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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Medically Refractory Lymphocytic Colitis Successfully Treated With Upadacitinib

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ABSTRACT

Lymphocytic colitis is a microscopic colitis characterized endoscopically by nearly normal-appearing colonic mucosa and histology demonstrating intraepithelial lymphocytosis. Microscopic colitis that is refractory to conventional therapies, including budesonide, is rare but challenging and with scarce evidence. Upadacitinib is a novel Janus kinase 1 selective inhibitor approved by the US Food and Drug Administration for atopic dermatitis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and moderately to severely active ulcerative colitis. We present the first case of lymphocytic colitis refractory to conventional and immunosuppressive therapies, which responded promptly to upadacitinib.

KEYWORDS: lymphocytic colitis; microscopic colitis; upadacitinib

INTRODUCTION

Microscopic colitis (MC), which consists of collagenous colitis (CC) and lymphocytic colitis (LC), causes chronic watery diarrhea that significantly impairs quality of life.[1] MC is diagnosed by normal or mild findings in colonoscopy with specific pathological findings which distinguished CC and LC with similar clinical manifestations. MC is associated with an increased risk of subsequent inflammatory bowel disease (IBD) and other autoimmune diseases, including celiac disease. Risk factors of MC include women in their fifth or older decade of life; people who smoke cigarettes; and certain medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), or serotonin selective receptor inhibitors.[1] Treatment of MC includes cessation of the potential offending agents and use of budesonide, which has strong evidence of efficacy.[2] A recent nationwide cohort study showed that fewer than 5% of patients with MC did not respond to budesonide and require other immunosuppressive therapies.[3] On the other hand, there are no randomized controlled studies for biologics or small molecule therapies in MC, and only case reports or small case series are available. Previous reports describe the effectiveness of tumor necrosis factor-alpha (TNFα) antagonists and α4β7-integrin antagonists as treatments of refractory MC.[4–7] There are no reports of Janus kinase inhibitors (JAKinibs) to treat MC. In this study, we report a patient with medically refractory LC who was successfully treated with a selective JAK-1 inhibitor, upadacitinib.

CASE REPORT

A 61-year-old woman was diagnosed with LC at 49 years when she developed persistent watery diarrhea. She had been treated with systemic steroids and budesonide with a partial response and infliximab, which was discontinued because of pericarditis and joint pain before she was referred to our hospital. Other etiologies, including celiac disease, chronic infections, or medication-induced, were ruled out. In addition to the intermittent use of systemic steroids and budesonide, tacrolimus responded well for the first several months, but severe diarrhea relapsed, regardless of high trough levels of tacrolimus. Other immunosuppressive therapies including vedolizumab, tofacitinib, and ozanimod were tried in order, but none of them showed remarkable efficacy. She never smoked and had no chronic exposures to NSAIDs, PPIs, or other potential offending medications for LC. She had been managed on colesevelam and short-term induction use of budesonide 9 mg/day with persistent watery diarrhea 6 to 8 times per day, nocturnal episodes, and mildly elevated C-reactive protein (CRP) levels of 5 to 11 mg/mL (Figure 1). Subsequently, her symptoms progressed to worsening urgency with

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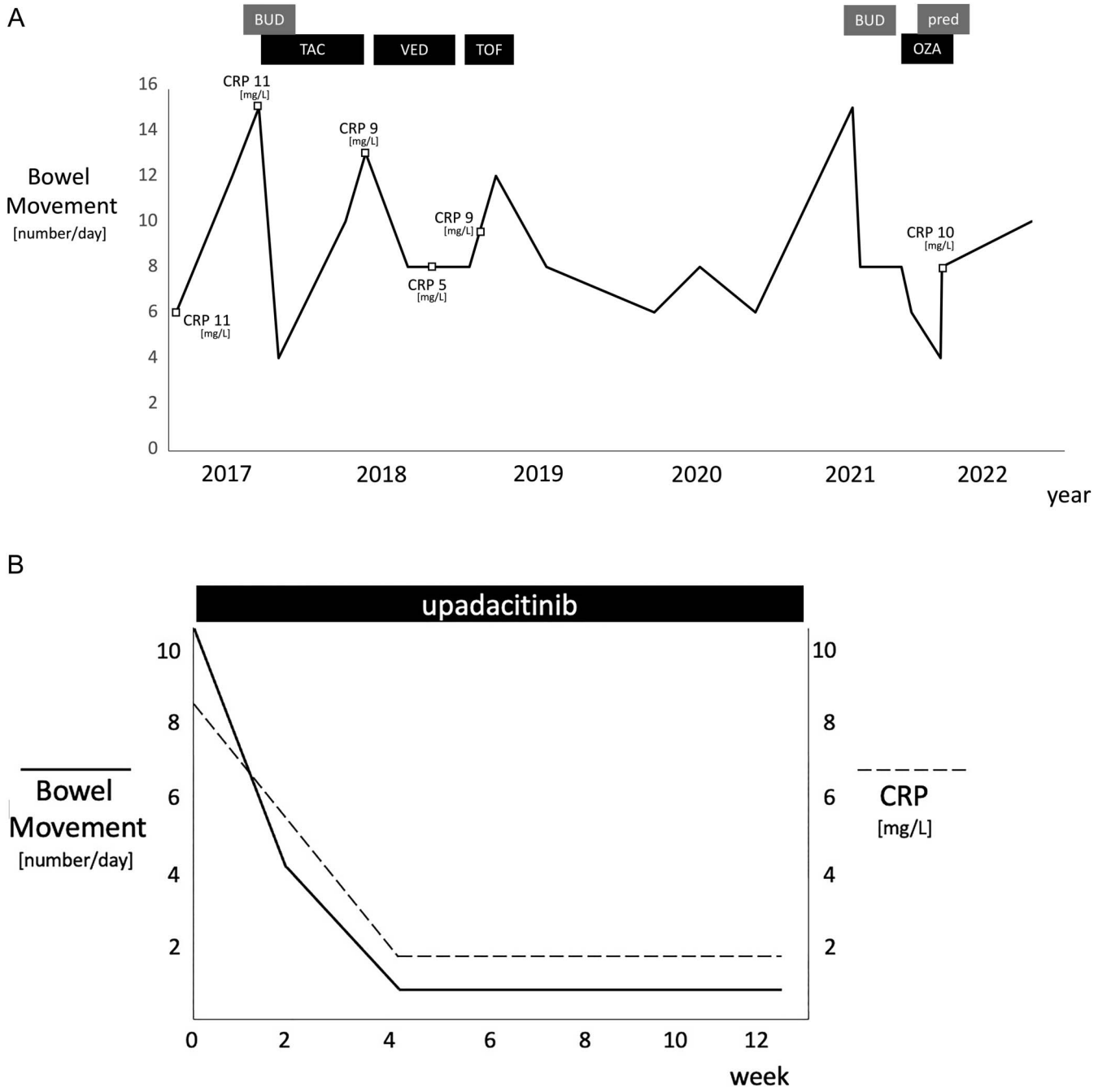

Figure 1. (A) Clinical course before upadacitinib induction therapy. CRP, C-reactive protein; BUD, budesonide; pred, prednisone; TAC, tacrolimus; VED, vedolizumab; VED, tofacitinib; OZA, ozanimod. (B) Clinical course at upadacitinib induction therapy. CRP, C-reactive protein.

incontinence, abdominal pain, and knee joint pain. Laboratory results revealed long-standing elevated CRP with a level of 10 mg/L and mildly positive anti-cyclic citrullinated peptide antibody (27 IU/mL) with negative rheumatoid factor. Magnetic resonance imaging did not demonstrate erosions or bone marrow signals to suggest rheumatoid arthritis. A colonoscopy was performed which showed no inflammation with visible vascular pattern throughout the entire colon. Nontargeted colon biopsies obtained during the colonoscopy (and multiple prior examinations) showed increased lymphocytic infiltration without a significant subepithelial collagen band, consistent with active LC (Figure 2). Upadacitinib 45 mg once daily was initiated for LC and to treat the joint pain. Her symptomatic diarrhea improved within 2 weeks, and her joint pain subsided. She described 1 formed stool a day, and at week 8 after starting therapy, her CRP and fecal calprotectin (<3 mg/L and <50 μg/mg, respectively) normalized for the first time in her medical history (Figure 1). At the time of this publication, she remains in clinical remission and has experienced no adverse effects including major adverse cardiovascular events and thrombosis.

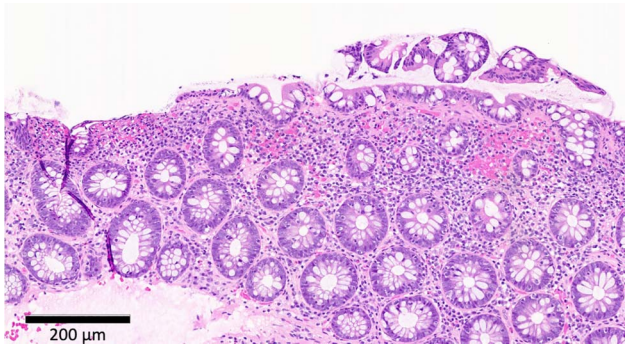

Figure 2. Hematoxylin and eosin stain of a nontargeted biopsy of the colon demonstrates increased lymphocytic permeation of the epithelium with a preserved crypt architecture.

DISCUSSION

This is the first case of refractory MC successfully treated with a JAKinib, and specifically, with upadacitinib. Although LC and CC are pathologically different, a subgroup of MC has been described to change histopathological findings from LC to CC and vice versa which develop similar clinical manifestations.[8] Recent guidelines for MC propose the combined treatment algorithm, which does not distinguish between the types.[9–11] In addition to avoiding risk factors such as NSAIDs, PPI, and smoking, budesonide is recommended for the treatment of MC. However, less than 5% of patients with MC have resistance to budesonide and require other immunosuppressive therapies, and evidence of other treatments of budesonide-refractory MC is scarce with only case reports or case series existing.[3]

Immunomodulators and biologics, including TNFα antagonists and α4β7-integrin antagonists, have been reported as therapies for refractory MC. A single-center retrospective study, which included 49 patients of MC treated with thiopurines and 12 patients with methotrexate, demonstrated complete response defined by <3 stools daily and <1 watery stool daily in 42% and 58% of patients, respectively.[12] A multicenter cohort study that enrolled 14 patients who were refractory to budesonide and treated with infliximab and adalimumab achieved clinical remission without steroids at 12 weeks in 5 of the 14 patients (all with infliximab). When combined with both first and second TNFα antagonists, 7 of the 14 patients were in clinical remission at 52 weeks.[4] An international case series that included 11 cases of budesonide-refractory MC treated with vedolizumab demonstrated that clinical remission was observed in 5 of the 11 patients after completing 3 infusions. Notably, 10 of the patients had not responded to at least 1 TNFα antagonist.[6]

Upadacitinib is a novel selective small molecule-targeting JAK-1 that has received US Food and Drug Administration approval for atopic dermatitis, rheumatoid arthritis, psoriatic arthritis, and moderately to severely active ulcerative colitis.[13] Blocking JAK-1 reduces interferon-γ and interleukin-6, which are involved in the pathogenesis of MC. Therefore, upadacitinib has a good rationale to be considered as a treatment of MC.[14–17] Although tofacitinib, a pan-JAKinib, was not effective at an induction dose of 10 mg twice a day in this case, we suggest that the unique mechanism of selective JAK-1 activity of upadacitinib provided improved efficacy. This observation in LC is important because there are no head-to-head trials in other disease states comparing tofacitinib with upadacitinib.[18]

In this case, we describe the prompt and significant effectiveness of upadacitinib for the treatment of multitherapy-refractory MC. Prospective studies are warranted to clarify the pathogenetic implications as well as the efficacy and safety of upadacitinib as a treatment for MC.

DISCLOSURES

Author contributions: Y. Miyatani and DT Rubin conceptualized and design the study. Y. Miyatani acquired, analyzed, and interpreted the data and drafted the manuscript. D. Choi analyzed the data and revised the manuscript for intellectual content. X. Du and J. Hart interpreted the data. DT Rubin critically revised the manuscript for intellectual content and is the article guarantor.

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Informed consent was obtained for this case report.

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