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Dual Biologic Therapy in an Adolescent With Camurati-Engelmann Disease and Crohn Disease

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Abstract: Camurati-Engelmann disease (CED) is a rare disorder caused by activating mutations in the TGF-β1 gene and characterized by hyperostosis of long bones and bone dysplasia. We describe a case of an adolescent with CED and moderate-severe Crohn Disease (CD). Infliximab improved gastrointestinal symptoms but was associated with worsening CED-associated bone pain. Clinical remission was successfully achieved with dual biologic therapy that included vedolizumab and ustekinumab. Possible reasons for this patient's clinical response are advanced and include speculation about the complex role of TGF-β1 signaling in the etiology of both CED and CD.

Key Words: inflammatory bowel disease, ustekinumab, vedolizumab, TGF-β1

INTRODUCTION

Camurati-Englemann disease (CED) is a rare autosomal dominant disorder characterized by hyperostosis of long bones resulting in bone pain and muscle weakness. It is caused by domain-specific missense mutations of the transforming growth factor-β1 (TGF-β1) genes resulting in an overactivation of TGF-β1 (1). CED therapy focuses on symptomatic management with corticosteroids, nonsteroidal antiinflammatory drugs, and losartan for its TGF-β1 inhibitory effects. TGF-β1 is a multifunctional protein and a profibrotic cytokine that plays a role in cellular differentiation of skeletal tissue and is also critical for immune cell maturation, signaling, and immune tolerance in the gut (1). TGF-β1 signaling serves an anti-inflammatory role and its loss has been very well documented in association with many chronic inflammatory processes (2). TGF-β1 is produced by many cell types including intestinal epithelial cells (IECs), and increased TGF-β1 signaling contributes to the suppression of inflammatory responses and induction of immune tolerance to luminal antigens via distinct signaling mechanisms that allow for generation of regulatory T (T_{reg}) cells (an immunosuppressive T cell line) (3). Isolated intestinal and colonic tissues from patients with IBD have shown increased TGF-β1 levels, leading to the hypothesis that the increased production of TGF-β1 by intestinal epithelia is a response to the active inflammation (4). However, research has also shown that TGF-β1 can act as a proinflammatory cytokine, potentiating inflammation in the presence of tumor necrosis factor α (TNFα, a proinflammatory cytokine) and increasing interleukin-6 (IL-6, acts as a proinflammatory cytokine) production by IECs (5). The opposing roles of TGF-β1 signaling are complex, and drivers of predominant pathways (pro- versus antiinflammatory) are unknown. The coincidence of CED and inflammatory bowel disease (IBD) is rare, with only one other report in the literature of a patient who improved on anti-TNFα therapy (6). Here, we describe the unique case of a patient with CED and Crohn Disease (CD) who experienced worsening bone pain on anti-TNFα therapy and was later successfully treated with alternative dual biologic therapy. This case provides insights into the complex molecular mechanisms of these diseases and illustrates potential for dual biologic therapy for precision medicine in the future.

CASE REPORT

A 13-year-old girl with a history of CED was referred for new onset of culture negative hematochezia and diarrhea. Her medical history was complicated by severe growth failure attributed to her primary bone disease, many years of prednisone therapy and caloric deficit. The patient was on methotrexate and losartan for management of CED-associated bone pain. Laboratory investigations revealed hemoglobin 12.8 g/dL, erythrocyte sedimentation rate 16 mm/h, albumin 4.4 g/dL, and fecal calprotectin 224 μg/g. Endoscopic investigation was recommended in addition to placement of a percutaneous endoscopic gastrostomy (PEG) tube for nutritional optimization, but the family refused all recommendations.

The patient returned 2 years later with recurrent hematochezia. A PEG tube placement was placed, and ileocolonoscopy revealed mildly friable mucosa in the distal ileum and discontinuous areas of ulcerated mucosa in the rectum and cecum. Biopsies showed focal active ileitis, chronic active inflammation of the left colon with mild-to-moderate active inflammation in the right colon. Biopsies from the rectum revealed chronic inactive proctitis; duodenal biopsies showed normal mucosa. Fibrosis was not observed. Infliximab induction was given at 5 $mg \cdot kg^{-1} \cdot dose^{-1}$ at 0, 2, and 6 weeks, and every 8 week maintenance dosing was planned. However, an infliximab level 4 weeks after the third induction dose was 2.3 μg/mL (no infliximab antibodies), and the fourth dose was increased to 10 $mg \cdot kg^{-1} \cdot dose^{-1}$. Hematochezia, diarrhea, and abdominal pain improved on anti-TNFα therapy, but bone pain worsened. Infliximab was discontinued after the fourth dose as the patient and family were convinced that the infliximab caused the increased bone pain. The pain decreased with time after the last infliximab dose. Treatment with budesonide was begun.

During a 2 months' follow-up visit, our patient reported improvement in bone pain but recurrence of hematochezia, diarrhea, and abdominal pain while on budesonide. Her clinical course was complicated by anemia and severe malnutrition, despite attempts at optimizing caloric intake. As infliximab was previously not tolerated, vedolizumab was started at 300 mg at 0, 2, and 6 weeks, and then maintenance therapy was given every 8 weeks.

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Abdominal pain and hematochezia improved after the first dose without recurrence of severe bone pain. Hematochezia recurred after the forth dose, and the dose interval was shortened to every 4 weeks with addition of hydrocortisone enemas nightly. Patient reported improvement in hematochezia. After completion of the seventh vedolizumab infusion, the patient's clinical course was further complicated with the development of severe pyoderma gangrenosum requiring hospitalization for debridement.

Addition of a second biologic agent was discussed with the family to address the pyoderma gangrenosum. Ustekinumab was added as a single loading dose of 260 mg IV followed by 45 mg subcutaneous injection every 28 days. Dose selection was based on the patient's weight of 20 kg. By 6 months of dual biologic therapy, clinical and biochemical remission were achieved with resolution of the pyoderma gangrenosum and substantial weight gain. Inflammatory markers decreased, and hemoglobin and albumin levels increased (Fig. 1). Body mass index increased by 41% over the first year of dual biologic therapy (Fig. 2). Bone pain remains well controlled.

DISCUSSION

IBD is rare in individuals affected by CED. In a previous report of a patient with CED and ulcerative colitis, infliximab successfully

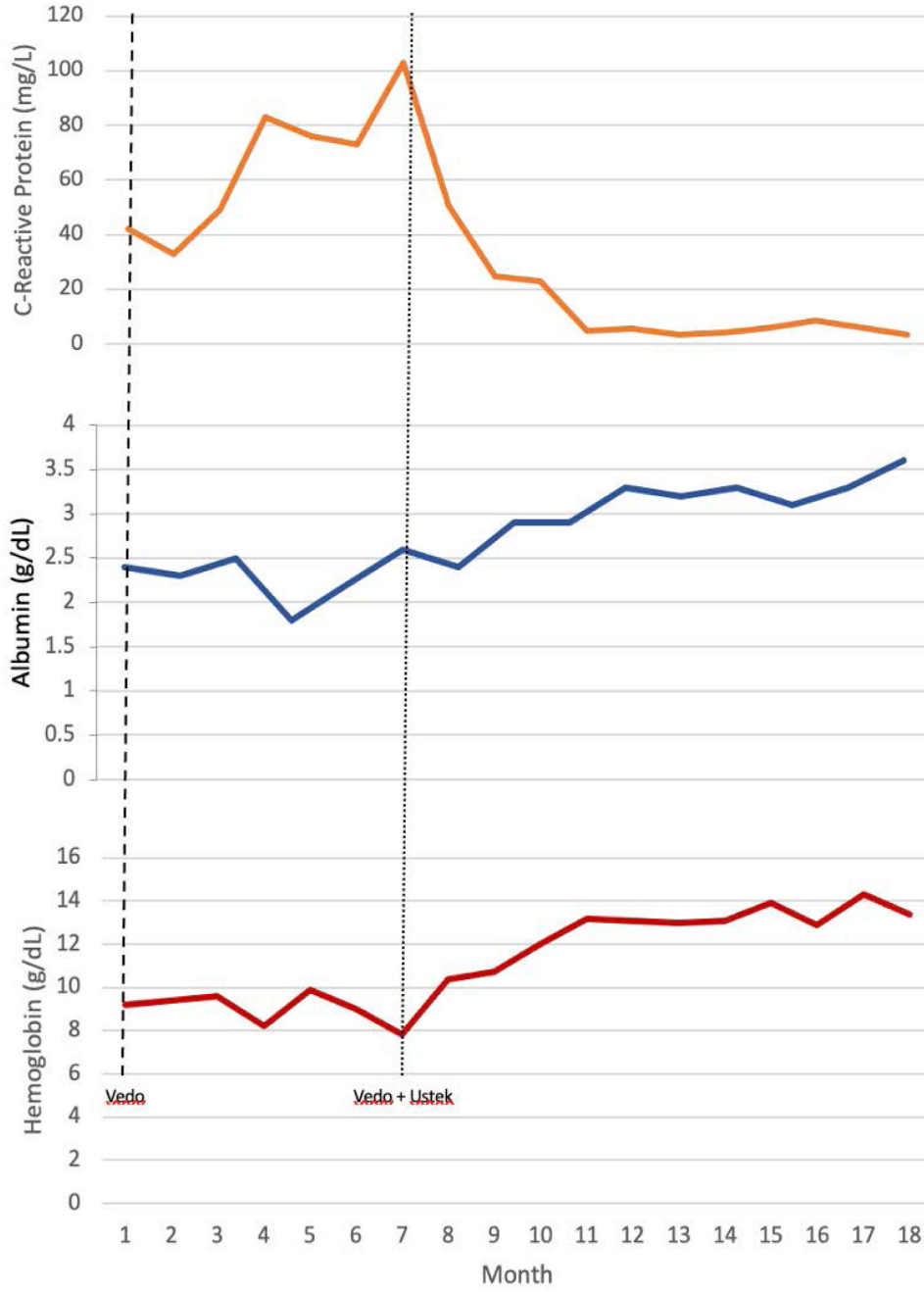

FIGURE 1. Albumin, hemoglobin, and C-reactive protein levels before and after initiating dual biologic therapy (Vedo: Vedolizumab; Ustek: Ustekinumab).

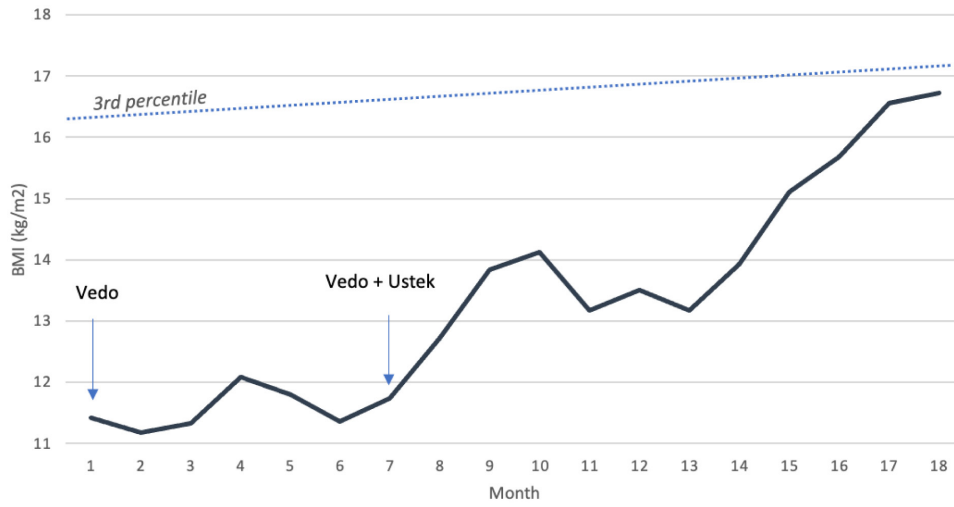

FIGURE 2. Recorded BMI levels before and after initiating dual biologic therapy (Vedo: Vedolizumab; Ustek: Ustekinumab). BMI, body mass index.

controlled both gastrointestinal symptoms and CED-associated bone pain (6). However, this was not the case in our patient who experienced worsening bone pain despite improvement in gastrointestinal outcomes while on infliximab. This heterogeneity in clinical response to infliximab warrants further exploration of the effect of treatments on the underlying predominant molecular mechanisms in CED and IBD.

TGF-β1 signaling plays a role in both diseases. Increased activation of TGF-β1 is the pathophysiological hallmark of CED, as it modulates the function of both osteoblasts and osteoclasts, regulating bone formation and resorption, respectively (1). Although the immunosuppressive role of TGF-β1 signaling has been well described, prior studies have also documented the role of TGF-β1 as a proinflammatory cytokine in specific environments (5).

In vitro experiments conducted by McGee et al describe TGF-β1 as a potentially proinflammatory cytokine in the presence of TNFα (5). Evidence for this coinflammatory mechanism was also well described in bone marrow-derived mesenchymal stem cells (7). Interestingly, TNFα has also been shown to upregulate TGF-β1 production and signaling in some cell lines including lung fibroblasts, increasing risk for fibrogenesis (8). This phenomenon has not been completely explored in IECs. Our patient's gastrointestinal response to TNFα blockade with infliximab may be related to this coinflammatory mechanism.

TNFα modulates pain through several mechanisms and increases pain sensitization and processing in the central nervous system (6). Despite reported success of infliximab controlling CED-associated bone pain, we have no clear explanation why our patient's bone pain worsened while receiving TNFα blockade, and there remains a possibility that other unknown factors coincidentally contributed to our patient's bone pain exacerbation around the time of infliximab infusion. Another possible explanation is the presence of antiinfliximab antibodies that were not detected via commercial testing, however, that seems less likely given our patient's improved symptoms of hematochezia, diarrhea, and abdominal pain.

Vedolizumab was trialed for its intestinal cell selectivity and achieved an initial positive response in our patient, judged primarily by the clinical improvement of hematochezia and abdominal pain after the first dose without bone pain exacerbation. Vedolizumab works primarily by blocking α4β7 receptors, a gut-specific integrin that promotes homing of lymphocytes into intestinal sites. Its blockade leads to downregulation of the local inflammatory response. Similarly, studies have shown that active TGF-β1 downregulates α4β7 expression in murine gut mucosa serving an antiinflammatory role (9,10). This interaction is noteworthy and may have contributed to decreasing the available integrins for vedolizumab to bind to thereby blunting the clinical response in our patient.

Ustekinumab was the second alternative biologic agent added to our patient's treatment regimen and was administered in response to her developing pyoderma gangrenosum (PG), while on vedolizumab monotherapy. PG has been associated with active CD, especially with colonic involvement as in our patient (11). This ongoing clinical evidence for active CD led us to start ustekinumab with excellent clinical response and PG resolution without bone pain exacerbation. Published experience using ustekinumab to treat moderate-severe CD demonstrates clinical success in both anti-TNFα exposed and anti-TNFα naïve populations (12). Experience with ustekinumab use in pediatric IBD is increasing, with recent observations demonstrating a favorable efficacy and safety profile (13,14). Ustekinumab works primarily by binding to the p40 subunit common to both interleukin-12 (IL-12) and interleukin-23 (IL-23), preventing these cytokines from binding to the beta-1 subunit of their respective receptors. IL-12 and IL-23 signaling promote inflammation. IL-12 inhibits the differentiation of T_{reg} cells and increases the development of inflammatory helper T cells (cells that mediate an inflammatory response and release of proinflammatory cytokines) in the presence of TGF-β1 (15). This acts to reduce immune tolerance and increase inflammation. Our patient's response to ustekinumab may be attributed to the inhibition of this pathway. Interestingly, one study suggested that TGF-β1 exerts a counter-regulatory effect on the IL-12 signaling pathway to suppress inflammation, which might suggest that ustekinumab is potentiating an endogenous response in our patient (16). In addition to its interaction with the IL-12 pathway, one study suggested that TGF-β1 plays a role in augmenting IL-6 and IL-23-mediated Th17 differentiation (17). Th17 is a T helper cell subset that produces IL-17, a cytokine that signals and amplifies inflammatory processes. Inhibition of IL-23 signaling via ustekinumab interferes with Th17 differentiation, possibly contributing to our patient's response.

Another noteworthy study analyzed the effect of ustekinumab on serum levels of active TGF-β1, showing an overall decrease in serum levels after 28 weeks of therapy (18). This may have contributed to our patient's improved clinical response and controlled

CED-associated bone pain, assuming the proinflammatory role of TGF-β1 signaling in the gut. However, active TGF-β1 levels were not measured in our patient while on ustekinumab, and this effect is speculative, but her clinical and biochemical responses are notable.

The combined use of vedolizumab and ustekinumab has not been reported in patients with CED and IBD. The immune response and complexity of molecular mechanisms in this patient population is multidimensional and suggests potential benefit of dual biologic therapy targeting different inflammatory pathways. It is not yet clear if ustekinumab monotherapy would achieve a similar response in our patient, and discussion to remove vedolizumab has begun with her and her family.

This unique case provides the opportunity to explore overlapping molecular mechanisms in IBD and CED and the impact of different biologics on the activity of underlying inflammatory pathways. Moreover, our results suggest a potential alternative treatment with either ustekinumab monotherapy or possible dual biologic therapy with vedolizumab and ustekinumab. Understanding the role and effect of targeted therapy on TGF-β1 could prove to be critical for the successful management in this patient population. Although TNFα blockade with infliximab therapy has previously shown efficacy in managing both disease states, our results suggest a positive outcome with the use of dual biologic therapy with vedolizumab and ustekinumab.

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