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Concise report

Emergence of severe spondyloarthropathy-related entheseal pathology following successful vedolizumab therapy for inflammatory bowel disease

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Abstract

Objectives. Vedolizumab (VDZ) blocks α4β7 integrin and is licenced for the treatment of IBD. It has been associated with mild SpA-related features, including sacroiliitis and synovitis. Herein we report a series of cases demonstrating the emergence of severe SpA-associated enthesitis/osteitis following successful IBD therapy with VDZ.

Methods. We evaluated 11 VDZ-treated patients with IBD across seven centres who developed severe active SpA and/or enthesopathy, with the aim of characterizing the VDZ-associated SpA or entheseal flares. Imaging features demonstrating particularly severe disease were recorded.

Results. De novo SpA developed in 9 of 11 patients and flare of known SpA in 2 patients, with 4 patients requiring hospitalization due to disease severity. Available data showed that one of seven cases were HLA-B27 positive. The median time from VDZ initiation to flare was 12 weeks, with IBD well controlled in 7 of 10 patients (no data for 1 patient) at flare. Severe SpA enthesitis/osteitis was evident on MRI or US, including acute sacroiliitis ($n = 5$), extensive vertebral osteitis ($n = 1$), peri-facetal oedema ($n = 1$) and isolated peripheral enthesitis ($n = 3$). Due to arthritis severity, VDZ was discontinued in 9 of 11 patients and a change in therapy, including alternative anti-TNF, was initiated.

Conclusion. Severe SpA, predominantly HLA-B27 negative, with osteitis/enthesitis may occur under successful VDZ treatment for IBD, including in subjects with prior anti-TNF therapy for intestinal disease.

Key words: vedolizumab, α4β7 integrin, Crohn's, ulcerative colitis, spondyloarthritis, spondylarthritis, ankylosing spondylitis, axial SpA, enthesitis, mucosal vascular addressin cell adhesion molecule-1 (MADCAM-1)

Rheumatology key messages

- Vedolizumab for IBD can induce *de novo* severe SpA or enthesitis especially in anti-TNF failures.
- This manifestation can occur in HLA-B27-negative patients where vedolizumab therapy renders IBD quiescent.
- SpA or enthesitis is likely independent of α4β7-MADCAM-1/VCAM-1 interaction at the joint or entheseal tissue.

Introduction

SpA represents the most common extra-intestinal manifestation of IBD and occurs in ~30% of patients with IBD [1]. Conversely, subclinical IBD is present in the 50–60% of axial SpA patients [2]. Indeed, both IBD and SpA share common immunopathogenetic, clinical and therapeutic characteristics [3]. In terms of therapy, IBD and SpA both

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CLINICAL SCIENCE

show good responses to anti-TNF inhibitor. However, etanercept, a soluble receptor fusion protein anti-TNF, and anti-IL-17 blockers are efficacious in SpA but ineffective in IBD and are even associated with *de novo* IBD development [4]. Vedolizumab (VDZ), a humanized IgG1 monoclonal antibody that inhibits $\alpha4\beta7$ integrin, has been approved for the treatment of IBD and works by selectively blocking lymphocyte homing to the gut. The converse reaction has been observed with this therapy, namely in cases with good IBD efficacy where subjects occasionally experienced predominantly mild paradoxical flares of inflammatory spinal disease that permitted therapy continuation [5, 6]. We report a series of VDZ-treated patients who developed a new diagnosis of *de novo* severe SpA including severe enthesitis/osteitis that resulted in a switch or addition of therapy.

Methods

Following the presentation of an index case with severe arthropathy at our institution**,** we liaised with other centres to determine whether a new or existing severe SpA diagnosis had occurred following VDZ-treated IBD. Clinical, biochemical and imaging characteristics within case records were identified as part of a clinical evaluation. Information was collected via a specifically designed pro forma to obtain key characteristics about the onset and type of disease development at baseline and outcome up to 6 months, where available. Written patient consent was obtained from all subjects. Research ethics approval was not required, as patients had already been managed as part of standard practice and identified retrospectively for evaluation. Depending on the site of maximal disease severity, patients had either vendor-specific fat suppression or short tau inversion recovery (STIR) sequence performed on MRI (nine patients) and/or musculoskeletal US of diseased entheses (three patients) at their host institutions as part of their clinical care.

Results

We identified 11 patients (5 male, 6 female). The mean age was 42.5 years (SD 13.7). The median time from VDZ initiation to the development of inflammatory spinal symptoms was 12 weeks [interquartile range (IQR) 7–20]. There were 9 of 11 patients who developed *de novo* SpA/enthesopathy and only 2 with a flare of pre-existing SpA, that was quiescent at therapy commencement, 1 of which was remarkably extreme (Table 1, patient 1). Psoriasis was present in 4 of 10 patients, only 1 patient out of 7 was HLA-B27 positive (no data for 4 patients) and 2 of 9 were smokers (no data for 2 patients). All but two patients had previously failed treatment with TNF inhibitors for IBD.

Four patients were hospitalized due to the severity of SpA or entheseal disease and were investigated for suspected sepsis. Patient 1, who presented with intense back pain and an initial low-grade fever mimicking sepsis, was subsequently excluded after an extensive infection screen and blood cultures following a 3 week period of hospitalization. The most frequent clinical SpA phenotypes identified were axial SpA (8/11), peripheral SpA (8/11), both axial and peripheral SpA (5/11) and US- or MRI-positive enthesitis (3/11) (Table 1). All cases fulfilled either the axial (6/11) or peripheral (7/11) classification criteria of the Assessment of SpondyloArthritis international Society (ASAS). Axial involvement was also present in five of seven patients with peripheral SpA. ASAS axial criteria were not met in four patients due to disease of too a short duration, disease onset at >45 years of age, axial disease not involving the sacroiliac joints or and HLA-B27-negative status. Serum CRP was elevated in 9 of 11 patients, with a mean value of 56.7 mg/L.

Acute bilateral sacroiliitis determined by MRI was demonstrated in five patients, one of whom also showed evidence of radiographic bilateral grade 2 sacroiliitis, suggesting previous indolent undiagnosed disease. Patient 4 developed new-onset SpA with extreme spinal vertebral body and end-plate oedema at T6–11 on MRI (STIR) and inflammatory Romanus lesions at the T12 and L3–4 vertebral bodies (see Fig. 1A and 1B). Severe spinal peri-facetal oedema was identified on MRI (STIR) in one patient (Fig. 1C).

The IBD activity was well controlled or low in 7 of 10 VDZ-treated patients during SpA onset or flare and was active in only 3 of 10 patients (no data for 1 patient). Following VDZ discontinuation in nine patients, eight switched to alternative therapies, including golimumab, adalimumab, certolizumab pegol, sulphasalazine, ustekinumab and bilateral sacroiliac joint injections, and one patient was given compassionate treatment with tofacitinib and zolendronate for enthesitis, having failed prior anti-TNF. Only two patients continued VDZ, one combined with oral corticosteroid and MTX and the other in combination with etanercept. The corresponding outcomes are listed in Table 1.

Discussion

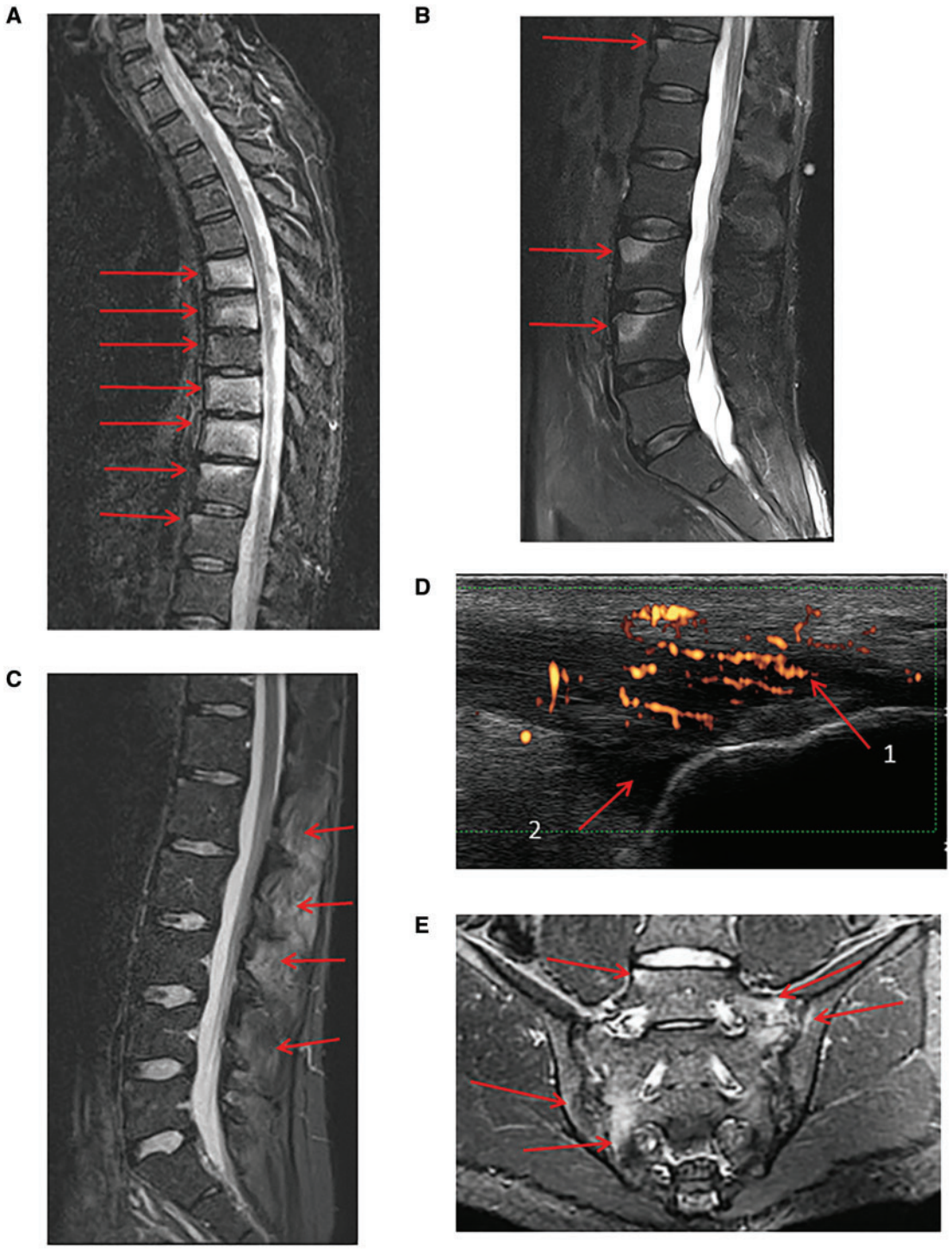
Herein we report severe, mostly *de novo* SpA development in 9 of 11 patients after VDZ treatment. The severity of SpA was such that 80% of VDZ-treated cases required discontinuation despite predominantly good gut responses for IBD. We found more aggressive disease, including severe enthestis/osteitis, compared with the two previous studies, which reported milder flares and therapy continuation [5, 6]. The severity of our cases was established by a high CRP at presentation in 9 of 11 subjects: 6 cases demonstrating grade 2–3 MRI-determined bone marrow oedema lesions on axial imaging, 3 patients with severe enthesitis lesions displayed on MRI or US (Fig. 1D) and 4 patients that required hospitalization. These cases were also predominantly HLA-B27 negative, which is not unusual for IBD, but is atypical for AS, and previous anti-TNF failure, which may suggest a phenotype of treatment-resistant IBD. Although five of seven patients responded well to TNF inhibitor re-treatment at 6 months, we remain cautious about possible secondary non-response given the history of prior TNF failure. We suspect that treatment resistance may be drug specific rather than a complete class effect, given that these were mostly

Table 1 Characteristics and outcomes of patients with severe SpA or enthesitis

Patient number	1	2	3	4	5	6	7	8	9	10	11
Age, years, M/F	28, M	48, M	33, F	50, M	35, F	40, F	21, F	52, M	45, F	44, F	72, M
Hospitalized	Y	N	N	N	Y	Y	N	N	Y	N	N
Vedolizumab exposure (weeks)	14	20	20	6	8	10	5	12	4	52	20
Pre-existing SpA	Y	N	N	N	N	N	N	N	Y	N	N
axSpA	Y	Y	Y	Y	Y	N	Y	N	Y	Y	N
perSpA	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y
Osteitis or enthesitis	+++	++	++	+++	NA	++	++	+++	+++	+++	+++
MRI/US (imaging feature)	MRI: extreme perifacetal spinal vertebral oedema	MRI: bilateral sacroiliitis	MRI: bilateral sacroiliitis	MRI: extensive severe thoracolumbar vertebral oedema/osteitis and IRLs	MRI: negative, nr-axSpA	MRI: enthesitis/ periostitis distal tibiofibular	MRI: right-sided sacroiliitis (also XR-positive, fulfilling mNY criteria)	US: marked Achilles enthesitis PD positive	MRI: bilateral sacroiliitis	MRI: bilateral sacroiliitisUS: knee synovitis, hand flexor tenosynovitis, PD positive	US: elbow, knee and wrist synovitis, common extensor enthesitis
HLA-B27	N	NA	NA	N	Y	NA	N	N	N	N	NA
Smoker (cpd)	15	NA	NA	25	N	N	N	N	N	N	N
EAMs (uveitis, PsO)	N	N	PsO	N	PsO	N	N	N	PsO	N	PsO
IBD type/ activity	CD/low/ controlled	IC/low/ controlled	CD/NA	CD/active (high)	UC/low/ controlled	UC/low/ controlled	IC/low/ controlled	CD/active (moderate)	UC/low/ controlled	CD/active (high)	UC/low/ controlled
CRP at flare (mg/L)	216	<5	<5	24	24	28	55	68	33	80	88
Concomitant DMARD	MTX 15 mg o.w.	AZA 150 mg o.d.	Pred 0.5 mg o.d.	None	None	Pred 4 mg o.d.	None	None	MTX 7.5 mg o.w.	No	Pred 15 mg o.d.
TNFi failure	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N
Previous TNFi/ DMARDs	IFX, ADA, CZP	ADA, IFX	AZA, IFX, ADA	IFX, ADA	MSZ, CYSP, IFX, ADA	6-MP, AZA, ADA	IFX	6-MP, AZA	IFX, Secukinumab, ADA	IFX, CZP, GLM	None
Vedolizumab discontinued	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y
Treatment change	GLM	Patient declined treatment for SpA	Bilateral sacroiliac joint injection and switched to UST	CZP	CZP: intolerance; SZP: intolerance; switched to GLM	TOFA + ZOL	ADA	ADA + Pred	VDZ + Pred 10 mg o.d. + apremilast; developed significant depression. Apremilast switched back to MTX 7.5 mg o.w.	ETN + VDZ	ADA
Outcome	Moderate IBD and SpA activity at 6 months, CRP 58, BASDAI 6.9 (previous 8.8)	IBD in remission at 6 months (colonoscopy normal); SpA outcomes: NA	NA	IBD: controlled; SpA: mild to moderate activity at 6 months, CRP 19	IBD in remission. SpA activity is moderate at 6 months	Periostitis and enthesitis resolved at 6 months	Mild axSpA. Skin and perSpA in remission at 1 month	Achilles enthesitis much improved. Moderate CD activity at 1 month	IBD/SpA/skin PsO all well controlled at 6 months	IBD and SpA in drug-controlled remission at 6 months	NA

Y: yes; N: no; NA: not available; cpd: cigarettes per day; EAMs: extra-articular manifestations; nr: non-radiographic; o.d.: once daily; o.w.: once weekly; Osteitis or enthesitis: +mild, ++moderate, +++severe; CD: Crohn's disease; UC: ulcerative colitis; IC: intermediate colitis; IRLs: inflammatory Romanus corner lesions; PD: power Doppler; XR: X-ray; TNFi: TNF inhibitor; ADA: adalimumab; CZP: certolizumab pegol; CYSP: ciclosporin; GLM: golimumab; IFX: infliximab; MSZ: mesalazine; MTX: methotrexate; Pred: prednisolone; TOFA: tofacitinib; UST: ustekinumab; VDZ: vedolizumab; ZOL: zolendronate; M: male; F: female.

Fig. 1 Observed MRI and US appearances of severe SpA-related entheseal pathology. (**A**, **B**) MRI sagittal STIR images show extreme multilevel thoracolumbar osteitis with severe high-signal vertebral body and endplate changes from T6 to T11, including large IRLs at T12, L3 and L4. (**C**) MRI sagittal STIR images of severe peri-facetal oedema extending into adjacent para-lumbar tissue, as indicated by the relevant arrows (patient 1). (**D**) Achilles tendon enthesitis demonstrated on US (longitudinal plane), with increased tendon thickness, hypoechogenicity, loss of the tendon fibrillar pattern and increased power Doppler signal indicating hypervascularity from inflammation at the tendon enthesis insertion into the calcaneum (1) and retrocalcaneal bursitis (2). (**E**) Severe bilateral sacroiliitis with bone marrow oedema (high signal) predominantly at the sacral side of the joint (Leeds grade 3) and also IRL at the region of the anterior L5 corner demonstrating osteitis. IRL: inflammatory Romanus lesion.



infliximab and adalimumab failures. One intriguing aspect of our series is that these VDZ-treated cases were at the highest severity for SpA flares and possibly more severe than flares linked to conventional IBD-associated SpA, the latter of which are linked to gut activity in peripheral SpA [7].

In two previous reports, the first case series included five subjects with new SpA: three axial and two peripheral SpA in patients with IBD following VDZ, and four of five cases with controlled gut activity [5]. In the second study there were four cases of Crohn's disease: three cases of new axial and peripheral SpA, one with enthesitis, and one case of peripheral SpA reactivation, with controlled gut activity in two of four cases [6]. The former study reported only one of five patients as having severe sacroiliitis and one of five with severe tenosynovitis, and generally milder disease in the remaining patients. These cases, particularly the latter study, seem comparatively mild in severity, given only one had positive axial disease features (sacroiliitis) defined by MRI, another with only inflammatory polyarthralgia and one case of exacerbation of pre-existing polyarthralgia without reported imaging evidence of synovitis [6]. However, all our cases demonstrated either active imaging-defined disease, elevated CRP or both, in line with marked disease severity.

We also noted good gut responses in 7 of 10 (no data for 1 patient) of our treated cases, a predominant axial phenotype (8/10) and HLA-B27 negativity (6/7; no data for 4 patients), in line with the trend in the aforementioned case series. What distinguished our case phenotype was the severity of disease encountered, including extensive multilevel thoracolumbar osteitis, extreme peri-facetal oedema on MRI and elevated CRP levels. The previous reports were milder overall and the calibre of axial disease demonstrated by MRI appeared to be mild to moderate for sacroiliitis in three patients in the first series, with only one MRI-positive axial case in the second series [5, 6]. Severity grading for MRI did not feature in the reports of the two prior studies, although US evidence of a wrist effusion and severe tenosynovitis was described in one case, supporting the pattern of severe enthesopathy and peripheral SpA. Hospitalization was warranted in four of our cases, compared with the prior reports, which significantly highlights the symptom severity and associated acute disease impact and disability.

Interestingly, in common with the second series, most of our cases had failed a previous anti-TNF, but in the former series, four of five subjects were anti-TNF naïve [5]. This variation suggests that the induced SpA is independent of previous anti-TNF use and therefore not linked to a lag effect from cessation of anti-TNF. Crucially, unlike the other reports, VDZ therapy needed to be discontinued in most ($n = 9$) of our patients due to SpA severity, and alternative therapy was initiated. It remains to be determined whether TNF inhibitor failure in some way represents a predisposition to a more severe musculoskeletal pathology.

Given that all but one patient were TNF experienced, it could be argued that discontinuing anti-TNF therapy may have played a role in unmasking and facilitating SpA, with the absence of TNF inhibition no longer inactivating subclinical or undetected SpA and therefore increasing the susceptibility of SpA development or flare. The expectation would be a flare soon after anti-TNF discontinuation, but instead the temporal relationship observed between VDZ initiation and SpA development or flare (median duration 12 weeks) may be more suggestive of a mechanistic link between blockade of $\alpha4\beta7$ and the induction or facilitation of SpA or enthesitis. Compared with the other reported case series where the mean time to flare was less (60–64 days), our slightly longer duration to flare might also contribute to the severity of our cases. Nonetheless, the effects of TNF inhibitor discontinuation may be linked with the SpA flares through possible previous suppression of underlying clinically unrecognized SpA pathology. Another limitation of our study is that we are unable to provide accurate data on the incidence of VDZ-induced SpA, which would require large observational cohort studies. Although the existing data are currently limited, some cohort studies suggest VDZ may be effective for extra-intestinal manifestations, including arthritis [8, 9]. However, an analysis of data from six clinical trials of VDZ in IBD did not report on significant SpA disease onset or flares [10]. Arthralgia was recorded in adverse event reporting in phase 3 studies for ulcerative colitis and Crohn's disease, and there was no difference between VDZ-treated subjects compared with placebo, with arthralgia present in 13.5% of the VDZ-treated group compared with 13.3% for placebo in Crohn's disease and 9% compared with 9.1%, respectively, in ulcerative colitis [11, 12].

Mechanistically, inhibition of $\alpha4\beta7$ integrin prevents lymphocyte homing and subsequent inflammatory cascade amplification at the level of the intestine, but may not restore underlying or primary abnormal gut permeability. It is noteworthy that more than half of SpA cases have subclinical gut inflammation with abnormal intestinal barrier function [7]. Such a scenario would permit bacterial antigens, cytokines, adjuvants and pathogen-associated molecular pattern molecules access to the systemic circulation and deposition in the peripheral skeleton at regions of entheseal tissue. T-lymphocytes that express $\alpha4\beta7$ integrin bind to specific adhesion molecules for their transportation into areas of intestinal tissue. Mucosal vascular addressin cell adhesion molecule-1 (MADCAM-1) is exclusive to gut mucosal tissue and is important for the adhesion and facilitation of migration of $\alpha4\beta7$ integrin expressing lymphocytes from the circulating blood vessels to the gut. MADCAM-1 and vascular cell adhesion molecule-1 (VCAM-1) bind to $\alpha4\beta7$ integrin and behave as a ligand, permitting the interception of $\alpha4\beta7$ integrin–expressing T-lymphocytes ($CD4^+$ or $CD8^+$) and their distribution into mucosal or vascular tissue. The likely non-dependence of entheseal and joint tissue on $\alpha4\beta7$–MADCAM-1/VCAM-1 interaction would not hinder adaptive T-cell responses at those locations and offer an explanation for these severe flares (Supplementary Fig. S1, available at *Rheumatology* online). In essence, compartmentalization of both innate and adaptive

immune mechanisms between the gut–enthesis/bone axis might account for these differential therapy responses.

To summarize, we report a predominant pattern of clinically quiescent IBD associated with severe SpA or enthesitis, HLA-B27 negativity, and the need to discontinue VDZ therapy. There have been some reports of continuation of VDZ with the addition of an anti-TNF or ustekinumab, but these reports were in patients with refractory IBD in the face of milder SpA, and more comprehensive safety and efficacy data will be required with such an approach [13–15]. As we anticipate increasing use of $\alpha 4\beta 7$ inhibition, awareness of this paradoxical reaction and specific phenotype among rheumatologists and gastroenterologists alike can facilitate combined management decisions for effective treatment of IBD and SpA or enthesitis.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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