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Churg-Strauss Syndrome in Patients Treated With Omalizumab

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Background: Churg-Strauss syndrome (CSS) is a rare systemic vasculitis associated with asthma, eosinophilia, sinusitis, and pulmonary infiltrates. CSS has been reported in association with asthma therapies.

Materials and methods: The objective is to describe the characteristics of CSS in patients treated with the anti-IgE antibody omalizumab (Xolair; Genentech Inc; South San Francisco, CA). A retrospective review of available data to identify cases of CSS was performed using the Novartis Argus global drug safety database for omalizumab in asthma patients.

Results: We identified 34 potential cases of CSS. Of these, 13 cases fulfilled at least four of the six criteria identified in the American College of Rheumatology classification criteria. Eight of the patients in these 13 definite or probable cases (62%) had CSS symptoms prior to receiving omalizumab or described symptom onset just after corticosteroid weaning. Six of the 13 patients (46%) were confirmed as having been treated with corticosteroids for what was perceived to be severe asthma; when corticosteroids were tapered in conjunction with omalizumab treatment, CSS symptoms appeared just after the tapering. There were 4 other cases of possible CSS, and the remaining 17 patients were judged to not have CSS.

Conclusions: CSS may develop in patients receiving asthma medications who have an underlying eosinophilic disorder that is unmasked by the withdrawal of therapy with corticosteroids, or in patients who delay therapy in favor of other medications. Omalizumab treatment may unmask CSS due to the weaning of corticosteroids in some asthma patients or may delay corticosteroid treatment allowing for CSS to manifest.

Trial registration: ClinicalTrials.gov Identifier: NCT00252135 (CHEST 2009; 136:507–518)

Abbreviations: ACR = American College of Rheumatology; ANCA = antineutrophil cytoplasmic antibody; CI = confidence interval; CSS = Churg-Strauss syndrome

Churg-Strauss syndrome (CSS) is a rare, systemic, small-vessel vasculitis belonging to a group of hypereosinophilic syndromes, a heterogeneous collection of disorders characterized by the presence of

marked peripheral blood eosinophilia, tissue eosinophilia, or both, often without an identifiable cause.¹ CSS is associated with significant peripheral eosinophilia and constitutional symptoms, but it differs from hypereosinophilic syndrome in that it is characterized by the presence of asthma and eosinophilic vasculitis involving one or more organ systems, including the lungs, sinuses, heart, skin, GI tract, nervous system, and musculoskeletal system.¹

Although the cause is unknown, CSS has both allergic and autoimmune features. Patients typically have a history of asthma, and the presentation can be subacute or one of severe acute systemic illness.¹ In many cases, CSS is precipitated by withdrawal of inhaled or systemic corticosteroids.² When cases of CSS became apparent following the use of novel leukotriene modifiers, Wechsler and colleagues^{3,4}

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described the emergence of CSS following the initiation of treatment with these new asthma medications. This led to the notion that CSS could be unmasked in patients receiving asthma medications who have an underlying eosinophilic disorder masked by corticosteroid treatment or that delayed onset of corticosteroids by steroid-sparing alternatives for what is perceived to be only asthma may allow for the syndrome to become manifest.

In that regard, the newest class of asthma therapy has also recently been associated with CSS cases; reports^{5–10} of CSS have been received in the post-marketing setting for omalizumab. Omalizumab (Xolair; Genentech Inc; South San Francisco, CA; and Novartis; San Carlos, CA) is a recombinant, humanized monoclonal antibody that selectively binds to human IgE.^{11,12} It has been approved by the US Food and Drug Administration for the treatment of adults and adolescents with moderate-to-severe persistent allergic asthma. Clinically, omalizumab reduces asthma exacerbations, improves symptom control, decreases rescue medication use, and improves quality of life, allowing a decrease of corticosteroid dosing in patients who remain symptomatic on moderate-to-high doses of inhaled or systemic corticosteroids.^{13–21}

In this study, we utilized the Novartis global safety database (Argus) to evaluate the incidence and prevalence of CSS in omalizumab-treated patients. We conclude that, consistent with the literature, omalizumab may enable weaning from corticosteroids in some asthma patients, thereby unmasking CSS, and that health-care providers should be aware of the signs and symptoms of CSS.

MATERIALS AND METHODS

As these were reviews of anonymous cases reported to the pharmaceutical company and/or to the US Food and Drug Administration, neither patient consent nor internal review board approval was required.

Data Source

In this report, we sought to determine the number of cases of CSS diagnosed in patients who had been treated with omalizumab using the global safety database (Argus) maintained by Novartis. All serious adverse events from clinical trials of omalizumab and all spontaneous reports of adverse events, irrespective of reporter causality assessment, are coded in the Novartis database. The validated extraction of safety data for research reports was carried out by Novartis.

Search and Selection Strategy

A cumulative search was performed for omalizumab covering the time period from June 2003 to 30 June 2007, with the following criteria: (1) *Medical Dictionary for Regulatory Activi-*

ties high-level group term “vascular inflammations”; or (2) *Medical Dictionary for Regulatory Activities* high-level terms “eosinophilic disorder” and “vasculitides.”²²

Clinical Analysis

Following review of the search results, case reports and all available clinical information were reviewed by a CSS expert (M.E.W.) who classified cases as “definite/probable CSS,” “possible CSS,” or “definitely not CSS” based on American College of Rheumatology (ACR) criteria for the classification of CSS sensitivity and specificity vs other defined vasculitis syndromes.²³ According to these criteria, a patient can be classified as having CSS if he/she meets at least four of the six following: (1) asthma; (2) eosinophilia $> 10\%$ (1.5×10^9 cells/L); (3) mononeuropathy (including multiplex) or polyneuropathy; (4) nonfixed pulmonary infiltrates; (5) paranasal sinus abnormality; and (6) the presence of extravascular eosinophils in a biopsy specimen.

Patients in definite/probable cases had signs and symptoms consistent with four of the six ACR criteria. A biopsy-proven vasculitis was not required in order to consider vasculitis to qualify as one of the symptoms. Surrogate symptoms of vasculitis were acceptable evidence. This included the appearance of vasculitis as evidenced by the results of an electromyogram or nerve conduction study, or by the presence of antineutrophil cytoplasmic antibodies (ANCA).^{24–26} Since the indication for omalizumab was asthma in all 34 cases, asthma was present in all of the reports. Reporting rates based on the number of reported events and the number of patient years of exposure was approximated for each classification category of CSS.

RESULTS

On the basis of sales data, the patient exposure of omalizumab was estimated to be equivalent to approximately 87,500 person-years. Following our database search, 34 potential CSS cases were identified, including 28 spontaneous reports and 6 reports from clinical trials.

Definite/Probable Cases of CSS

Of the 34 cases found in the global safety database, 13 were identified to be definitely or probably CSS (Table 1). The mean length of time receiving omalizumab therapy at the time of diagnosis was 159 days (range, 15 to 365 days). Four of these patients were women, and nine patients were men. Their ages ranged from 37 to 81 years, with the majority being 40 to 60 years old (eight patients). All 13 patients experienced asthma and eosinophilia. Four patients experienced neuropathy, two with a diagnosis of mononeuritis multiplex. Pleural effusion was described in at least 6 of the 13 cases. In 8 of the 13 cases, oral corticosteroid weaning had occurred just prior to the onset of the CSS symptoms, and in the remaining cases a CSS diagnosis was established, but not enough information was provided for further assessment.

Table 1—Definite or Probable Cases of CSS in the Novartis Global Safety Database

Case No.	AE Verbatim Term (Preferred Term)*	Age, yr/Sex	Seriousness Criteria	Length of Time Receiving Omaliuzumab at		Event Resolution	Symptoms	Omaliuzumab/Steroid Weaning Played a Role?	Comments
				Time of Event	Not reported				
PHBS2006US17236/231930	CSS (allergic granulomatous angitis)	66/F	Medically significant	Not reported	Not reported	Not reported	Increased eosinophils; pericarditis; pleural nodules	No/NEI	
PHBS2005US16803/219484	Systemic and pulmonary hypereosinophilia (Loeffler syndrome, eosinophilia)	57/M	Death	36 d	Death on 16 October 2005		Eosinophilic pneumonia; eosinophils heart/kidney/ lung	Yes/yes (unmasking when steroids weaned)	Patient had long-standing Loeffler syndrome, history of eosinophilic pneumonia; prostatitis diagnosed October 13, 2005, treated with ciprofloxacin, died October 16, 2005; GI symptoms, GERD, gastritis, esophagitis; autopsy revealed focal eosinophilic nephritis, bilateral ventricular cardiomegaly, and extensive eosinophilic myocarditis with widespread myocytolysis; Loeffler syndrome identified by autopsy
PHBS2006US15014/230215	Hypereosinophilia, eosinophilic infiltration (eosinophilia)	37/M	Medically significant	305 d	Unchanged		Eosinophils; sinus disease; GI infiltration	Yes/yes (unmasking when steroids weaned)	History of sinusitis, neuropathy symptoms of tingling in right lower extremity; prior to omalizumab therapy, AEC = 1,900 cells/ μ L; during steroid wean, AEC = 8,504 cells/ μ L; GI symptoms, diarrhea; eosinophils prior to omalizumab therapy and peak within 3 mo of receiving omalizumab (AEC = 1,976 cells/ μ L, 1 mo after omalizumab therapy start and 8,504 cells/ μ L, 9 mo after omalizumab start)
PHBS2004US14584/210203	Polymyositis (polymyositis)	45/M	Hospitalized	175 d	Resolved		Eosinophils; sinus disease; pulmonary infiltrate; neuropathy	No/yes	Elevated creatine kinase and myoglobin levels, swelling in right leg with pain in calf; hematuria; nerve conduction test suggestive of some peripheral neuropathy; subject had history of nasal polyps but no sinusitis. Chest CT scan results, bilateral ground-glass infiltrates, mostly in upper lobe (right more than left), no pleural effusion; 2001 chest CT scan results, hilar adenopathy plus some infiltrates and atelectasis in right lower lobe; eosinophils reported, 42%
PHBS2004US15061/210203	Axonal mononeuropathy multiplex, presumed CSS (mononeuropathy multiplex)	43/M	Hospitalized, disability	239 d	Patient "responding to therapy; condition stabilizing," disabled		Eosinophils plus p-ANCA; vasculitis	Yes/yes (unmasking when steroids weaned)	History of "extensive sinusitis" on brain MRI; lumbar spine MRI findings: narrowing, disc herniation, annular tear; mononeuritis multiplex reported, weakness and numbness in hands and feet, claw hands, foot pain; radiograph results: marginal spondylosis in thoracic spine; sural nerve biopsy findings: "no vasculitis or thrombosis but massive acute axonal degeneration, consistent with necrosis or transection of entire trunk shortly proximal to examined level; strongly suggestive of vasculitis lesion just proximal to biopsy site"; results of fluorescence study performed in serology laboratory, reported as negative; eosinophils reported to be 74%
PHBS2006US10671/227299	CSS (allergic granulomatous angitis)	59/M	Medically significant	365 d	Improving		Eosinophils; mononeuritis multiplex; vasculitis	No/no	Hypertension, history of sinusitis, nasal polyps; GI symptoms: abdominal discomfort, GERD; testis/epididymis biopsy results: "CSS (vasculitis and eosinophilia) and mononeuritis complex"

(Continued)

Table 1—Continued

Case No.	AE Verbatim Term (Preferred Term)*	Age, yr/Sex	Seriousness Criteria	Length of Time Receiving Omalizumab at Time of Event	Event Resolution	Symptoms	Omalizumab/Steroid Weaning Played a Role?	Comments
PHRM2007FR00652/36049	CSS (allergic granulomatous angitis), lingering pseudosurgical abdominal syndrome, intestinal subocclusion (subileus), tumorous formation in the left cheek with eosinophilic infiltrate (neoplasm skin)	55/M	Hospitalized, life- threatening, medically significant	359 d	Complete recovery	Sinus disease; eosinophils in tissue; pulmonary infiltrate; massive eosinophils; increased C-reactive protein	No/yes	Patient had hypertension and nasal polyps; intestinal subocclusion reported; ENT scan results: massive infiltrates of sinuses and maxillary glands; abdominal scan/MRI results: "infiltrations of retroperitoneal and peritoneal area and infiltration of mesenteric under renal area until pelvis with small intestine subocclusion in relation with the infiltration"; no proteinuria or nephropathy; cheek biopsy results: eosinophil cellularly without vasculitis; bronchial biopsy results: eosinophil mucus infiltration with degranulated mature eosinophils and eosinophil lysis with surface erosion; eosinophils reported to be 16%
PHRM2007FR01274/240120	Pulmonary embolism (pulmonary embolism), severe CSS complicated by PE (allergic granulomatous angitis), cerebral vasculitis (cerebral vasculitis)	77/M	Hospitalized, life- threatening	43 d	Improving	Eosinophils Cerebral vasculitis	No/yes	Nasal polyps, polypectomy; cerebral vasculitis and confusional syndrome, hand-motor deficiency; cerebral MRI results: multiple signal abnormalities corresponding with recent ischemic lesions at the diffusion sequences; reporter noted history of Horton disease, no eosinophilia prior to omalizumab therapy in December 2006, and no corticosteroid therapy in preceding year as evidence for relatedness; cardiomyopathy, thoracic pain, segmental hypokinesia with normal coronarography, troponin level increased ($\times 150$); "absence of eosinophilia before omalizumab" reported (no eosinophil values provided)
PHBS2005US13916/217521	Eosinophilia	51/F	Hospitalized	15 d	Resolving	Eosinophils; pulmonary infiltrate; arthritis; sinusitis; increased ESR	NE/NEI	History of sinusitis, fibromyalgia; irritable bowel; radiograph (August 29, 2005) results: small areas of focal alveolar infiltrate in right lower and upper lobe; superior segment of left lower lobe, no PE; heart size and mediastinal contour normal; radiograph (September 6, 2005) results: multifocal bilateral consolidation, improvement in right middle and left lower lobes, left hilar adenopathy present and showing regression; left lower lobe biopsy results: minimal nonspecific chronic inflammatory bronchial mucosa and lung parenchyma, no granulomas, no evidence of malignancy; eosinophils reported to be 43%
PHBS2006US05841/224083	CSS (allergic granulomatous angitis), increased eosinophils (eosinophil count increased)	81/F	Hospitalized	105 d	Condition unchanged, subject discharged from hospital	Eosinophils; increased IgE	NE/NEI	Mononeuritis complex; muscle and nerve biopsies performed; no results reported; eosinophils reported to be 70%

(Continued)

Table 1—Continued

Case No.	AE Verbatim Term (Preferred Term)*	Age, yr/Sex	Seriousness Criteria	Length of Time Receiving Onalizumab at Time of Event	Event Resolution	Symptoms	Onalizumab/Steroid Weaning Played a Role?	Comments
PHBS2005US08766/215317	Hyper eosinophilia syndrome (hyper eosinophilic syndrome)	66/F	Hospitalized/ medically significant	120 d	Improving	Increased IgE	NEI/NEI	Pulmonary hypertension, asymmetric LVH 2 cm, heart failure, valve involvement, arrhythmia; radiographic results: mediastinal lymphadenopathy, small right pulmonary nodule. Chest CT results: small pleural effusion (left greater than right), right hilar, subcarinal, precarinal adenopathy, 5-mm right middle lobe nodule; bone marrow biopsy results: no evidence of malignancy, 25% cellularity, granulocytic hyperplasia primarily due to eosinophils; mediastinoscopy results: reactive changes in precarinal and precordial lymph nodes; elevated RF level (314 IU/mL); eosinophils reported to be 80%.
PHBS2006US04642/235997	CSS (allergic granulomatous angitis), eosinophilia (eosinophilia), eosinophils 51% (eosinophil count increased)	47/M	CSS; medically significant	62 d	"Rapidly normalized" after initiation of oral steroids	Sinus disease; eosinophils; pulmonary infiltrate; systemic disease	Yes/yes (unmasking when steroids weaned)	"Other suspected causes identified included use of montelukast (Singulair; Merck; Whitehouse Station, NJ) and being off steroids 5 weeks before the event"; after event, patient tapered steroids slowly; history of sinusitis, nasal polyps with polypectomy; symptoms of neuropathy; proteinuria, positive for ketones; elevated ESR; unspecified GI/cardiac symptoms; radiograph results: biapical opacities and diffuse interstitial markings, normal after oral corticosteroid therapy started; eosinophil count prior to omalizumab, 0; 2 mo after omalizumab therapy initiation, laboratory results were as follows: ESR, 81; eosinophil count, 51% (normal 0–5); neutrophil count, 30%; WBC count, 18,600 (normal 4–11); and complement C4, 42.3; urine protein level was "30" and urine was positive for ketones.
PHBS2005US11804/216735	Possible CSS (allergic granulomatous angitis)	55/M	Death	84 d	Condition improved prior to patient's death	Sinusitis; eosinophils p-ANCA positive; rash with vasculitis; mononeuropathy	No/yes	Patient had hypertension "likely related to vasculitis/steroids" and neuropathy; radiograph results: questionable nodule in right midlung zone with stranding or scar; skin biopsy results: leukocytoclastic vasculitis with prominent eosinophil component; sural nerve biopsy results: patchy loss of large myelinated fibers, acute degeneration of large myelinated fibers, perineural and perivascular plasma cell aggregates and reactive endothelium, with no evidence of vasculitis; patient died of pancytopenia attributed to cyclophosphamide therapy; eosinophils reported to be 63%.

All reports were either spontaneous or spontaneous literature reports. F = female; M = male; AE = adverse event; AEC = absolute eosinophil count; ESR = erythrocyte sedimentation rate; GERD = gastroesophageal reflux disease; NEI = not enough information; ENT = ear, nose, and throat; PE = pulmonary embolus; LVH = left ventricular hypertrophy; p-ANCA = perinuclear ANCA; RF = rheumatoid factor.

*Asthma was an indication for all cases.

Possible Cases of CSS

Four of the 34 cases found in the global safety database were considered to be possible cases of CSS because reported symptoms did not fulfill four of the six diagnostic CSS symptoms outlined by the ACR definition (Table 2). Three of these patients were women, and the ages of all patients ranged from 42 to 66 years. One patient, a 42-year-old man, experienced asthma, pulmonary infiltrates, and rapidly progressive glomerulonephritis but was ultimately diagnosed with ANCA-negative renal vasculitis. The second patient, a 66-year-old woman, experienced asthma, eosinophilia, diarrhea, and nausea. The third patient, a woman (age not reported), experienced vasculitis, was positive for perinuclear ANCA, and was referred to a rheumatologist. The fourth patient presented with asthma, eosinophilia, sinus disease, and pulmonary infiltrates but did not have definitive evidence of vasculitis. For these patients, either not enough information was available or CSS had not yet developed. It should be noted that CSS might potentially develop in these patients, but it is not clear whether it would.

Definitely Not CSS

The remaining 17 reports found in the global safety database were determined not to be CSS, as evidenced by diagnoses that included phlebitis, Wegener granulomatosis, temporal arteritis, hypersensitivity reaction, and Bell palsy (Table 3).

DISCUSSION

Our analysis of the omalizumab global safety database revealed several definite or probable cases of CSS in patients who received omalizumab. In the majority of cases, there was preexisting evidence of CSS (*eg*, eosinophilia, severe asthma, and sinus disease) prior to omalizumab administration. In a subset of patients with severe asthma undergoing management with corticosteroids in conjunction with omalizumab or prior to omalizumab exposure, tapering of corticosteroid therapy resulted in the emergence of CSS. Similar to cases of CSS unmasking previously reported with the use of leukotriene modifiers and corticosteroids,^{3,27,28} omalizumab does not appear to be directly causative in any of the documented cases of CSS.

It should be noted that there are limitations associated with confirming (or refuting) a diagnosis of CSS by using a large database and that there are limitations to the ACR classification criteria for CSS. For each case reported, we used the information made available to us; however, not all cases had

enough information to provide a fully informed evaluation. For these cases, a CSS diagnosis was not able to be made due to insufficient data.

CSS and Asthma Therapy

The association between CSS and different asthma therapies has been the subject of debate over the last decade due to several reports^{3,4} of CSS unmasking following the initiation of treatment with leukotriene modifiers and other asthma therapies. In those cases, CSS was observed to be unmasked in patients receiving asthma medications who had an underlying eosinophilic disorder masked by corticosteroids or in patients receiving steroid-sparing alternative medications that delayed onset of corticosteroid therapy for the treatment of what was perceived to be only asthma. In the majority of such patients, the syndrome dramatically improves with corticosteroid therapy. Compounds associated with CSS unmasking include prednisone, zafirlukast, montelukast, fluticasone, budesonide, and salmeterol.^{2,27,28} Indeed, in a study²⁹ that examined the link between asthma treatments and CSS, 47 cases of possible or definite CSS were identified. While there was a strong association between leukotriene modifiers and CSS in the crude analyses, this disappeared in the adjusted models when controlling for other asthma drugs. This finding suggested that severe asthma and exposure of multiple controller medications, including corticosteroids, is associated with, but not necessarily the cause of, CSS development.

CSS and Omalizumab

In addition to the cases examined here, there have been additional reports of CSS associated with omalizumab. In the first case of CSS following omalizumab administration,⁶ symptoms improved with corticosteroids. In later reports,^{5,7,9,10,30} CSS unmasking was associated with the cessation or tapering of asthma therapy in omalizumab-treated patients. Each of these reports relates important information regarding the relative roles of IgE and eosinophilia in patients with asthma and CSS, and also about the role that anti-IgE may play in patients with these conditions. In some cases, anti-IgE addresses the underlying asthma, but eosinophilia may nonetheless ensue. For such patients, the binding of IgE may be sufficient to control the underlying asthma but may not be sufficient to address the underlying cause of eosinophilia. While in certain cases the binding of an allergen to crosslinked IgE can result in a mitigation of the allergic cascade and a reduction of cytokines that can result in abrogation of both eosinophilia and asthma symptoms, this may

Table 2—Possible Cases of CSS in the Novartis Global Safety Database

Case No./ GNE MCN	AE Verbatim Term (Preferred Term)*	Age, yr/Sex	Seriousness Criteria	Length of Time		Event Resolution	Symptoms	Omalizumab/Steroid Weaning Played a Role?	Comments
				Receiving Omalizumab at Time of Event	Receiving Steroid at Time of Event				
PHNU2006DE03110/230247	Vasculitis, p-ANCA positive	Unknown/F					Asthma; vasculitis plus ANCA (no eosinophilia, CSS usually p-ANCA)	NEI/NEI	
PHBS2004US08493/207306	Eosinophilia (eosinophilia)	66/F	Hospitalized	122 d		Not reported	Asthma; very high eosinophil level (63%)	NEI/NEI	GI symptoms; subject underwent bone marrow biopsy (date/results not reported); eosinophils reported to be 63%
PHBS2005US07939/214838	Idiopathic vasculitis (vasculitis), acute renal failure (renal failure acute)	42/M	Hospitalized	73 d		Resolving	Asthma; pulmonary infiltrates; increased creatinine (ANCA negative)	NEI/NEI	Serum creatinine level 3.0–5.1, proteinuria, nephritis, acute renal failure; fever, chills, dyspnea, cough developed in patient in mid-March 2005; treated with azithromycin and prednisone, recovered, then worsened again in early April; did not improve with azithromycin alone; in April, found to have renal failure, treated, and improved; radiograph results: bilateral chest infiltrates, minimal bibasilar atelectasis; renal biopsy specimens: diffuse segmental necrotizing and crescentic glomerulonephritis, evidence of interstitial nephritis with eosinophils and multinucleated giant cells
PHBS2003US10157/202320	Eosinophilia (differential diagnosis) (eosinophilia), other eosinophilic lung disease (differential diagnosis) (pulmonary eosinophilia)	51/F	Not reported	Asthma; sinus disease; pulmonary infiltrate; borderline eosinophilia; no vasculitis		No/NEI	History of sinusitis; arm pain originating at injection site reported; radiograph results: nodular density around mid- thoracic spin, no infiltrates or infections; biopsy not done; likely diagnoses: asthma flare and pulmonary eosinophilia	NEI/NEI	

See Table 1 for abbreviations not used in the text.

*Asthma was an indication for all cases.

Table 3—Cases in the Global Safety Database That Were Definitely Not CSS

Case No./ GNE MCN	AE Verbatim Term (Preferred Term)*	Age, yr/Sex	Seriousness Criteria	Length of Time on Omalizumab at Time of Event	Event Resolution	Symptoms	Omalizumab/Steroid Weaning Played a Role?	Comments
PHHO2001CA07257/Not available	Hyper eosinophilia (hyper eosinophilic syndrome)	54/F	Nonserious	Asthma; eosinophilia; no vasculitis	NEI/NEI	Likely diagnosis: hyper eosinophilia	NEI/NEI	
PHRM2007FR01746/243755	Right deep phlebitis (phlebitis deep)	50/F	Medically significant	Phlebitis; no clear vasculitis or eosinophilia	No/no	Likely diagnosis: phlebitis	NEI/NEI	GI symptoms; subject underwent bone marrow biopsy (date/results not reported); eosinophils reported to be 63%
PHRM2007FR01345/240835	Generalized urticarial vasculitis very pruritic predominantly on trunk (leukocytoclastic vasculitis)	30/F	Medically significant	Vasculitis; no eosinophilia or other CSS features	NEI/NEI	Likely diagnosis: leukocytoclastic urticarial vasculitis		
PHRM2007FR00755/236584	Subocclusive syndrome (subleus), phlebitis (phlebitis), urticaria on thorax and thighs (urticaria)	46/F	Hospitalized, disability	No eosinophilia; no vasculitis	Possible/no (symptoms developed in patients after each injection)	Likely diagnoses: subocclusive syndrome, phlebitis		
PHHO2006US18002/251279	Methicillin-resistant Staphylococcal infection (Staphylococcal infection)	30/M	Hospitalized, life-threatening	Asthma; pneumonia plus methicillin-resistant <i>Staphylococcus aureus</i>	No/no	Likely diagnosis: asthma exacerbation		
PHNU2007PL00541/Not available	Eosinophilia (eosinophilia)	Unknown/F	Not reported	Eosinophilia; cough; no vasculitis	NEI/NEI	Likely diagnosis: persistent cough and eosinophilia		
PHHO2007US07055/240179	Kawasaki syndrome (Kawasaki disease)	11 wk/F	Hospitalized	No asthma; no eosinophilia	NEI/No	Likely diagnosis: Kawasaki syndrome		
PHHO2006US04003/206062	Aspergillosis pneumonia (bronchopulmonary aspergillosis)	58/F	Death	No eosinophilia	No/no	Likely diagnosis: Aspergillosis pneumonia		
PHBS2005US15808/218514	Wegener granulomatosis (Wegener granulomatosis)	60/F	Medically significant	Asthma	No/NEI	Likely diagnosis: Wegener granulomatosis		
PHHO2005GB10717/GNE	Liver hemangioma (hemangioma of liver)	68/F	Hospitalized	Asthma	No/no	Likely diagnosis: temporal arteritis		
PHBS2005US07751/214598	Erythema nodosum (erythema nodosum)	41/F	32 d	No eosinophilia; no vasculitis	NEI/NEI	Likely diagnosis: erythema nodosum		
PHBS2005US07476/214678	Eosinophilic scleroderma (scleroderma); eosinophilic-like myalgia/myositis (myositis)	Unknown/F	Medically significant	Eosinophilia; no vasculitis	NEI/NEI	Eosinophils prior to omalizumab therapy and peak within 3 mo of receiving omalizumab; not reported; likely diagnosis: eosinophilic scleroderma		
PHBS2005US03366/212861	Leukocytoclastic vasculitis	47/F	Medically significant	Asthma; no eosinophilia or other features of CSS	NEI/NEI	Likely diagnosis: leukocytoclastic vasculitis		

(Continued)

Table 3—Continued

Case No./ GNE MCN	AE Verbatim Term (Preferred Term)*	Age, yr/sex	Seriousness Criteria	Length of Time on Omalizumab at Time of Event	Event Resolution	Symptoms	Omalizumab/Steroid Weaning Played a Role?	Comments
PHBS2005U503382/212536	Bell palsy (facial palsy), eosinophilia (eosinophilia)	66/M	Medically significant	Asthma; eosinophilia; no vasculitis	No/possibly (steroids tapered to 2 mg/d)	Likely diagnosis: Bell palsy and eosinophilia		
PHBS2004U511633/208748	Eosinophilia (eosinophilia)	38/F	Hospitalized	Asthma; eosinophilia; possible vasculitis	No/NEI (eosinophilia preceded symptoms)	Per reporter, eosinophilia predated omalizumab therapy; Patient hospitalized for eosinophilia, abdominal pain described as probable GERD; omalizumab therapy continued, patient received dose September 16, 2004; GI symptoms: heartburn, stomach pain, anorexia; abdominal CT scan results negative; eosinophils prior to omalizumab therapy and peak within 3 mo of receiving omalizumab; not reported, 23%; likely diagnosis: abdominal pain and eosinophilia		
PHBS2004U508400/207029	Phlebitis (phlebitis)	Unknown/ unknown	Not reported		No/no	Likely diagnosis: phlebitis		

See Table 1 for abbreviations not used in the text.

*Asthma was an indication for all cases.

Table 4—CSS Incidence and/or Period Prevalence Estimates in the General Population

Source	Population	Incidence/Million Person-Yr	Period Prevalence/Million Persons
Watts et al ³⁵	General—Norwich, UK	2.4 (95% CI, 0.9–5.3)	
Watts et al ³⁶	General—Norwich, UK	Using ACR criteria: 2.7 (95% CI, 1.3–4.8) Using Hammersmith criteria: 3.4 (95% CI, 1.9–5.6)	
Watts et al ³⁷	General—Norwich, UK	3.1 (95% CI, 1.7–5.2)	
	General—Lugo, Spain	0.9 (95% CI, 0.1–3.2)	
Watts et al ³⁸	General—Tromsø, Norway	0.5 (95% CI, 0.06–1.8)	
Gonzalez-Gay et al ³⁹	General—Spain	1.31 (95% CI, 0.87–1.96)	
Reinhold-Keller et al ⁴⁰	General—North and South Germany		North: 7 (95% CI, 0–14) South: 2 (95% CI, 0–7)
Reinhold-Keller et al ⁴¹	General—North and South Germany	North: 1 (95% CI, 0–3) South: 1 (95% CI, 0–2)	
Reinhold-Keller et al ⁴²	General—North Germany	1	
Haugeberg et al ⁴³	General—Norway		13
Dadoniene et al ⁴⁴	General—Lithuania	1.3 (95% CI, 0.5–2.9)	
Mohammad et al ⁴⁵	General—Sweden		14 (95% CI, 0.3–27)
Mahr et al ⁴⁶	General—France		10.7 (95% CI, 5–17)
Martin et al ⁴⁷	Patients exposed to newly marketed drugs—UK		6.8 (95% CI, 1.8–17.3)
	Patients exposed to non-anti-asthma drug—UK		1.8 (95% CI, 0.05–10.2)

not be the case for all patients who may have asthma or eosinophilia that is the result of other mechanisms.

Several studies^{22,28,35–48} have examined the incidence and prevalence of CSS in both general and asthmatic populations. CSS incidence in the general population ranges from 0.5 to 1.3 cases per million person-years (Table 4). The overall prevalence varies to a large degree, from 2 to 14 cases per million persons. Within the asthma patient population, CSS rates are far greater (Table 5).

In our analysis of the Novartis safety database, considering the 87,500 cumulative person-years of omalizumab exposure through July 2007 and the four reports of possible CSS, the reporting rate of CSS in

the United States is estimated to be 46 cases per million person-years (95% confidence interval [CI], 14.5 to 110.3 cases per million person-years). When the 13 definite/probable cases are considered, the reporting rate is estimated to be 149 cases per million person-years (95% CI, 82.6 to 247.7 cases per million person-years). When both definite/probable and possible reports of CSS are taken into account, the reporting rate is estimated to be 194 cases per million person-years (95% CI, 117.0 to 304.7 cases per million person-years). It should be noted that our values are crude adverse event reporting rates for CSS that are not equivalent to incidence rates and should be viewed with caution.³¹ Furthermore, it is probable that the prevalence of omalizumab-associated

Table 5—CSS Incidence and/or Period Prevalence Estimates in the Asthma Patient Population

Source	Population	Incidence/Million Person-Yr	Period Prevalence/Million Persons
Martin et al ⁴⁷	Patients exposed to anti-asthma drug—UK		64.4 (95% CI, 13.3–188.1)
Wechsler et al ²⁸	General Practice Research Database—UK	6–18	
Wechsler et al ²⁸	Asthma plus exposure to zafirlukast or montelukast—US	Approximately 60	
Loughlin et al ⁴⁸	Asthma plus no use of leukotriene receptor antagonists—US	Definite CSS: 0 (90% CI, 0–23.0) to 67 (90% CI, 22.5–160.6) Probable CSS: 583	
Harrold et al ²²	Population with three or more dispensing of an asthma drug	Definite/probable CSS: 34.6 (95% CI, 21.4–53.0)	

CSS is even higher, owing to underreporting and poor physician recognition since this remains a rare entity and since it may be masked by continued corticosteroid therapy.

Nonetheless, data from our study and from the literature suggest that a causal relationship between omalizumab and CSS is unlikely to exist. Given the amount of clinical exposure and considering the patient population treated with omalizumab, case reports of CSS are to be expected, especially since asthma is among the diagnostic criteria for CSS. The analysis of spontaneous reports does not appear to show a direct safety risk for CSS in omalizumab-treated patients.

CSS Treatment With Omalizumab

There is evidence suggesting that omalizumab therapy may be of benefit to CSS patients. In one report,³² a man presented with asthma symptoms requiring therapy with high-dose inhaled and systemic corticosteroids. Attempts at tapering the systemic corticosteroids resulted in the worsening of asthma and upper respiratory complications. CSS, which was controlled with systemic corticosteroids and, later, with cyclophosphamide and azathioprine, was diagnosed in the patient. Approximately 17 years later, omalizumab was started as a treatment for the severe asthma. Within 15 days of the initiation of omalizumab therapy, asthma symptoms, lung function, and eosinophilia improved.

In a second report examining a refractory variant of CSS, the unmasking of CSS developed after the withdrawal of steroid therapy in two patients.³³ In these cases, anti-IgE therapy with omalizumab resulted in marked clinical improvement. Given its steroid-sparing effects and its beneficial effect on reduction of eosinophils, omalizumab may provide a benefit to CSS patients. One possibility is that the primary benefit comes from improved pulmonary function, although further studies are needed.³⁴

CONCLUSIONS

While omalizumab is an effective therapy for many patients with asthma, clinicians should be vigilant for signs and symptoms of CSS in any asthmatic patient in whom corticosteroid doses are tapered while receiving this therapy and in patients treated with omalizumab in favor of corticosteroids. Since unrecognized underlying CSS remains possible in the moderate-to-severe asthma population for which omalizumab therapy is indicated, physicians should learn to recognize the signs and symptoms of CSS and be alert for the development of vasculitis and/or infiltration of extrapulmonary tissue eosinophilia,

both of which distinguish CSS from eosinophilic asthma. In patients newly diagnosed with CSS, management with corticosteroids and other corticosteroid-sparing agents such as cyclophosphamide or azathioprine is recommended. Whether omalizumab actually has beneficial effects in these patients based on its antiinflammatory effects remains to be proven in prospective clinical trials.

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Churg-Strauss Syndrome in Patients Treated With Omalizumab

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