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 licensed for the treatment of inflammatory bowel disease (IBD). It has been associated with mild spondyloarthritis (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 7 centres that developed severe active SpA and/or enthesopathy with the aim of characterising 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 cases requiring hospitalisation due to disease severity. Available data showed that 1/7 cases were HLA-B27 positive. The median time from VDZ initiation to flare was 12 weeks with IBD well controlled in 7/10 (no data 1 case) at flare. Severe SpA enthesitis/osteitis was evident on magnetic resonance imaging (MRI) or ultrasound 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 cases 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 vedolizumab treatment for IBD, including in subjects with prior anti-TNF therapy for intestinal disease.

Keywords

Vedolizumab, α4β7 integrin, Crohn's, Ulcerative colitis, Spondyloarthritis, Spondylarthritis, Ankylosing Spondylitis, Axial SpA, Enthesitis, MADCAM-1.

Introduction

The Spondyloarthritides (SpA) represent the most common extra-intestinal manifestation of inflammatory bowel disease (IBD) and occur in approximately 30% of patients with IBD[1]. Conversely, subclinical IBD is present in the region of 50-60% of axial SpA cases[2]. Indeed, both IBD and SpA share common immunopathogenetic, clinical and therapeutic overlaps[3]. In terms of therapy, IBD and SpA both show good responses to anti-tumour necrosis factor inhibitor (TNF) therapy. 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 α4β7 integrin, has been approved for the treatment of IBD and works through selectively blocking lymphocyte gut homing. 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 to therapy.

Materials and methods

Following the presentation of an index case with severe arthropathy at our institution**,** we liaised with other centres to determine whether 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 proforma 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 cases had either vendor specific fat suppression or short tau inversion recovery (STIR) sequence performed on magnetic resonance imaging (MRI) (9 patients), and/or musculoskeletal ultrasound of diseased entheses (3 patients) at their host institutions as part of their clinical care.

Results

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

Four patients were hospitalised due to the severity of SpA or entheseal disease and were investigated for suspected sepsis. For example, patient 1 who presented with intense back pain and an initial low grade fever mimicking sepsis that was subsequently excluded after an extensive infection screen and blood cultures following a 3 week period of

hospitalisation. The most frequent clinical SpA phenotypes identified were: axial SpA (8/11), peripheral SpA (8/11), both axial and peripheral SpA involvement in (5/11), and ultrasound or MRI positive enthesitis in 3/11 (table 1). All cases fulfilled either the axial (6/11) or peripheral (7/11) assessment of SpondyloArthritis international society (ASAS) classification criteria. Axial involvement was also present in 5 of 7 cases with peripheral SpA. ASAS axial criteria was not met in 4 cases due to disease of too short duration, disease onset above 45 years of age, axial disease not involving the sacroiliac joints, and HLA-B27 negative status. Serum C-reactive protein (CRP) was raised in 9/11 patients with a mean value of 56.7 mg/L.

Acute bilateral sacroiliitis determined by MRI was demonstrated in 5 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 (IRLs) at T12 and L3-4 vertebral bodies (see figure 1 A,B). Severe spinal peri-facetal oedema was identified on MRI (STIR) in one patient (figure 1, C).

The IBD disease activity was well controlled or low in 7 of 10 VDZ treated patients during SpA onset or flare, and active in only 3/10 patients (no data 1 patient). Following VDZ discontinuation in 9 patients, 8 have switched to alternative therapies including golimumab, adalimumab, certolizumab pegol, sulphasalazine, ustekinumab, bilateral sacroiliac joint injections, and one patient was given compassionate treatment with tofacitinib and zolendronate for enthesitis having failed prior anti-TNF. Only 2 patients continued VDZ, one combined with oral corticosteroid and methotrexate, and the other in combination with etanercept. The corresponding outcomes are listed per patient in table 1.

Discussion

Herein, we report severe, mostly de novo SpA development in 9 of 11 cases post-VDZ treatment. Such was the severity of SpA 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 to the two previous studies that reported milder flares and therapy continuation[5,6]. The severity of our cases was established by a high CRP at presentation in 9/11 subjects, 6 cases demonstrating grade 2-3 MRI determined bone marrow oedema lesions on axial imaging, 3 patients with severe enthesitis lesions displayed by MRI or ultrasound imaging (figure 1, D), and 4 patients that required hospitalisation. These cases were also predominantly HLA-B27 negative, which is not unusual for IBD, but atypical for AS, and previous anti-TNF failures which may suggest a phenotype of treatment-resistant IBD. Although 5 of 7 patients responded well to TNFi retreatment 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 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 the previous two reports, the first case series included 5 subjects with new SpA, 3 axial and 2 peripheral SpA, in patients with IBD following VDZ, and 4/5 cases with controlled gut activity[5]. In the second study, there were 4 cases of Crohn's disease: 3 cases of new axial and peripheral SpA, 1 with enthesitis, and 1 case of peripheral SpA reactivation with

controlled gut activity in 2/4 cases[6]. The former study reported only 1/5 patients as having severe sacroiliitis and 1/5 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 imaging, 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 7/10 (no data in 1) of our treated cases, a predominant axial phenotype (8/10), and HLA-B27 negativity (6/7, no data in 4), 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 cases in the first series with only one MRI positive axial case in the second case series[5,6]. Severity grading for MRI did not feature in the reports of the two prior studies, although ultrasound evidence of a wrist effusion and severe tenosynovitis was described in one case supporting the pattern of severe enthesopathy and peripheral SpA. Hospitalisation was warranted in 4 of our cases in comparison to 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 anti-TNF, but in the former series 4/5 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 lag effect from cessation of anti-TNF. Crucially, unlike the other reports, VDZ therapy needed to be discontinued in most (n=9) of our cases due to SpA severity and alternative therapy was initiated. It remains to be determined whether TNFi failure in some way represents a predisposition to a more severe musculoskeletal pathology.

Given that 9 of 11 patients were TNF experienced, it could be argued that discontinuing anti-TNF therapy may have played a role in unmasking and facilitating SpA, albeit 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 to flare soon after anti-TNF discontinuation, but instead the temporal relationship observed between VDZ initiation and SpA development or flare, median duration of 12 weeks, may be more suggestive of a mechanistic link between blockade of α4β7 and the induction or facilitation of SpA or enthesitis. In comparison to 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 TNFi discontinuation may be linked with the SpA flares through possible previous suppression of underlying clinically unrecognised 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 is currently limited, some cohort studies suggest vedolizumab may be effective for extra-intestinal manifestations including arthritis[8,9]. However, an analysis of data from 6 clinical trials of vedolizumab 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 UC and CD and there was no difference between VDZ treated subjects

in comparison to placebo with arthralgia present in 13.5% of the vedolizumab treated group compared with 13.3% for placebo in CD, and 9% compared with 9.1% respectively in UC[11,12].

Mechanistically, inhibition of α4β7 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 over half of SpA cases have subclinical gut inflammation with abnormal intestinal barrier function[7]. Such a scenario would permit bacterial antigens, cytokine, adjuvant, and pathogen-associated molecular pattern molecules (PAMPs) access to the systemic circulation and deposition in the peripheral skeleton at regions of entheseal tissue. T-lymphocytes that express α4β7 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 α4β7 integrin expressing lymphocytes from the circulating blood vessels to the gut. MADCAM-1 and vascular cell adhesion molecule-1 (VCAM-1) bind to α4β7 integrin and behave as a ligand permitting the interception of α4β7 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 α4β7-MADCAM-1/ VCAM-1 interaction would not hinder adaptive T cell responses at those locations and offer an explanation for these severe flares (figure 2). In essence, compartmentalisation of both innate and adaptive immune mechanisms between the gut-enthesis/bone axis might account for these differential therapy responses.

To summarise, we report a pattern of predominantly HLA-B27 negativity and clinically quiescent IBD associated with severe SpA or enthesitis 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 approach[13–15]. As we anticipate increasing use of α4β7 inhibition, awareness of this paradoxical reaction and specific phenotype amongst rheumatologists and gastroenterologists alike, can facilitate combined management decisions for effective treatment of IBD and SpA or enthesitis.

Key messages

- Vedolizumab for IBD can induce de novo severe SpA or enthesitis in previous anti-TNF failure.
- 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 joint, or entheseal tissue.

Patient consent

Consent was obtained in all patients in this study.

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Table 1.

Characteristics and outcomes of patients with severe SpA or enthesitis

Legend:

Y: yes; N: no; NA: not available; cpd: cigarettes per day; EAMs :extra-articular manifestations; nr: non-radiographic; +ve : positive; -ve : negative; o.d: once daily; o.w: once weekly; CD: Crohn's disease; UC: ulcerative colitis; IC: intermediate colitis; IRLs: inflammatory Romanus corner lesions; PD: Power Doppler; XR: X-ray; TNFi: tumour necrosis factor inhibitor; ADA: adalimumab; CZP: certolizumab pegol; CYSP: cyclosporine; GLM: golimumab; IFX: infliximab; MSZ: mesalazine; MTX: methotrexate; Pred :prednisolone; TOFA: tofacitinib; UST: ustekinumab; VDZ: vedolizumab; ZOL: zolendronate.

Figure 1.

Observed MRI and ultrasound imaging appearances of severe SpA related entheseal pathology

Legend:

Images A and B (patient 4): MRI sagittal STIR images showing extreme multilevel thoracolumbar osteitis with severe high signal vertebral body and endplate changes from T6-11 including large inflammatory Romanus lesions at T12, L3, L4 vertebrae.

Image C (patient 1): MRI sagittal STIR images of severe peri-facetal oedema extending into adjacent para-lumbar tissue as indicated by the relevant arrows.

Image D (patient 8): Achilles tendon enthesitis, demonstrated on ultrasound (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).

Image E (patient 10): Severe bilateral sacroiliitis with BMO (high signal) predominantly at the sacral side of the joint (Leeds grade 3) and also IRL at the region of anterior L5 corner demonstrating osteitis.

Figure 2

A Proposed Model to Explain New Onset Severe SpA under Vedolizumab therapy

Description/ legend

Subclinical gut inflammation is a hallmark of SpA and is linked to the magnitude of MRI determined spinal osteitis. Successful therapy with vedolizumab may alleviate symptoms but would be unlikely to restore intrinsic barrier dysfunction which has been genetically and experimentally demonstrated in IBD. Such a scenario permits systemic translocation of adjuvant, cytokines, other bacterial PAMPs and antigens to the systemic circulation and to enthesis and bone. These factors contribute to innate immune activation via biomechanical stressing and interactions with tissue resident myeloid and innate immune cells. Dendritic cell migration from the enthesis to the regional lymph nodes then prime and

expand T cells which then home to the enthesis in a non-MADCAM-1 dependent fashion. It remains to be determined whether α4β7 reactive lymphocytes locate to enthesis by virtue of being trapped outside the gut compartment and then gaining access to the enthesis via one of several adhesion molecules activated at sites of inflammation. The inadvertent deposition of gut-derived antigens at enthesis and the inappropriate homing of these cells might explain these severe paradoxical inflammatory arthropathies in successfully treated IBD. Finally, prior TNFi therapy cessation might contribute to the timing of VDZ induced disease flare.