

Administration of Anti-IgE to a Churg-Strauss Syndrome Patient

Pedro Giavina-Bianchi Mara Giavina-Bianchi Rosana Agondi Jorge Kalil

Division of Clinical Immunology and Allergy, University of São Paulo, São Paulo, Brazil

Key Words

Anti-IgE • Asthma • Churg-Strauss syndrome • Eosinophilia • IgE • Severe asthma • Vasculitis

Abstract

Background: Treatment of the Churg-Strauss syndrome (CSS) remains a challenge. Many patients relapse after achieving remission, and a substantial proportion of them present adverse drug reactions with relevant morbidity. In most patients, severe asthma and upper respiratory symptoms persist, requiring continuous therapy. The aim of the present study is to describe a patient with CSS who was administered anti-IgE. **Case Report:** A 46-year-old male patient with CSS followed up for 17 years is described. Upon treatment, CSS showed remission but asthma failed to improve despite high-dose inhaled corticosteroids, long-acting β_2 -agonists and several courses of systemic steroids. In order to better control asthma, anti-IgE was administered. Following omalizumab administration, asthma symptoms (according to clinical features and lung function tests) and eosinophilia improved. **Conclusions:** Anti-IgE offers the potential not only to decrease asthma activity but also to reduce the risk of morbidity that can result from currently available treatment options. Whether it can also affect the activity of other CSS components is an open question. As far as we know, there are no published reports about the prescription of omalizumab to patients with CSS and with non-allergic asthma. Anti-IgE improved our patient's asthma and decreased

the eosinophil blood count but did not worsen the outcome of CSS. However, large and long-term studies are necessary before a more widespread utilization of anti-IgE in CSS patients can be implemented.

Copyright © 2007 S. Karger AG, Basel

Introduction

The Churg-Strauss syndrome (CSS) is a necrotizing systemic vasculitis of medium and small blood vessels, characterized by asthma, eosinophilia and eosinophilic or granulomatous tissue inflammation [1–3]. Its description was made by the pathologists Churg and Strauss in 1951 [4].

Besides asthma and upper respiratory symptoms that are present in almost all patients, there is clinical evidence of systemic vasculitis. The most frequently involved organs are the peripheral nervous system, lung parenchyma and skin, but the gastrointestinal system, kidney, heart and central nervous system are also affected [5–8]. CSS is manifested in three consecutive phases: a prodromal phase consisting of respiratory manifestations (rhinosinusitis and asthma); a second phase of peripheral blood eosinophilia and eosinophilic tissue infiltrates, and a third phase consisting of vasculitic systemic manifestations [9].

The immunopathogenesis of CSS is still poorly known. T-helper type 2 lymphocytes are supposed to orchestrate

the immune response during the first and second phases of disease and autoimmunity to contribute to the formation of vasculitic lesions present in the third phase. Anti-neutrophil cytoplasmic antibodies, especially anti-myeloperoxidase, are found in one third to one half of CSS patients [7].

CSS diagnosis and treatment remain a challenge due to the rarity of this disease. Its prevalence is 13/1,000,000 in the general population [10].

Corticosteroids are the cornerstone of therapy and permit disease activity control in the great majority of cases. However, a quarter to half of CSS patients relapse within 2 years of achieving remission, and a substantial proportion of them present adverse drug reactions with relevant morbidity [5–8]. Asthma is not considered in the definition of CSS remission, although most patients remain with asthma and upper respiratory symptoms requiring continuous therapy.

When CSS threatens a patient's life or the function of a vital organ, an intravenous pulse of corticosteroids with cyclophosphamide is indicated to avoid irreversible major organ damage or death. Other alternative therapies may be added with some success, especially in severe cases, including methotrexate, cyclosporine, azathioprine, mycophenolate-mofetil, intravenous immunoglobulin, plasmapheresis, interferon- α and anti-TNF blocking agents (infliximab and etanercept). Nevertheless, none of them is fully effective and they are also associated with adverse reactions, some of them being troublesome [11–13].

Omalizumab is a recombinant humanized monoclonal antibody against IgE that has been used in severe allergic asthma with good effectiveness [14, 15]. There is no report in the literature on the prescription of omalizumab to patients with CSS.

The objective of the present study is to describe a patient with CSS treated with omalizumab for 3 months.

Case Report and Methods

Methods

This study describes a CSS patient who received omalizumab to help manage his difficult-to-control asthma. Clinical parameters, lung function tests and eosinophil blood count were compared before and after anti-IgE administration. Comprehensive laboratory testing was performed to identify possible adverse drug reactions. Lung function tests were carried out with a Koko spirometer (Pulmonary Data Service Instrumentation, Louisville, Ky., USA) and blood cell count by an automatic analyzer (Cobas Micros; Roche, Basel, Switzerland). The study was approved by our Institutional Review Board and the patient was informed and gave his consent.

Case Report

Identification. J.S.S. is a 46-year-old, male, white, married salesman born in São Paulo, where he resides.

History of the Present Illness. He first presented with asthma symptoms 17 years ago. They were mild in the beginning, but worsened until they became severe. High doses of inhaled and systemic corticosteroids were prescribed. Eighteen months later, when systemic corticosteroid was being tapered, the patient also complained of upper respiratory symptoms, asymmetric foot pain and lower limb numbness. Pan-sinusitis and pulmonary infiltrates were observed. Whenever the patient tried to decrease systemic corticosteroids, his asthma and foot pain worsened. After 6 months, he walked with difficulty due to lower limb weakness and showed palpable purpura on the legs. At that time he also presented epididymo-orchitis and doxycycline was added to the therapy.

Past Medical History. Hypertension diagnosed 2 years ago was being treated with losartan (50 mg). The patient denied diabetes, atopic diseases during childhood or smoking habits. There was no family history of immunodeficiency, or atopic or autoimmune diseases.

Laboratory Findings. At the time of diagnosis, 15 years ago, laboratory findings were: leukocytes: 18,800/mm³; eosinophils: 30% (5,640/mm³); IgE: 398 IU/ml (normal range: <100 IU/ml); stool examination: negative; skin prick test: negative, and in vitro specific IgE test (RAST) to aeroallergens: negative. Electromyography confirmed the diagnosis of multiple mononeuropathy, as suspected from the symptoms. A sural nerve biopsy showed eosinophilic inflammatory infiltrate and necrotizing vasculitis, which confirmed the diagnosis of CSS. Anti-neutrophil cytoplasmic antibody was negative, but the patient was already taking corticosteroids.

Therapy and Clinical Follow-Up. After diagnosis confirmation, the systemic corticosteroid dose was increased and cyclophosphamide was administered. Mononeuropathy, purpura and epididymo-orchitis improved progressively, and after 6 months the patient was free of symptoms, without sequelae. Cytotoxic drugs (cyclophosphamide and azathioprine) were taken for 3 years. Upon treatment, CSS showed remission and pan-sinusitis improved, but asthma failed to improve. The patient remained with daily asthma symptoms, walking dyspnea, significant impairment in exercise practice and two hospital admissions per year, during all these years. Treatment consisted of high doses of inhaled corticosteroids (ciclesonide), long-acting β_2 -agonists (formoterol) and many pulses of systemic corticosteroids.

Anti-IgE Administration. Seventeen years after disease onset, administration of anti-IgE was proposed in order to improve asthma control. At that time, patient IgE level was 369 IU/ml and his weight was 83 kg. Skin tests and in vitro specific IgE test remained negative. The patient received six doses of omalizumab 300 mg for 3 months. Each dose was divided in half and administered in separate sites, every 2 weeks. Fifteen days after treatment initiation, the patient began to notice significant improvement in asthma symptoms, with less dyspnea when walking and feeling better when playing tennis. Thoracic auscultation was normal, as opposed to previous physical examinations performed before anti-IgE administration. Lung function tests and eosinophilia improved (table 1). The results of a thorough laboratory testing remained normal.

Table 1. Clinical and laboratory findings before and after anti-IgE administration

	Before treatment	After treatment	
		15 days	3 months
Auscultation	wheezing	normal	normal
Peak flow	420	500	500
FEV ₁ , liters	1.87 (61%) ^a	2.11 (68%) ^a	2.12 (70%) ^a
Leukocytes, cells/mm ³	9,300	7,800	9,900
Eosinophils, cells/mm ³	660 (7.1%) ^b	234 (3%) ^b	99 (1%) ^b
IgE level, IU/ml	369	ND	ND

FEV₁ = Forced expiratory volume in 1 s; ND = not done.
^a Percent predicted.
^b Percent of total blood leukocytes.

Discussion

The patient described here had the diagnosis of CSS confirmed, regardless of the classification used (American College of Rheumatology [1], Chapel Hill Consensus Conference [2] or Lanham et al. [3]). At the time of diagnosis, severe asthma, pan-sinusitis, mononeuropathy, epididymo-orchitis and palpable purpura were present. He achieved CSS remission like >80% of patients treated with corticosteroids and cytotoxic drugs. However, relapses occur in 25–50% of patients and >70% require low-dose systemic corticosteroid maintenance therapy for persistent severe asthma [5–8].

In the patient studied, asthma onset preceded CSS symptoms by 1 year, a shorter period than mentioned in literature, which is associated with a poor prognosis. The present patient continued with difficult-to-control asthma, with many hospital admissions and high doses of inhaled corticosteroids, long-acting β_2 -agonists and many pulses of systemic corticosteroids.

After anti-IgE administration, asthma improvement was noted according to clinical characteristics and lung function tests. This was expected, and recent studies have demonstrated the effect of omalizumab on severe allergic asthma [14, 15].

In addition, a marked improvement in eosinophilia was observed. During these 17 years of CSS, the patient often presented increased eosinophil blood counts, even when he was on systemic corticosteroids. It is noteworthy that this patient had not been taking systemic corticosteroids during the last 3 months and therefore anti-IgE might be involved in the reduction of these cells. Although the eosinophil count usually rises prior to a vasculitic relapse, and therefore is a marker of activity, it is not possible to state that with omalizumab the patient has

a lower chance of CSS relapse. On the other hand, a recent report described a temporal association between anti-IgE use and the development of CSS [16].

By blocking IgE, omalizumab inhibits part of the Th2 immune response, thus, decreasing the recruitment and activation of effector cells of the inflammatory process, including eosinophils. Besides the IgE blockage effect, studies have shown anti-allergic and anti-inflammatory properties of anti-IgE, e.g. the reduction in circulating and tissue eosinophils [17, 18]. Recently, another study demonstrated an increase in eosinophil apoptosis and a decrease in GM-CSF+, IL-2+ and IL-13+ T lymphocytes in omalizumab-treated patients [19].

Like 75% of CSS subjects [7], the present patient had increased levels of serum IgE, but negative in vivo and in vitro specific IgE tests. In spite of high IgE levels, other features of the patient's disease, such as late onset and no family history of atopy, suggest non-allergic asthma. This increased IgE could be non-specific, as a result of polyclonal immunoglobulin production during a Th2-type immune response, or mono-oligoclonal to some unknown triggering antigen(s). Regardless of its clonal feature, our results suggest that IgE may be involved in the mechanisms leading to peripheral eosinophilia in this CSS patient.

IgE levels were not reassessed after treatment with omalizumab as total serum IgE levels are known to be elevated during therapy as a result of IgE-anti-IgE immune complex formation [20]. This elevation may persist for up to 1 year after treatment. Therefore, IgE levels during this period should not be used to monitor therapeutic response or to determine future dosing.

The expanding range of biologic agents capable of modulating the immune response has opened up a new era in the management of vasculitic diseases. Anti-IgE

offers the potential not only to decrease asthma activity but also to reduce the risk of morbidity that can result from currently available treatment options. Whether it can also impact on the activity of other components of CSS is an open question. According to this case report, anti-IgE has improved asthma and decreased eosinophil

blood counts without increasing the clinical activity of CSS. However, large and long-term studies are required before widespread utilization of omalizumab in CSS. As far as we know, there are no reports in the literature about the prescription of anti-IgE to patients with CSS and non-allergic asthma.

References

- ▶ 1 Masi AT, Hunder GG, Lie JT, et al: The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum* 1990;33:1094–1100.
- ▶ 2 Jennette JC, Falk RJ, Andrassy K, et al: Nomenclature of systemic vasculitides: proposal of an international consensus conference. *Arthritis Rheum* 1994;37:187–192.
- ▶ 3 Lanham JG, Elkon KB, Pusey CD, Hughes GR: Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine (Baltimore)* 1984;63:65–81.
- ▶ 4 Churg J, Strauss L: Allergic granulomatosis, allergic angiitis and periarteritis nodosa. *Am J Pathol* 1951;27:277–294.
- ▶ 5 Keogh K, Specks U: Churg-Strauss syndrome. *Semin Respir Crit Care Med* 2006;27:148–157.
- ▶ 6 Oh MJ, Lee JY, Kwon NH, Choi DC: Churg-Strauss syndrome: the clinical features and long-term follow-up of 17 patients. *J Korean Med Sci* 2006;21:265–271.
- ▶ 7 Guillevin L, Pagnoux C, Mouthon L: Churg-Strauss syndrome. *Semin Respir Crit Care Med* 2004;25:535–545.
- ▶ 8 Guillevin L, Lhote F, Gayraud M, et al: Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore)* 1996;75:17–28.
- ▶ 9 Lanham JG: Churg-Strauss syndrome. *Br J Hosp Med* 1992;47:667–673.
- ▶ 10 Watts RA, Carruthers DM, Scott DG: Epidemiology of systemic vasculitis: changing incidence or definition? *Semin Arthritis Rheum* 1995;25:28–24.
- ▶ 11 Danieli MG, Cappelli M, Malcangi G, et al: Long term effectiveness of intravenous immunoglobulin in Churg-Strauss syndrome. *Ann Rheum Dis* 2004;63:1649–1654.
- ▶ 12 Tsurikisawa N, Taniguchi M, Hiroshi S, et al: Treatment of Churg-Strauss syndrome with high-dose intravenous immunoglobulin. *Ann Allergy Asthma Immunol* 2004;92:80–87.
- ▶ 13 Jayne DR, Chapel H, Adu D, et al: Intravenous immunoglobulin for anti-neutrophil cytoplasmic antibodies-associated systemic vasculitis with persistent disease activity. *Q J Med* 2000;93:433–439.
- ▶ 14 Humbert M, Beasley R, Ayres J, et al: Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;60:309–316.
- ▶ 15 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;155:1828–1834.
- ▶ 16 Winchester DE, Jacob A, Murphy T: Omalizumab for asthma (correspondence). *N Engl J Med* 2006;355:1281–1282.
- ▶ 17 Noga O, Hanf G, Kunkel G: Immunological and clinical changes in allergic asthmatics following treatment with omalizumab. *Int Arch Allergy Immunol* 2003;131:46–52.
- ▶ 18 Djukanovic R, Wilson SJ, Kraft M, et al: Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med* 2004;170:583–593.
- ▶ 19 Noga O, Hanf G, Brachmann I, et al: Effect of omalizumab treatment on peripheral eosinophil and T-lymphocyte function in patients with allergic asthma. *J Allergy Clin Immunol* 2006;117:1493–1499.
- ▶ 20 US Food and Drug Administration: Briefing document on safety. Omalizumab (Xolair) (recombinant humanized monoclonal antibody to IgE) for treatment of allergic asthma. <http://www.fda.gov/cder/foi/label/2003/omalgen062003LB.pdf>.