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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Ozanimod Therapy in a Patient With Ulcerative Colitis and Multiple Sclerosis: Hitting 2 Birds With 1 Stone

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ABSTRACT

Simultaneous occurrence of multiple sclerosis (MS) and ulcerative colitis (UC) is seldom encountered by clinicians and poses unique challenges. The sphingosine-1-phosphate receptor modulator ozanimod has been recently approved for UC. Ozanimod can be used in such scenarios where it can treat both conditions, reducing the need for multiple targeted therapies. We report the first case of successfully treated multiple sclerosis and UC with ozanimod.

KEYWORDS: oral small molecules; multiple sclerosis; ulcerative colitis

INTRODUCTION

Immune mediated inflammatory diseases (IMIDs) are a heterogenous group of chronic disabling conditions of unknown etiology characterized by immune mediated damage to target organs in genetically predisposed individuals. IMIDs share similar pathogenic immune pathways, and the presence of one IMID increases predisposition to others.[1] Inflammatory bowel disease (IBD) is a IMID involving the gastrointestinal tract, often has a complicated clinical course requiring life-long therapy and is associated with a significant burden to patients and impaired quality of life. IBD, IMIDs involving joints (psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, and juvenile inflammatory arthritis), and skin (psoriasis) are often associated with each other. A recent study showed that a quarter of patients with IBD are associated with IMIDs.[2] Multiple sclerosis (MS) is also an IMID involving the central nervous system (CNS) and know to be associated with IBD. Simultaneous occurrence of both diseases poses therapeutic challenges for patients and physicians. Antitumor necrosis factor agents which are highly effective for IBD can cause demyelinating lesions in CNS and are contraindicated in MS, whereas interferon β-1a which is effective in MS may trigger colitis.[3–5] Patients may be coprescribed multiple immunosuppressants to control both conditions. A better understanding of systems biology may enable better treatment through targeting of common immune pathways. For example, biologics targeting interleukin (IL)-23 are effective for both IBD and psoriasis, anti-IL17 therapy is effective for psoriasis and axial spondyloarthropathy, and anti-IL6 is effective for rheumatoid arthritis and juvenile inflammatory arthritis.[6] Similarly, sphingosine-1-phosphate receptor (S1PR) modulators have the potential to treat both ulcerative colitis (UC) and MS.[7] We report the first case in the literature of successfully treated MS and UC with an S1PR modulator ozanimod.

CASE REPORT

We report a 52-year-old woman diagnosed with extensive UC (E3—beyond splenic flexure) 22 years ago, initially managed with prednisone, mesalamine, and azathioprine. Oral mesalamine was stopped because of intolerance (worsening of diarrhea), and after few months of azathioprine therapy, she developed lung abscess complicated by aspergillus requiring lobectomy of the right middle lobe. Her UC was maintained with intermittent local mesalamine enema for the following 20 years without the need for systemic immunosuppressants.

Ten years ago, she was evaluated for deranged transaminases (aspartate aminotransferase: 298, alanine aminotransferase: 234, alkaline phosphatase: 570, and gamma-glutamyl transferase: 1,192) and epigastric pain. On evaluation, radiological imaging showed a mass lesion of size 5.5 cm in the right lobe of the liver and biopsy was consistent with intrahepatic cholangiocarcinoma after which she underwent right hepatic lobectomy. The postoperative histopathology confirmed poorly differentiated cholangiocarcinoma without

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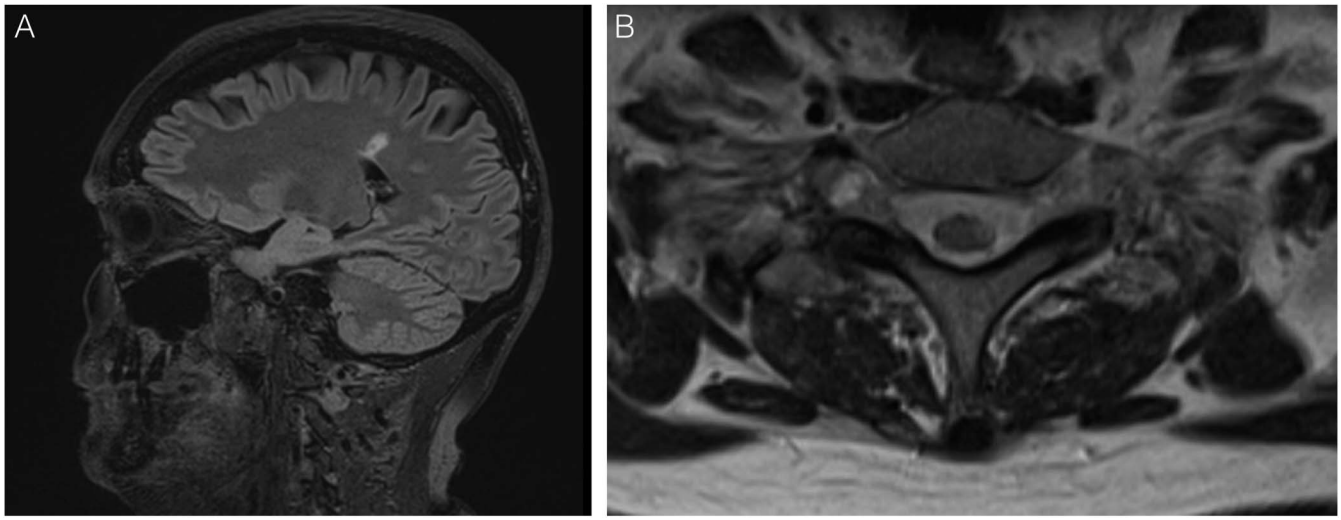

Figure 1. T2 weighted fluid-attenuated inversion recovery magnetic resonance images demonstrating (A) periventricular lesion and (B) lesion in cervical spinal cord consistent with multiple sclerosis.

involving resection margins or evidence of cirrhosis or primary sclerosing cholangitis. There has been no recurrence on subsequent follow-up scans, and there were no features consistent with primary sclerosing cholangitis on magnetic resonance cholangiopancreatography. Further evaluation led to a diagnosis of alfa-1 antitrypsin deficiency with very low serum levels (0.4 g/L).

In 2016, she experienced abnormal sensations over the right side of her abdomen and right lower limb. She was diagnosed with relapsing MS after 2 relapses that same year, and magnetic resonance imaging features were consistent with MS (Figure 1). She was initiated on glatiramer acetate with good disease control.

Over the past 12 months, she experienced increased stool frequency, rectal bleeding, and urgency. Colonoscopy showed features of active disease with a modified Mayo endoscopic score of 2 diffusely involving colonic mucosa extending between the rectum and hepatic flexure of the colon (Figure 2). She also had a relapse of MS symptoms over the past 6 months. She was started on ozanimod (0.23 mg/day on days 1–4, 0.46 mg/day on days 5–7 and followed by 0.92 mg/day as maintenance therapy thereafter) to treat both UC and MS, and glatiramer acetate was stopped. On repeat evaluation 6 months after the initiation of ozanimod, she was in clinical and endoscopic remission (modified Mayo endoscopic score 0) and her MS also remains stable (Figures 3). No concomitant steroids or immunosuppressive therapy was prescribed during this period.

DISCUSSION

MS and UC share common pathophysiology. The estimated prevalence of MS in IBD is 0.2% and for IBD in MS is 0.6%.[8] However, anti-TNF-induced MS and interferon-β1-triggered UC confound accurate estimations. S1PRs are present in multiple organ systems in the human body and associated with diverse biological functions. There are 5 different types of S1PRs located in different tissues carrying out different functions such as lymphocyte trafficking, angiogenesis, smooth muscle function, endothelial barrier function, maintenance of nerve cells, and cardiac and nerve cell conduction.[9] S1PR modulators are oral small molecules that inhibit lymphocyte trafficking by binding to S1PR on the surface of lymphocytes resulting in sequestration of lymphocytes in peripheral lymphoid organs such as lymph nodes and spleen, which is reflected by leukopenia in patients after the initiation of these drugs.

First generation and second generation S1PR modulators are approved for the treatment of MS (fingolimod, siponimod, ozanimod, and ponesimod). Phase III randomized controlled trials (SUNBEAM and RADIANCE) in relapsing-remitting MS have demonstrated superiority of ozanimod with fewer clinical relapse rate compared with interferon β-1a.[10,11] Ozanimod acts by targeting $S1PR_1$ and $S1PR_5$ receptors and is the only S1PR modulator approved for induction and maintenance of clinical remission in

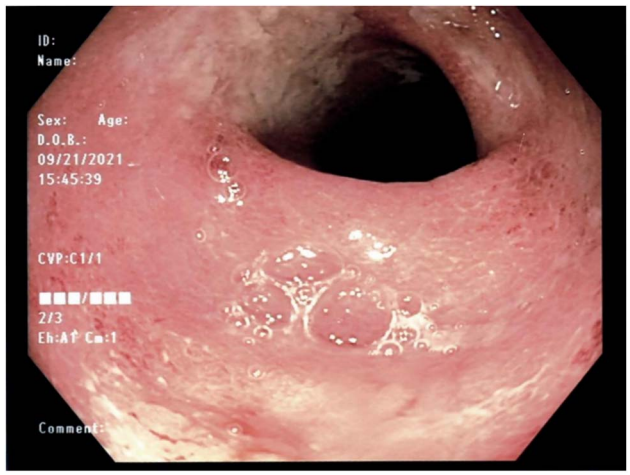

Figure 2. Endoscopic image before initiation of ozanimod showing active disease with complete loss of vascular pattern, mild mucosal bleeding, and erosions with exudates.

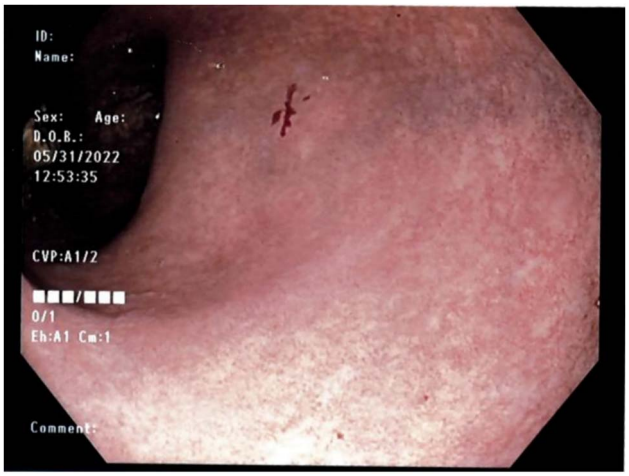

Figure 3. Endoscopic image 6 months after the initiation of ozanimod showing normal mucosa suggestive of endoscopic remission.

moderate to severe UC based on the results of phase-III (TRUE-NORTH) trial.[12] In this trial, ozanimod was associated with significantly higher proportion of clinical remission compared with placebo both in induction (18.4% vs 6%, $P < 0.001$) and maintenance phases (37% vs 18.5%, $P < 0.001$). A phase II open label, single arm study of ozanimod (STEPSTONE) in Crohn's disease (n = 69), showed clinical remission in 39%.[13] Phase III trials in Crohn's disease are currently in recruiting stage (NCT03440372, NCT03440385). The dosing schedule for UC and MS is similar with gradual escalation of dose over 7 days, followed by once daily administration. There are no recommended dose adjustment strategies available for UC or MS. If there is an interruption in treatment for more than 2 weeks after 28 days of initiation, ozanimod dose should be reintroduced gradually. Adverse events such as bradycardia, macular edema, elevated transaminases, hypertension, and increased risk of viral infections such as herpes zoster can be seen in patients on S1PR modulators, and these off-target effects can be explained by the widespread presence of S1PR in various organ systems.

In this case, ozanimod resulted in clinical and endoscopic remission of UC and controlling MS disease activity, indicating S1PR modulators can be safe and effective agents in patients with MS and UC. A previous case report showed successful therapy of MS and UC with fingolimod.[14] Therapeutic agents targeting common immune pathways reduce immunosuppressant burden in patients with more than 1 IMID.

DISCLOSURES

Author contributions: SK Vuyyuru: initial draft and approval of the manuscript. SA Morrow: review and approval of the manuscript. V. Jairath: conception of the idea, review, and final approval of the manuscript and is the article guarantor.

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Informed consent was obtained for this case report.

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