Case Report

Differential Effects of Integrin Blockade on Gut and Sacroiliac Joint Inflammation

To the Editor:

αEβ7, is a prototypic gut integrin that regulates homing of memory and effector T cells to the gut. Vedolizumab is an anti-αEβ7, monoclonal antibody and is approved by the US Food and Drug Administration to treat ulcerative colitis and Crohn disease (CD). However, vedolizumab has been associated with the development of arthritis flares or new-onset arthritis in some patients with ulcerative colitis or CD. It is unclear why αEβ7 integrin blockade has paradoxical consequences in the gut and joint, despite the respective ligands being expressed at both sites. Here, we sought to analyze the profile of CD8+ T cells using mass cytometry from a patient with CD who developed sacroiliitis coincident with continued vedolizumab treatment.

This case report received research ethics board approval from the University Health Network (#08-0126).

The patient, a White male, was diagnosed with ileal CD at age 30 in 2013. He received a course of budesonide shortly after diagnosis, but without clinical benefit. In 2016, he began developing symptoms of back pain. In 2018, a rheumatology assessment diagnosed nonspecific back pain on the basis of (1) nondiagnostic radiographs of the pelvis and spine, (2) normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), (3) negative HLA-B27, and (4) noninflammatory clinical features of the pain. The CD disease activity was recorded as 12 in early 2019, according to the Harvey-Bradshaw Index (HBI), indicating moderate clinical activity. Vedolizumab was initiated, which successfully resolved the patient’s CD clinical activity by 2020 (HBI = 4). However, by late 2020, the patient’s back pain worsened. A second rheumatology assessment included a magnetic resonance imaging (MRI) scan, which showed profound diffuse bone marrow edema, consistent with active sacroiliitis (Figures 1A,B). Vedolizumab was discontinued and treatment was switched to adalimumab (ADA). Three months after ADA initiation, a follow-up MRI scan revealed a marked reduction in the degree of subchondral bone marrow edema bilaterally (Figures 1A,B). Specifically, Spondyloarthritis Research Consortium of Canada MRI scores fell from 62 on the initial MRI to 2 on the follow-up MRI (Figure 1B). ESR, CRP, and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) declined significantly with the switch from vedolizumab to ADA and remained stable (Figure 1C).

Mass cytometry of peripheral blood mononuclear cells (PBMC) revealed that αEβ7, expression, central to retention of T cells within the gut, was increased compared to healthy controls (HCs) during treatment with vedolizumab. After the transition from vedolizumab to ADA, there was a decline in αEβ7, expression, which remained low with continued ADA treatment. This pattern also tracked with the following cellular profile: CD103+, CD69−, CD103+, integrin αL, CD103−integrin αL, as well as with ESR/CRP and BASDAI values (Figure 2A). Integrin αL, as the αLβ2 heterodimer, is responsible for inflammatory cell infiltration in mouse models of colitis and arthritis. Expressions of CXCR3 and CXCR4 increased with continued vedolizumab treatment and tracked with ESR/CRP and BASDAI scores. Across all timepoints, a marked elevation of CXCR3 and CXCR4 expression was observed, compared to that in HCs (Figure 2A). CXCR3 regulates T cell migration into inflamed microenvironments by promoting commitment to an enhanced effector rather than a memory fate. The CXCR4-CXCL12 receptor ligand combination may also play a role in recruitment of inflammatory cells to the joint.

PD-1+ and TIGIT+ expression remained low compared to that in HCs and throughout the 4 timepoints, implicating CD8+ T cell dysregulation. CD38+ expression was slightly lower than in HCs but continued to decline steadily regardless of the treatment (Figure 2B). This is unexpected, since CD38 upregulation usually occurs upon activation and differentiation of lymphocytes when mature. It is possible that the high CXCR3 expression could have primed the blood CD8+ T cells to a more effector instead of memory profile, hence the low CD38 frequencies. Treatment with ADA was followed by an elevated granzyme A and B expression, and these tracked in a reciprocal pattern to that of ESR/CRP and BASDAI values. Further, granzyme expression was much lower compared to that in HCs, with granzyme A being the most frequent subset and granzyme K being the least frequent (Figure 2B). The lower granzyme profile has been reported previously in axial spondyloarthritis (axSpA) and may reflect cells pivotal to the development of sacroiliitis. However, its elevation upon ADA treatment implicates a recovery of cytotoxic T lymphocyte (CTL) functionality and homeostasis.

During treatment with vedolizumab, there was a shift in integrin usage and a dysregulated CTL profile. This may relate to the acceleration of sacroiliitis with this treatment, despite gut inflammation being well controlled at the same time. This implicates differential effects of vedolizumab on gut and joint inflammation. Peripheral CD8+ T cell expressions of integrin αLβ2, integrin αL, CXCR3, and CXCR4 were markedly elevated after vedolizumab treatment.

Overall, these observations are suggestive of a scenario whereby upon blocking αEβ7 integrin, a shift in CTL trafficking mechanisms occurred. Further, CTL functionality may be affected. It cannot be determined with confidence whether resolution of the sacroiliac inflammation, and the related immune profiles, were attributable to the discontinuation of vedolizumab or the initiation of ADA.

Current concepts of the pathogenesis of axSpA are grounded in (1) the tropism for the sacroiliac joint in the inflammatory process, and (2) the contribution of clinical or subclinical gut inflammation. However, current mechanistic explanations linking both events are lacking. The dissociation of gut-joint inflammation is not well understood.
The response to integrin blockade seen in this case may provide informative clues for future studies to unravel this relationship.

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Figure 2. Integrin, checkpoint, and granzyme profile of CD8+ T cells during vedolizumab and adalimumab. (A) Frequency of integrins expressed as a percentage of CD8+ T cells and median expression of CXCR3 and CXCR4 on CD8+ T cells. In the top figure, ESR/CRP/BASDAI values are overlaid with integrin frequency and CXCR3 and CXCR4 median values, whereby dashed lines represent ESR, CRP, and BASDAI, and solid lines represent the integrin CD103( integrin αE)+β7+, CD103+CD69−, CD103+CD49a( integrin α1)−, CD103−CD49a+, CXCR3, and CXCR4. In the bottom figure, boxplots of integrin frequencies and CXCR3 and CXCR4 median expression from 5-7 HC samples are plotted next to line graph of integrin frequencies and CXCR3/CXCR4 median values from case patient. (B) Frequency of checkpoint and granzyme proteins expressed as a percentage of CD8+ T cells. In the top figure, ESR/CRP/BASDAI values are overlaid with checkpoint and granzyme protein frequency values, whereby dashed lines represent ESR/CRP/BASDAI as before, and solid lines represent PD1+CD8+, TIGIT+CD8+, CD38+CD8+, GZMA+CD8+ (granzyme A), GZMB+CD8+ (granzyme B), and GZMK+CD8+ (granzyme K). In the bottom figure, boxplots of checkpoint and granzyme protein frequencies from 7 HC samples are plotted next to line graph of checkpoint and granzyme protein frequencies from case patient. ADA: adalimumab; ADA_1: first adalimumab time-point (May 2021); ADA_2: second adalimumab time-point (June 2021); BASDAI: Bath Ankylosing Spondylitis Disease Activity Index (orange solid line); CRP: C-reactive protein (green solid line); ESR: erythrocyte sedimentation rate (purple solid line); HC: healthy control; VEDO: vedolizumab; VEDO_1: first vedolizumab time-point (September 2019); VEDO_2: second vedolizumab time-point (February 2021).