Interstitial Nephritis Secondary to Vedolizumab Treatment in Crohn Disease and Safe Rechallenge Using Steroids: A Case Report

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Vedolizumab is a gut-selective humanized monoclonal antibody that binds selectively to the α4 β7 integrin and acts as a lymphocyte-homing antagonist. It is indicated in ulcerative colitis and Crohn disease. We report a case of acute interstitial nephritis following vedolizumab infusion in a 55-year-old white woman treated for severe Crohn disease resistant to several therapies. Other kidney disease causes were ruled out. Glucocorticoids were administrated, leading to full renal recovery. In the absence of other therapeutic options, vedolizumab was re-administered along with transient corticosteroids; this treatment was well tolerated. Fewer than 10 cases of immunoallergic acute interstitial nephritis following treatment with monoclonal antibody have previously been reported in the literature. The pathophysiology of delayed-type hypersensitivity secondary to monoclonal antibody therapeutics is discussed in this case report.

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Vedolizumab is a gut-selective humanized monoclonal antibody binding selectively to the α4 β7 integrin and acting as a lymphocyte homing antagonist.[1] It has shown its efficacy in patients with moderately to severely active Crohn disease as induction and maintenance treatment.[2] Meta-analyses have reported good tolerance as compared to placebo; the most frequent adverse effects were infusion-related reactions, pyrexia, nausea/vomiting, headache, fatigue, nasopharyngitis, arthralgia, upper respiratory tract infection, dizziness, rash, and abdominal pain.[3]

We report a case of acute kidney injury following infusion of vedolizumab in a patient with no other therapeutic option, and its safe re-administration using steroids before and after administration of the antibody.

Case Report

A 55-year-old woman was admitted in May 2016 to the emergency unit for vomiting, asthenia, high fever, and myalgia evolving for 6 days. She had a history of Crohn disease diagnosed in 1999, resistant to several therapies, including mesalazine, azathioprine, methotrexate, and anti–tumor necrosis factor (TNF) therapies (infliximab, certolizumab, and adalimumab), and underwent colectomy with ileostomy in 2014. Symptoms started a few hours after a first injection of vedolizumab (300 mg). She had no other medication, and adalimumab administration had been discontinued 2 months earlier. Her vital signs were normal except for a low-grade fever. Physical examination revealed pustular cutaneous lesions compatible with pyoderma gangrenosum, and no other potential site of infection.

Laboratory findings showed the following values: elevated serum creatinine (4.6 mg/dL [410 μmol/L] with estimated glomerular filtration rate [eGFR] of 10 mL/min/1.73 m^2 [as determined using the isotope-dilution mass spectrometry–traceable 4-variable MDRD [Modification of Diet in Renal Disease] Study equation]), as compared to 0.9 mg/dL (80 μmol/L; eGFR, 67 mL/min/1.73 m^2) before; blood urea nitrogen, 18 mmol/L (50.4 mg/dL); hypoalbuminemia (albumin, 3 g/dL); hemoglobin, 10.5 g/dL; high white blood cell count (14.2 $\times 10^3$/μL), predominantly neutrophils with moderate hypereosinophilia (eosinophils, 0.6 $\times 10^3$/μL); no lymphopenia; high C-reactive protein (1,238 nmol/L [130 mg/L]); and negative results for blood cultures. Urinalysis showed hematuria, proteinuria (protein excretion, 0.96 g/d), leukocyturia (leukocytes, 200/μL) without eosinophiluria, and urine culture examination gave negative results. Hepatitis B virus, hepatitis C virus, and human immunodeficiency virus (HIV) serologic tests and blood and urinary testing for mycobacteria (using the QuantiFERON-TB ELISA [Quest Diagnostics]) were negative. Antineutrophil cytoplasmic antibody, antinuclear antibody, and anti–glomerular basement membrane antibody tests were negative; serum protein electrophoresis results and complement component (C3 and C4) concentrations were normal. Acute urinary obstruction was excluded by ultrasound.

Kidney biopsy showed interstitial edema with massive interstitial infiltrate consisting of lymphocytes, plasma cells, histiocytes, and granuloma formation (giant cells and epithelioid cells without caseous necrosis) associated with acute tubular injury (Fig 1). Immunofluorescence microscopy was negative.

The final diagnosis was acute interstitial nephritis (AIN) secondary to vedolizumab. Glucocorticoid (1 mg/kg/d) was administrated, with a full renal recovery within 1 month (serum creatinine, 1 mg/dL [88 μmol/L]; eGFR,

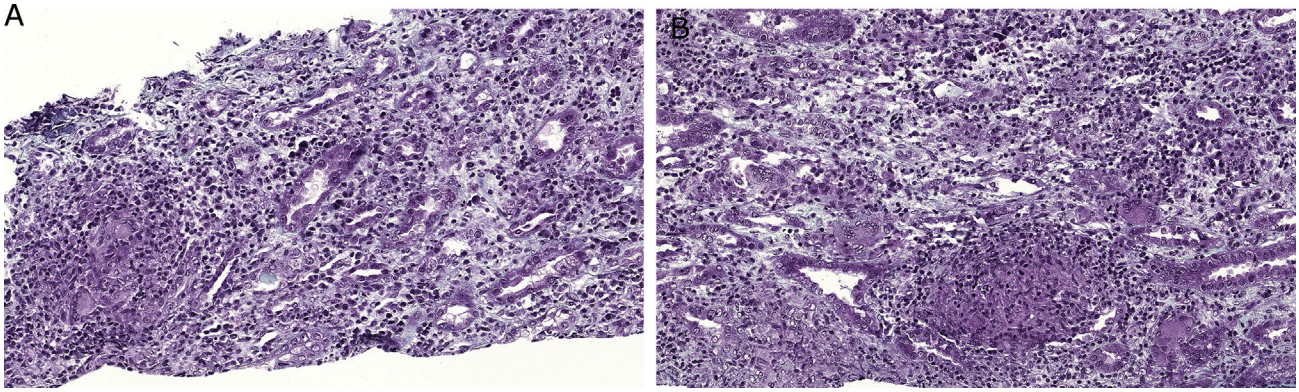

Figure 1. Kidney biopsy specimen. (A, B) Interstitial inflammation and edema with epithelioid and giant cell granuloma, acute tubular injury (trichrome Masson stain; original magnification, ×100 and ×200, respectively).

63 mL/min/1.73 m^2; and no proteinuria). Glucocorticoid dosage was tapered over 4 months (Fig 2). In the absence of any possible alternative treatment, vedolizumab (150 mg once, then 300 mg monthly) was administered again, but under cover of transient corticosteroid therapy each time (40 mg from the day before to the day after the infusion). Neither infusion-related reactions nor renal adverse effects were observed after 7 other infusions.

Discussion

We report a case of AIN in a patient treated with vedolizumab and safe vedolizumab rechallenge using systematic steroid use. The temporal relationship between vedolizumab infusion and symptoms followed by the discovery of AIN, along with the absence of other medication, implicates vedolizumab as the cause, especially because no other cause was found.

In a retrospective review of native kidney biopsy specimens in 83 patients with inflammatory bowel disease, interstitial nephritis was the second most common diagnosis, often in association with aminosalicylate therapy. Of 16 cases with interstitial nephritis, 7 were classified as acute; 5, as granulomatous; and 4, as chronic.[4] Although granuloma formations have been described in Crohn disease,[4] we excluded Crohn disease as the cause of this case of AIN because there was a clear temporal association with vedolizumab administration and no recent exacerbation of the disease. Mesalazine has been implicated in cases of chronic interstitial nephritis and rare cases of AIN or AIN on chronic interstitial nephritis[5]; however, our patient had no recent exposure to mesalazine. The pathologic presentation associated AIN with granuloma, as in some cases of drug-induced AIN.[6] There was no clinical evidence of tuberculosis or sarcoidosis.

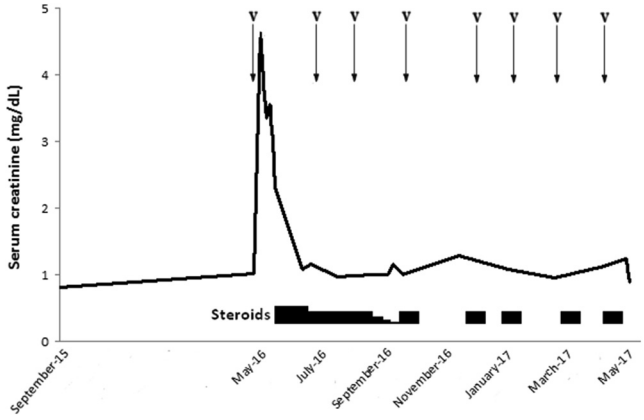

Figure 2. Evolution of serum creatinine concentrations before and after vedolizumab (v) administration and steroid treatment.

The main clinical trials with vedolizumab report that <5% of patients treated had an infusion-related reaction, but do not mention renal toxicity.[2,3] To our knowledge, no case of renal toxicity has been published since marketing authorization. The World Health Organization global individual case safety report database VigiBase[7] (accessed on March 22, 2017) contains 51 reports of suspected adverse reactions of renal and urinary disorders with vedolizumab from 9 countries in the world (our case excluded). Among these are 2 cases of nephritis (including 1 case of tubulointerstitial nephritis), 9 cases of kidney failure or reduced kidney function, and 2 other cases of nonspecified renal disorders, but other causes than the drug cannot be ruled out.

The gut selectivity of vedolizumab raises the question of the physiopathology of this drug-induced AIN. Drug-induced AIN is secondary to immune responses, often secondary to delayed-type hypersensitivity.[8] After oral or parenteral administration, drug components and metabolites can be found in renal tubulointerstitium. The drug or metabolite can mimic a tubular or interstitial antigen or can serve as a hapten after binding to a component of the tubular basement membrane or deposit in the interstitium, inducing an immune response. In humans, the mechanisms of injury are mostly cell mediated (mostly $CD4^+CD8^+$ T cells and monomacrophages), sometimes forming granuloma with T-helper cell type 1 (T_H1) polarization. The inflammatory reaction is associated with complement activation, leukocyte recruitment,