted therapies.

Dubash *et al.*'s [6] report also provides fascinating insights into the role of the gut in driving the pathogenesis of AS, the authors proposing that VDZ treatment diminishes gut mucosal immunological barriers to bacteria, reducing local inflammation and thereby reducing colitis, but permitting more bacterial egress, driving the process that leads to SpA. This is consistent with previously proposed models of the pathogenesis of AS. There is robust evidence that the gut microbiome is involved in AS, with AS cases showing dysbiosis [9, 10] and histopathological evidence of excess bacterial egress from the gut [11] and genetic studies highlighting that genetic predisposition to the disease significantly influences the gut mucosa [12]. It has previously been hypothesized that AS is caused by an exaggerated response to exposure to bacteria transgressing the gut mucosa, driving secretion of pro-inflammatory cytokines including IL-1, TNF and IL-23 [13, 14]. The demonstration in mice that excess TNF [15] or IL-23 [14] is sufficient to lead to development of axial SpA suggests that cytokine-driven processes may be sufficient to cause disease. An alternate hypothesis is that bacteria or bacterial components then pass to joints, leading to local inflammatory reactions [16]. In either model, HLA-B27 is thought to operate either

by shaping a pro-inflammatory gut microbiome or permitting excess bacterial migration through the gut wall through a form of gut mucosal immunodeficiency. Diminishing a key element of the gut mucosal barrier function, such as by inhibiting a major gut adressin using VDZ, would at least suggest the risk of a paradoxical effect in AS compared with IBD.

The reported experience highlights the importance that rheumatologists and gastroenterologists join forces to prospectively study the real effects of VDZ outside the gut. It also highlights the potential risks associated with simplistic repositioning of immunological targeted therapies between diseases. All medications currently in use or in human trials in AS that we are aware of have been repositioned from other indications. In many cases this is despite at least suggestive evidence from immunological or genetic studies that predict non-response or potential contrary treatment effects such as noted here with VDZ. Genetic studies in particular provide a powerful tool to identify potential issues with drug repositioning between diseases or likely side effects from targeting particular molecules, with many examples of discordant genetic associations existing where the same variant is associated in opposite directions in different diseases. For example, there are several ongoing drug development programs for inhibitors of the CD40–CD40L system despite the main genetic association of CD40 with RA [17] and autoimmune thyroid disease [18] being in the same haplotype block (tagged by rs1883832) but in the opposite direction of the association with multiple sclerosis [19] and IBD [20]. While such findings should not preclude drug development programs addressing similar targets, it indicates that they should be addressed with considerable caution, with careful monitoring for the likely predicted side effects.

With regard to VDZ, further research is required to determine the frequency of this complication, features that might predict its likely occurrence and its typical natural history and optimum management. Those unfortunate patients that develop this complication also represent a great opportunity to determine how the gut microbiome drives SpA pathogenesis, which may ultimately point to novel therapeutic or preventative approaches for this common condition.

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