

Persistent elevation of peripheral blood myeloid cell counts associated with omalizumab therapy

HOAN LINH BANH, JUNE TREVOY, HENRY PABST, JEREMY BEACH, AND DILINI VETHANAYAGAM

Omalizumab was approved by the U.S. Food and Drug Administration (FDA) in 2003 and Health Canada in 2005 for use in patients 12 years of age or older with moderate-to-severe persistent asthma whose symptoms are not controlled with inhaled corticosteroids, who have a serum immunoglobulin (Ig) E concentration of 30–700 IU/mL, and who also test positive for reactivity to a perennial airborne allergen.^{1,2}

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that binds to the Fc region of the IgE molecule and prevents IgE from interacting with high- or low-affinity IgE receptors (FcεR1 and FcεR11), resulting in a reduction of circulating free IgE.^{3,4} Omalizumab also down-regulates FcεR1 receptors in circulating basophils, mast cells, and circulating antigen-presenting cells; this is believed to result in the down-regulation of inflammatory responses mediated by helper T cells.^{4,5} Basophil, mast cell, and particularly eosinophil degranulation play a central role in allergic asthma that occurs in the presence of high IgE levels.^{6,7} Increased numbers

Purpose. A case of persistent hematologic abnormalities in a patient receiving long-term omalizumab therapy for severe asthma is reported.

Summary. During the course of her treatment at an asthma clinic, a 24-year-old woman was noted to have increased white blood cell counts, with elevated myeloid cell counts; the blood abnormalities were first documented more than 12 months previously. The woman had been taking omalizumab for more than 2 years and was also receiving immune globulin therapy for common variable immunodeficiency. Based on the results of bone marrow aspiration and biopsy, she was diagnosed as having mild neutrophilia, possibly related to past corticosteroid therapy, but there was no evidence of a malignancy, a hemophagocytic syndrome, or an infectious, myeloproliferative, or lymphoproliferative process. Pursuant to a multidisciplinary medication review, the use of omalizumab was identified as a potential factor in the myeloid cell elevations and discontinued. About 1 month after omalizumab

therapy was halted, the patient's myeloid cell counts normalized. The temporal association of omalizumab use and blood abnormalities in this case, coupled with the lack of data on the drug's long-term hematologic effects, suggests a need for cautious use and close monitoring of omalizumab therapy, particularly in younger patients.

Conclusion. A patient with asthma and common variable immunodeficiency developed an elevation of peripheral blood myeloid cells that was first noticed 29 months after the initiation of monthly omalizumab injections. Omalizumab was discontinued, and the abnormality persisted for 1 month after the last dose. The patient's blood count results remained within normal limits 3 months after the last dose.

Index terms: Antibodies; Asthma; Common variable immunodeficiency; Drugs, adverse reactions; Globulin immune; Hematologic diseases; Leukocytes; Myeloid cells; Omalizumab; Serums

Am J Health-Syst Pharm. 2012; 69:302-6

of eosinophils are associated with an increased severity of asthma.⁸⁻¹⁰

While the role of omalizumab in the long-term management of asthma

is yet to be fully defined, omalizumab is generally believed to be safe for use as an adjunct therapy. The results of industry-sponsored trials,

HOAN LINH BANH, B.Sc.Pharm., Pharm.D., is Associate Professor, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada. JUNE TREVOY, M.N., NP, is Nurse Practitioner, Rehabilitation Medicine, Alberta Health Services, Edmonton. HENRY PABST, M.D., FRCPC, is Professor of Pediatrics; JEREMY BEACH, M.B.B.S., M.D., FRCPC, is Associate Professor; and DILINI VETHANAYAGAM, M.D., FRCPC, is Associate Professor, Faculty of Medicine and Dentistry, University of Alberta.

Address correspondence to Dr. Banh at the Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, 5064B Dentistry/Pharmacy Centre, Edmonton, Alberta, T6G 2N8, Canada.

The authors have declared no potential conflicts of interest.

Copyright © 2012, American Society of Health-System Pharmacists, Inc. All rights reserved. 1079-2082/12/0215-0302\$06.00. DOI 10.2146/ajhp110277

as interpreted by FDA, suggested a possible risk of the development of immediate or delayed anaphylaxis requiring emergency self-treatment.¹¹ Data from one study also suggested an increased rate of cancer development in patients exposed to omalizumab relative to those who received a placebo, with the majority of cases involving epithelial or solid-organ cancers; only one case of hematologic or lymphatic cancer was noted.

We performed a MEDLINE search covering the period January 2000–March 2011 and using the Medical Subject Headings and PubMed terms *omalizumab*, *malignancies*, *hematologic disorders*, *myeloid cells*, *cancer*, and *neoplasm* in combination with the AND and OR delimiters. A similar search of the Cochrane Library was also conducted. The search identified a number of relevant articles.^{12–17} A systematic review of data from early clinical trials of omalizumab indicated the development of malignancies in a total of 25 (0.50%) of 5015 trial participants who received the drug, compared with 5 (0.18%) of a total of 2854 patients in the control groups.¹²

While information about omalizumab and the risk of malignancies remains sparse, there have been numerous reports of lymphoma and leukemia in both adults and children with the use of other biological therapies, such as the anti-tumor necrosis factor (anti-TNF) inhibitors.^{18–24} A meta-analysis of data from randomized controlled trials suggested there might be as much as a threefold increase in the risks of both solid-organ and hematologic malignancies associated with anti-TNF therapy in patients with rheumatoid arthritis.²⁵ Here we describe the case of a patient treated with omalizumab who developed a persistent elevation of peripheral blood myeloid cell counts.

Case report

A 24-year-old Caucasian woman

with steroid-dependent atopic asthma since childhood and a history of repeated hospitalizations, some requiring ventilation, was followed in the Edmonton Regional Severe Asthma Clinic (ERSAC) beginning in September 2008. She had been initiated on omalizumab by a respirologist about 2 years before her referral to the clinic. Notably, the patient also had common variable immunodeficiency with decreased IgG levels, which was treated with subcutaneous immune globulin therapy. During the time the patient was followed by ERSAC staff, her medications included

- Albuterol metered-dose inhaler (MDI) (with Aerochamber) 90 µg per puff, two inhalations as needed
- Fluticasone propionate (Flovent, GlaxoSmithKline) MDI (with Aerochamber) 250 µg per puff, two inhalations twice daily
- Fluticasone propionate–salmeterol (Advair, GlaxoSmithKline) MDI, fluticasone propionate 250 µg and salmeterol 25 µg per puff, two inhalations twice daily
- Ipratropium bromide MDI (with Aerochamber) 20 µg per puff, four inhalations four times daily
- Mometasone furoate nasal spray (Nasonex, Merck) 50 µg per spray, two sprays twice daily
- Omalizumab 300 mg subcutaneously every four weeks
- Immune globulin (Vivaglobin, CSL Behring Canada) 160 mg/L, 20 mL subcutaneously five times weekly
- Alendronate 70 mg orally every Saturday
- Cetirizine hydrochloride 20 mg orally once daily
- Omeprazole 20 mg orally once daily
- Ranitidine 150 mg orally twice daily
- Citalopram 20 mg orally every other day
- Calcium 500 mg (as the carbonate salt) orally three times daily
- Multivitamin, one tablet orally once daily
- Vitamin D₃ 1000 IU orally once daily

Over the course of the patient's asthma management at ERSAC, it was noted that the complete white blood cell counts (including platelets with differentials) in samples of her peripheral blood showed a persistent elevation of myeloid cells, by both absolute-count and percentage measures (Table 1); this was first noted 29 months after the first dose of omalizumab. Her absolute and percentage eosinophil and basophil counts were within normal limits throughout the period of clinic follow-up. A review of records provided by the woman's previous respirologist indicated that myeloid cell counts in her peripheral blood had been within normal limits before her referral to ERSAC.

A hematologic review, including bone marrow aspiration and biopsy, was obtained about a year after the myeloid-cell elevation was first noted. Histologic assessment of the bone marrow revealed normal cellularity and normal trilineage maturation. There was no evidence to suggest a myeloproliferative or lymphoproliferative process and no evidence of a hemophagocytic syndrome or malignancy. The final diagnostic determination, based on the results of the bone marrow-blood aspiration and biopsy, was mild neutrophilia with a left shift and normocellular bone marrow and normal trilineage maturation, with no evidence of an underlying hematologic disorder. The histology report also noted that the neutrophilia with left shift may have been related to the patient's use of steroid therapy. Infection was thought to be an unlikely cause of the elevated white blood cell and myeloid cell counts.

A thorough medication review was performed by two physicians, a nurse practitioner, and a pharmacist. Omalizumab was identified as a possible factor associated with the elevation of peripheral blood myeloid cells. Omalizumab therapy was subsequently discontinued, 42 months after treatment was initiated.

Table 1.
Myeloid Cell Counts in a Patient Treated with Omalizumab

Months After Initiation of Omalizumab Therapy	Absolute Myeloid Cell Count ($\times 10^9/L$) ^a
29	0.8
30	0.3
31	0.6
32	1.1
33	0.2
34	0.1
36	0.4
37	0.7
38	0.1
39	0.6
40	0.6
41	0.1
42 ^b	0.3
43	0.6
44	0
45	0
46	0

^aNormal value = 0 cells.

^bCorresponds with last dose of omalizumab.

After the discontinuation of omalizumab, the elevation of myeloid cells persisted for another month. Three months after the discontinuation of omalizumab, the patient's myeloid cell count was within normal limits, with no increases in neutrophils or monocytes.

Discussion

Peripheral blood myeloid cells are marrow-derived cells that include megakaryocytes, erythrocyte precursors, mononuclear phagocytes (monocytes and macrophages), and all of the polymorphonuclear leukocytes (neutrophils, basophils, and eosinophils).²⁶ In the case described here, the patient developed an abnormal peripheral blood myeloid cell count while receiving omalizumab; although this effect resolved fairly quickly after the discontinuation of omalizumab, it may not be a trivial adverse effect. It is theorized that abnormalities in the maturation of myeloid cells may be important in the later development of acute myelogenous leukemia.²⁶

The patient had been treated with subcutaneous immune globulin for common variable immunodeficiency, which was diagnosed long before her referral to ERSAC. Her serum IgG, IgA, and IgM concentrations were within normal limits during treatment with immune globulin. Common variable immunodeficiency is characterized by reduced Ig levels, particularly levels of IgG, IgA, and IgM²⁷; patients with this condition are susceptible to bacterial infections and are at increased risk for malignancies such as non-Hodgkin lymphomas and gastric cancers.²⁸⁻³⁰ The results of a longitudinal cohort study of 248 patients with common variable immunodeficiency (and previously diagnosed Hodgkin's disease) indicated that 2 patients who were receiving long-term systemic corticosteroid or methotrexate therapy developed additional malignancies or recurrent disease.²⁸ Most cases of non-Hodgkin lymphoma related to immunodeficiency are associated with T-cell defects (e.g., ataxia-telangiectasia, Wiskott-Aldrich syn-

drome in combination with common variable immunodeficiency).³¹ Our patient had received systemic pulse corticosteroid therapy since childhood, with the longest episode entailing three months of treatment with prednisone 30 mg once daily. She had never received methotrexate as part of her asthma treatment.

The literature includes a number of other reports of hematologic disorders associated with different monoclonal antibodies.^{22,24,25} FDA and Health Canada have issued notifications informing health care professionals that a completed analysis of the available information on TNF inhibitors indicated increased risks of lymphoma and other cancers associated with the use of these biological agents in children and adolescents after an average of 30 months of treatment; this may be particularly relevant given the risk of long-term TNF inhibitor use by younger patients with nonterminal conditions, the agencies cautioned.^{32,33} To date, however, there has been little concern about such effects in patients treated with omalizumab. Published data from clinical trials suggested increased rates of malignancies in patients treated with omalizumab relative to patients not receiving the drug, although the reported differences were not statistically significant.^{12,15} Those data must be interpreted with caution, since patients treated with omalizumab in clinical trials have generally been observed for only 12–24 months; consequently, the effect of long-term omalizumab therapy or use of the drug in patients who may be at increased risk for a malignancy or hematologic disorder is unknown.

An ongoing study—Epidemiologic Study of Xolair (Omalizumab): Evaluating the Clinical Effectiveness and Long-Term Safety in Patients With Moderate to Severe Asthma (EXCELS)—is investigating the safety of omalizumab use for the treatment of asthma during the period 2005–10.³⁴ According to an August

2009 FDA news release, preliminary data from the EXCELS trial suggested “a disproportionate increase in ischemic heart disease, arrhythmias, cardiomyopathy and cardiac failure, pulmonary hypertension, cerebrovascular disorders, and embolic, thrombotic, and thrombophlebotic events” associated with the use of omalizumab.³⁵ However, the FDA news release made no mention of a potential association between the use of omalizumab and the development of malignancy.

Severe thrombocytopenia has been reported in clinical trials of omalizumab, but in all controlled studies, there was no difference in the reduction of platelet counts from baseline between the omalizumab and control groups.¹⁴

Biological agents are increasingly available for many nonmalignant chronic conditions, including omalizumab for the treatment of asthma. Since the majority of patients treated with omalizumab have been observed for short periods only, the effect of longer exposure to omalizumab in patients who are at increased risk for malignancy is unknown.

The elevation of peripheral blood myeloid cells in our patient was observed after 29 months of treatment with omalizumab. Even though the patient had several factors predisposing her to an increased risk of developing a malignancy (e.g., common variable immunodeficiency, frequent systemic corticosteroid use), her myeloid cell counts returned to the normal range about 1 month after the discontinuation of omalizumab therapy, possibly due to the drug’s relatively short half-life (26 days).³⁶ The temporal association between the changes in myeloid cell counts and omalizumab discontinuation suggested that the use of the drug may have had a contributing role in the development of the blood abnormality.

The case reported here, coupled with the current lack of definitive information on the possible risk of

hematologic malignancies, suggests a need for cautious use of omalizumab and close monitoring of patients.

Conclusion

A patient with asthma and common variable immunodeficiency developed an elevation of peripheral blood myeloid cells that was first noticed 29 months after the initiation of monthly omalizumab injections. Omalizumab was discontinued, and the abnormality persisted for 1 month after the last dose. The patient’s blood count results remained within normal limits 3 months after the last dose.

References

1. Xolair (omalizumab) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2010 Jul.
2. Xolair (omalizumab) prescribing information. Dorval, Quebec, Canada: Novartis Pharmaceuticals Canada, Inc.; 2011 Jun 3.
3. Morjaria JB, Gnanakumaran G, Babu KS. Anti-IgE in allergic asthma and rhinitis: an update. *Expert Opin Biol Ther.* 2007; 7:1739-47.
4. Fahy JV, Fleming HE, Wong HH et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med.* 1997; 155:1828-34.
5. Boulet LP, Chapman KR, Cote J et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. *Am J Respir Crit Care Med.* 1997; 155:1835-40.
6. Lichtenstein LM, Bochner BS. The role of basophils in asthma. *Ann N Y Acad Sci.* 1991; 629:48-61.
7. Boyce JA, Broide D, Matsumoto K et al. Advances in mechanisms of asthma, allergy, and immunology in 2008. *J Allergy Clin Immunol.* 2009; 123:569-74.
8. Horn BR, Robin ED, Theodore J et al. Total eosinophil counts in the management of bronchial asthma. *N Engl J Med.* 1975; 292:1152-5.
9. Bousquet J, Chanaz P, Lacoste JY et al. Eosinophilic inflammation in asthma. *N Engl J Med.* 1990; 323:1033-9.
10. Frew AJ, Kay AB. Eosinophils and T-lymphocytes in late-phase allergic reactions. *J Allergy Clin Immunol.* 1990; 85:533-9.
11. Center for Biologics Evaluation and Research, Food and Drug Administration. BLA STN 103976/0, review of clinical safety data: original BLS submitted on June 2, 2000 and response to complete review letter submitted on December 18, 2002. Rockville, MD: Department of Health and Human Services; 2003.
12. Corren J, Casale TB, Lanier B et al. Safety and tolerability of omalizumab. *Clin Exp Allergy.* 2009; 39:788-97.
13. Buhl R, Soler M, Matz J et al. Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. *Eur Respir J.* 2002; 20:73-8.
14. Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review. *Chest.* 2011; 139:28-35.
15. Deniz YM, Gupta N. Safety and tolerability of omalizumab (Xolair), a recombinant humanized monoclonal anti-IgE antibody. *Clin Rev Allergy Immunol.* 2005; 29:31-48.
16. Townley RG, Agrawal S, Sapkota K. Omalizumab for pediatric asthma. *Expert Opin Biol Ther.* 2010; 10:1595-608.
17. Tan RA, Corren J. Safety of omalizumab in asthma. *Expert Opin Drug Saf.* 2011; 10:463-71.
18. Food and Drug Administration. Infliximab, etanercept and adalimumab label information. www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm (accessed 2010 Jul 7).
19. Rennard SI, Fogarty C, Kelsen S et al. The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2007; 175:926-34.
20. Stone JH, Holbrook JT, Marriott MA et al. Solid malignancies among patients in the Wegener’s Granulomatosis Etanercept Trial. *Arthritis Rheum.* 2006; 54:1608-18.
21. Bernstein CN, Blanchard JF, Kliever E et al. Cancer risk in patients with inflammatory bowel disease: a population-based study. *Cancer.* 2001; 91:854-62.
22. Brown SL, Greene MH, Gershon SK et al. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum.* 2002; 46:3151-8.
23. Mackey AC, Green L, Liang LC et al. Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2007; 44:265-7.
24. Diak P, Siegel J, la Grenade L et al. Tumor necrosis factor alpha blockers and malignancy in children: forty-eight cases reported to the Food and Drug Administration. *Arthritis Rheum.* 2010; 62:2517-24.
25. Bongartz T, Sutton AJ, Sweeting MJ et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA.* 2006; 295:2275-85.
26. Fey MF. Normal and malignant hematopoiesis. *Ann Oncol.* 2007; 18(suppl 1):i9-13.
27. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary im-

- munodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). *Clin Immunol.* 1999; 93:190-7.
28. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol.* 1999; 92:34-48.
 29. Cunningham-Rundles C. How I treat common variable immune deficiency. *Blood.* 2010; 116:7-15.
 30. Quinti I, Soresina A, Spadaro G et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. *J Clin Immunol.* 2007; 27:308-16.
 31. Smith MS, Webster AD, Dhillon AP et al. Orthotopic liver transplantation for chronic hepatitis in two patients with common variable immunodeficiency. *Gastroenterology.* 1995; 108:879-84.
 32. Food and Drug Administration. Tumor necrosis factor (TNF) blockers (marketed as Remicade, Enbrel, Humira, Cimzia, and Simponi) August 2009. www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm175843.htm (accessed 2011 Jul 18).
 33. Possible association of Remicade (infliximab) with hepatosplenic T-cell lymphoma in pediatric and young adult patients with Crohn's disease—for the public. www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/_2006/remicade_3_pc-cp-eng.php (accessed 2011 Jul 18).
 34. National Institutes of Health. A study of Xolair to evaluate effectiveness and long-term safety in patients with moderate to severe asthma. <http://clinicaltrials.gov/ct2/show/NCT00252135?term=EXCELS&rank=2> (accessed 2011 Jul 18).
 35. Food and Drug Administration. Cancer warnings required for TNF blockers. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm175803.htm (accessed 2011 Jul 18).
 36. Compendium of pharmaceuticals and specialties. Ottawa, Canada: Canadian Pharmacists Association. Xolair (omalizumab) [monograph online] (accessed 2011 Jan).

Copyright of American Journal of Health-System Pharmacy is the property of American Society of Health System Pharmacists and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.