

Tolerance and Efficacy with Simultaneous Use of Two Monoclonal Antibodies for a Patient with Hypereosinophilic Syndrome and Ulcerative Colitis

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The development and utilization of monoclonal antibodies (mAbs) have been of great interest in all fields of medicine. A substantial increase in the production and development of mAbs has occurred because these biologic agents are proving to be effective and less toxic given their targeted mechanism of action. However, data are limited on coadministration of two or more mAbs. With the increasing availability of mAbs and the comorbidities of some patients, assessment is needed of the ability to safely use multiple mAbs for an individual patient. Although the efficacy of coadministered mAbs may be inferred from their specific targets, we could find no literature reporting such a finding. Herein, we report our experience using two different classes of mAbs to treat hypereosinophilic syndrome and ulcerative colitis in a single patient.

Keywords: drug interactions, gastroenterology, hematology

Introduction

THE CRITERIA FOR defining hypereosinophilic syndrome (HES) were established more than 40 years ago by Chusid et al.,⁽¹⁾ and although revisions to the original criteria have been proposed,⁽²⁾ the core requirements continue to be substantial ($>1.5 \times 10^9$ cells/L) eosinophilia (or tissue eosinophilia) and associated symptoms after exclusion of secondary causes. Treatment of HES has advanced substantially over the past quarter century, progressing from use of prednisone and hydroxyurea to subsequent use of interferon α -2b⁽³⁾ and pegylated interferon (Peg-IFN) α -2b.⁽⁴⁾ For hypereosinophilic patients with clonal eosinophilia defined as the presence of *FIP1 L1-PDGFRa* fusion⁽⁵⁾ and for some hypereosinophilic patients without this mutation,⁽⁶⁾ the receptor kinase inhibitor imatinib mesylate is the drug of choice.

Other drugs hold possibilities for HES treatment. Mepolizumab, a humanized immunoglobulin G1 (IgG1) antibody against interleukin 5, has approval from the U.S. Food and Drug Administration for severe asthma only, although it has also been studied in eosinophilic esophagitis and HES.⁽⁷⁾ Studies have demonstrated its effectiveness and safety in HES,^(8,9) yet mepolizumab is currently available only as investigational therapy under a compassionate use protocol for HES.

Infliximab is a chimeric IgG1 κ antibody against tumor necrosis factor α (TNF α). It was initially approved in 1998 for Crohn's disease but now is also used for ulcerative colitis

(UC), rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. We report a patient requiring mepolizumab for difficult-to-control HES who subsequently required the addition of infliximab therapy to control UC.

Case Report and Results

A 25-year-old woman received a diagnosis of HES after presenting with fatigue, fevers, episodic presyncopal spells, abnormal liver enzyme tests, abdominal pain, and chronic diarrhea and with repeated increases in eosinophils (range, $40 \times 10^9/L$ to $69 \times 10^9/L$) (Table 1). Work-up was unremarkable for underlying etiologic factors, including *FIP1 L1-PDGFRa* fusion, *cKIT D816 V*, and *JAK2 V617F* mutation analyses and bone marrow biopsy. Results of T cell receptor gene rearrangement and flow cytometry were normal, with antibodies to CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD16, CD29, and CD45; κ and λ light chains; and γ and δ T cell receptors. A liver biopsy showed the presence of a prominent portal eosinophilic infiltrate. Comorbidities included depression, anxiety, and celiac disease treated with a gluten-free diet.

The patient's therapy was begun with prednisone, 40 mg daily, for HES. However, this regimen resulted in severe adverse effects, including headaches, mood swings, worsening depression with suicidal ideation, and weight gain. Therefore, prednisone therapy was tapered while initiating Peg-IFN α -2b at 50 μ g per week through subcutaneous injection. Unfortunately, the patient also noted intolerable

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TABLE 1. TIMELINE OF DIAGNOSTIC TESTS AND TREATMENT WITH EOSINOPHIL COUNTS

<i>Date</i>	<i>Eosinophil count^a × 10⁹/L</i>	<i>Test</i>	<i>Result/diagnosis</i>	<i>Treatment</i>
December 2011	29.39	Duodenal biopsy Colon biopsy	Total villous atrophy suggestive of celiac sprue Increased eosinophils in otherwise normal colonic mucosa	Prednisone, 40 mg/d orally
March 2012	4.90	—	Diagnosis of HES	Continued strict GFD
April 2012	1.30	—	—	Started Peg-IFN α -2b, 50 μ g SC
June 2012	0.38	—	—	Tapering prednisone Discontinued Peg-IFN α -2b Started hydroxyurea, 500 mg BID orally
August 2012	0.03	—	Diagnosis of <i>Clostridium difficile</i> infection	Ciprofloxacin and metronidazole
December 2012	1.10	Duodenal biopsy Colon biopsy	Normal Mild to moderately active colitis without granulomas and with increased eosinophils	Started mesalamine, enteric coated, once daily in morning
February 2013	0.05	—	—	Started mepolizumab, 750 mg IV; discontinued hydroxyurea
April 2013	0.10	Colon biopsy	Moderately active colitis, moderately increased lamina propria eosinophils, friable mucosa	—
May 2013	0.07	—	Idiosyncratic reaction to azathioprine	Started azathioprine, 50 mg/d orally Discontinued azathioprine immediately
June 2013	0.01	—	—	Started budesonide, 9.0 mg/d orally; unable to control colitis
December 2013	0.17	—	—	Started methotrexate, 25 mg/wk orally
February 2014	0.12	—	—	Discontinued methotrexate
March 2014	0.05	Ileum biopsy Colon biopsy	Focal active ileitis Mild to moderately active colitis	—
April 2014	0.27	Duodenal biopsy	Mild nonspecific chronic inflammation, no villous atrophy	—
August 2014	0.08	Colon biopsy	Inactive chronic colitis, eosinophils moderately increased	—
February 2015	0.20	Colon biopsy	Mild active colitis	—
August 2015	0.14	—	—	Fecal transplant for recurrent <i>C. difficile</i> infection
September 2015	0.20	—	—	Hydrocortisone replacement, 15 mg/d orally
December 2015	0.33	Colon biopsy	Moderately active colitis; CT of abdomen showed active IBD	Started infliximab, 5.0 mg/kg IV, while continuing mepolizumab
January 2016	0.09	—	—	Continuing infliximab and mepolizumab
April 2016	—	—	Recurrent <i>C. difficile</i> infection after taking antibiotics for facial infection	—
May 2016	0.14	—	—	Infliximab level 15 μ g/mL (reference range, >5.0 μ g/mL) Mepolizumab reduced to 600 mg IV

Dash indicates not applicable.

^aReference range for eosinophil count is 0.05–0.50 × 10⁹/L.

BID, twice daily; CT, computed tomography; GFD, gluten-free diet; HES, hypereosinophilic syndrome; IBD, inflammatory bowel disease; IV, intravenous; Peg-IFN, pegylated interferon; SC, subcutaneous.

adverse effects with Peg-IFN, including nausea, severe headaches, depression with suicidal ideation, and increased liver enzyme levels. At that time, her prednisone therapy had been reduced to 2.5 mg per day. These symptoms required cessation of Peg-IFN, and a trial with hydroxyurea was begun. However, hydroxyurea was unable to control the patient's eosinophilia and she continued to have persistently increased liver enzymes, requiring discontinuation of hydroxyurea and reinitiation of prednisone. After all these therapies failed, she began receiving monthly infusions of mepolizumab (750 mg) through a compassionate use protocol (clinicaltrials.gov study ID MHE104317: A Compassionate Use Open-Label Study of Anti IL-5 Treatment [Mepolizumab] in Subjects with Hypereosinophilic Syndrome). Her eosinophil counts normalized and she was able to reduce her regimen of systemic corticosteroids.

During this period, the patient received a diagnosis of repeated *Clostridium difficile* infection requiring multiple courses of antibiotic therapy. She underwent multiple colonoscopies with biopsy and endoscopies for severe and refractory abdominal pain and gastrointestinal bleeding. Colon biopsies—performed while she was receiving mepolizumab and prednisone, 1.0 mg per day (peripheral eosinophil count, $0.03 \times 10^9/L$)—showed moderate active chronic colitis without granulomas or specific features and a moderate increase in lamina propria eosinophils. With therapy for the eosinophilia, the colonic histologic architecture continued to be abnormal with crypt abscesses and cryptitis, which are not features of simple eosinophilic colitis. The patient's subsequent biopsies showed continued crypt architecture distortion consistent with UC with the eosinophilia controlled.

The patient began an oral mesalamine treatment that did not control her symptoms, thereby requiring a trial of azathioprine (TPMT in the heterozygous range). Immediately after beginning azathioprine therapy, she had fevers up to 103°F, hypotension refractory to fluids, tachycardia, and neutrophilia. Her diagnosis was an idiosyncratic drug hypersensitivity reaction to azathioprine,⁽¹⁰⁾ necessitating its discontinuation. The patient's therapy was subsequently changed to oral budesonide. However, this treatment did not adequately control her colonic disease, and a trial of methotrexate for corticosteroid-sparing was not tolerated.

After multiple hospitalizations for flares of UC, her options for control were total colectomy, intravenous (IV) cyclosporine, and a trial of an anti-TNF α monoclonal antibody (mAb). After much discussion with the patient and her family, we decided to begin IV infliximab treatment at 5 mg/kg at weeks 0, 2, and 6 and thereafter every 8 weeks while continuing to administer IV mepolizumab at 750 mg monthly. The administrations of infliximab and mepolizumab were staggered by 2 to 3 weeks as logistically feasible for the patient, to isolate potential individual adverse effects from each mAb and to prevent possible problems from contemporaneous administration of two IV treatments of mAbs.

At 6-month follow-up, the patient had continued receiving both mAbs and had maintained a good response to both. Her erythrocyte sedimentation rate and C-reactive protein level had normalized within a few weeks of initiating infliximab therapy. She also had resolution of abdominal pain, diarrhea, incontinence, and bloody stools and reported a marked improvement in quality of life. She was able to taper the pred-

nisone therapy and stop its use, with improvement in her cushingoid features and other prednisone-related adverse effects, but continued taking replacement doses of hydrocortisone for adrenal insufficiency. Total eosinophil count stayed within the reference range, even with tapering and discontinuation of prednisone.

Shortly after beginning the infliximab therapy, the patient had headaches and worsened anxiety, which were managed symptomatically. Her laboratory tests including liver enzymes and creatinine levels showed normal results. In addition, C3, C4, and cryoglobulin levels stayed within the normal range. Raji cell assay (ARUP Laboratories), performed to exclude immune complex formation, was negative. Four months after starting infliximab therapy, she was hospitalized for treatment with vancomycin, IV metronidazole, and a fecal transplant for resistant *C. difficile* infection and for abdominal pain that developed after antibiotic treatment for a facial infection. No associated eosinophilia was found at that time.

Discussion

The mAbs are changing the treatment approach to many disorders. By some estimates, more than 60 mAbs have been approved for treatment of diseases ranging from inflammatory bowel disease to various malignancies (source: Mayo Clinic Pharmacy). In the future, more than one mAb may be used in the treatment of an individual patient, and therefore information about the tolerance and compatibility of these agents when used in combination may gain increasing importance. Our patient received both humanized (mepolizumab) and chimeric (infliximab) mAbs. Both processes increase an antibody's similarity to naturally produced antibodies in humans, although chimeric antibodies carry a larger stretch of nonhuman protein.^(11,12)

Mepolizumab is a humanized mAb against interleukin 5 that prevents binding of interleukin 5 to the receptor complex on the eosinophil surface and thereby prevents its effects on eosinophil activation, survival, proliferation, and maturation.⁽¹³⁾ In our patient, from an immunologic standpoint, we were uncertain of how infliximab, a chimeric anti-TNF α antibody, would affect T_H1 and T_H2 cytokines and eosinophils, given that TNF α is involved in the pathogenesis of both T_H1 diseases, such as rheumatoid arthritis,⁽¹⁴⁾ and T_H2 diseases, such as asthma.⁽¹⁵⁾

We further hypothesized that coadministration of mepolizumab and infliximab would likely not result in drug interactions that would raise concerns for efficacy or safety, given their largely unrelated targets, although careful monitoring was continued while the patient was taking both mAbs. In addition, we staggered the doses of these mAbs to decrease the likelihood of interaction. Nonetheless, at the outset we could not exclude the possibility that the additional introduction of a chimeric mAb might elicit an immune response to itself or in some manner influence the effect of the initial antibody. Fortunately, the mAbs appeared to work well individually and independently of each other. Moreover, we detected no evidence of complement activation, formation of immune complexes, or renal failure. Subsequently, we have been able to reduce the patient's dose of mepolizumab to 600 mg IV administered every month, from the starting dose of 750 mg—a 20% reduction. This case illustrates the clinical

value, safety, and efficacy of using different types of mAbs for disparate disorders in the same patient. To our knowledge, it is the first report of such use.

Author Disclosure Statement

No competing financial interests exist.

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