

## Workshop summary report

# The relationship of asthma therapy and Churg-Strauss syndrome: NIH workshop summary report

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The Churg-Strauss syndrome (CSS) is a distinct form of vasculitis that is notable for its eosinophilia and frequent associations with asthma and sinusitis. Because there has been an increasing recognition that CSS can develop in patients with asthma and that CSS might be associated with specific asthma treatments, the National Heart, Lung, and Blood Institute, the National Institute of Allergy and Infectious Diseases, the Office of Rare Diseases, National Institutes of Health, and the US Food and Drug Administration jointly sponsored a workshop to consider interrelationships among CSS, asthma, and asthma therapeutics and to assess what is known about underlying mechanisms of CSS. Issues related to the criteria for defining and diagnosing CSS were reviewed, including the contemporary understanding that diagnostic biopsies need only reveal eosinophilic perivascular infiltrates and that asthma need not be present when CSS develops. From published reports and reports to the US Food and Drug Administration, treatment of patients with asthma with any of 3 cysteinyl leukotriene receptor antagonists, a 5-lipoxygenase inhibitor, and inhaled corticosteroids has been associated with CSS development. It is unknown whether these agents were eliciting CSS. A variety of physiologic and study design issues might lead to the reported associations of these drugs with CSS. Because many asthma patients receiving these therapies were able to diminish their systemic corticosteroid therapy, it is possible that incipient CSS was unmasked by lessened steroid use. The underlying pathophysiologic mechanisms of CSS, however, are unknown, and there is no means of identifying which patients with asthma might be at risk for CSS. Accordingly, investigations with the goals of defining the underlying pathophysiologic processes of CSS and establishing the

relationships of asthma and its therapies to CSS are needed. (*J Allergy Clin Immunol* 2001;108:175-83.)

**Key words:** Asthma, Churg-Strauss syndrome, vasculitis, leukotriene antagonists, eosinophilia, sinusitis, corticosteroids

Among the major forms of vasculitis, Churg-Strauss vasculitis is notable both for its distinct association with blood and lesional eosinophilia and for its frequent association with allergic rhinoconjunctivitis, sinusitis, and especially asthma. There has been an increasing recognition that Churg-Strauss vasculitis can develop in patients with asthma and that Churg-Strauss vasculitis might be associated with specific asthma treatments. The National Heart, Lung, and Blood Institute, the National Institute of Allergy and Infectious Diseases, and the Office of Rare Diseases Research of the National Institutes of Health, in conjunction with the US Food and Drug Administration (FDA), convened a 2-day workshop on September 15, 2000, to consider the relationship of asthma therapies and the Churg-Strauss syndrome (CSS). The purposes of the workshop were to (1) explore the nature of the relationship between asthma therapy and CSS, (2) examine published reports and postmarketing spontaneous reports of eosinophilic syndromes, CSS, and systemic eosinophilia, (3) consider potential underlying mechanisms for CSS, (4) identify gaps in our knowledge and key issues to be addressed, (5) establish the important research questions, and (6) identify areas for future research directions.

Although CSS is a distinct and well-recognized form of vasculitis, there are a number of issues that make the recognition and diagnosis of CSS and an understanding of its relationship to either the clinical or the underlying pathogenetic manifestations of asthma highly problematic. These uncertainties are pertinent both to the clinical approach to patients with asthma receiving contemporary antiasthmatic therapies and to investigative considerations aimed at identifying the interactions among asthma, CSS, and therapies of asthma.

The workshop participants acknowledged that virtually nothing is known about the underlying pathophysiology of CSS vasculitis, which is likewise true of several other forms of vasculitis and many related hyper-eosinophilic syndromes, including the idiopathic hyper-eosinophilic syndrome (HES). Furthermore, the relationship of the asthma component of CSS to other forms of asthma remains unclear—ie, is CSS vasculitis an uncom-

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**Abbreviations used**

ACR: American College of Rheumatology  
 CSS: Churg-Strauss syndrome  
 CysLT1: Cysteinyl leukotriene receptor 1  
 FDA: US Food and Drug Administration  
 HES: Hypereosinophilic syndrome

mon complication that can arise in any (and frequently in atopic) patients with preexisting sinusitis and asthma, or is the asthma associated with CSS (which is often later-onset asthma) attributable to a pathophysiology different from that of other forms of asthma? Because many patients with asthma are now more aggressively treated with corticosteroids, it is possible that the initiation of other antiasthmatic therapies is not directly eliciting CSS but is rather, by enabling the tapering of systemic steroids, permissive in allowing incipient CSS to become manifest. If so, which patients with asthma are at risk for the development of full-blown CSS, and more fundamentally, what pathophysiologic processes are being unmasked by steroid tapering?

In addition, the increasing awareness of the complexities of cysteinyl leukotriene biology might be pertinent. There are at least 2 cysteinyl leukotriene receptors, including cysteinyl leukotriene receptor 1 (CysLT1), which is the target of specific antiasthmatic therapies (montelukast, zafirlukast, and pranlukast), and these leukotriene receptors are being found in a multitude of tissues and cells. Likewise, cysteinyl leukotrienes might have roles in regulating diverse cellular responses. Thus, alterations in cysteinyl leukotriene-mediated actions, perhaps in concert with genetic polymorphisms that provide for differential responses to agents (including corticosteroids) that regulate leukotriene actions in subsets of patients, might be contributory to the development of CSS in some individuals with asthma. Given the absence of understanding of the pathophysiologic basis for the asthmatic and vasculitic manifestations of CSS, other, as yet unanticipated mechanisms might also be important. In considering these possibilities and in contemplating the types of investigations that are needed to understand the underlying pathophysiology of CSS and its relationship to asthma, a variety of issues bearing on this syndrome were scrutinized.

**CSS: HISTORICAL ASPECTS**

Starting about 1940, reports began to appear identifying a subset of patients with polyarteritis nodosa who were distinct because they frequently had concomitant allergic diseases (including asthma) and characteristically developed eosinophilia and pulmonary infiltrates. In 1951, Churg and Strauss reported from autopsies of 13 patients a pathologic triad of allergic granulomatosis, allergic angiitis, and periarteritis nodosa.<sup>1</sup> The recognition of this pathologic triad was critical in establishing CSS as a distinct form of vasculitis, but it is now considered that the diagnosis of CSS does not require pathologic documentation of this full triad and it is not based solely on histopathology.

In clinical practice, CSS remains primarily a clinical diagnosis dependent largely on the evaluation and judgement of clinicians. In its common presentation, CSS is often a triphasic illness.<sup>2</sup> In the first, prodromal phase, the patient experiences allergic rhinitis and asthma of variable severity, the latter not infrequently developing in adulthood. The second phase is characterized by blood eosinophilia and eosinophilic tissue infiltrates. The third phase features potentially life-threatening vasculitis that can involve multiple organs but often involves the lung, the heart, the gastrointestinal tract, and the nervous system. Although this triphasic pattern is common, it is by no means uniform, and the literature is replete with reports of patients who present initially with acute vasculitic complications. Delayed diagnosis and treatment might contribute to death from vasculitic complications involving the heart, the gastrointestinal tract, or other organs.<sup>3</sup>

**AVAILABLE DEFINITIONS OF CSS AND THEIR LIMITATIONS**

The currently available definitions of CSS are presented in Table I.

**Pathologic criteria of Churg and Strauss**

On the basis of their original autopsy studies, Churg and Strauss identified 3 pathologic features characteristic of what is now referred to as CSS: (1) necrotizing vasculitis of small and medium-sized arteries and veins, (2) eosinophil infiltration around involved vessels and in tissues, and (3) extravascular granulomas.<sup>1</sup> A rigid reliance on the need for all 3 of these pathologic features to be demonstrable in biopsied or autopsied tissues, however, is now considered to be unnecessary for the diagnosis of CSS. Granulomas are difficult to find in biopsies and even some autopsy tissues.<sup>2</sup> Moreover, experienced pathologists, including Dr Andrew Churg, now recognize that CSS vasculitic lesions in evolution, as seen in patients undergoing diagnostic biopsies, can exhibit only eosinophilic perivascular infiltrates (Fig 1). The limitations of requiring all 3 of the "classic" pathologic features to be demonstrable for making the diagnosis of CSS are exemplified in a recent study of 23 patients diagnosed by other criteria as having CSS; in only 4 of the 23 patients were all 3 pathologic features demonstrable.<sup>4</sup>

Thus, though the classic pathologic triad was critical in helping identify CSS as a distinct form of vasculitis, it is not reasonable to expect that patients with CSS will necessarily demonstrate all 3 of these findings in biopsied tissues to make the diagnosis of CSS. Accordingly, knowledgeable clinicians will accept evidence of perivascular eosinophilic infiltrates as being supportive of the clinicopathologic diagnosis of CSS. Because some pathologists, however, might still feel compelled to find all 3 "classic" pathological features<sup>5</sup> before they interpret biopsies as diagnostic of, or even compatible with, CSS, medical and pathologic records could fail to record findings indicative of the diagnosis of CSS.

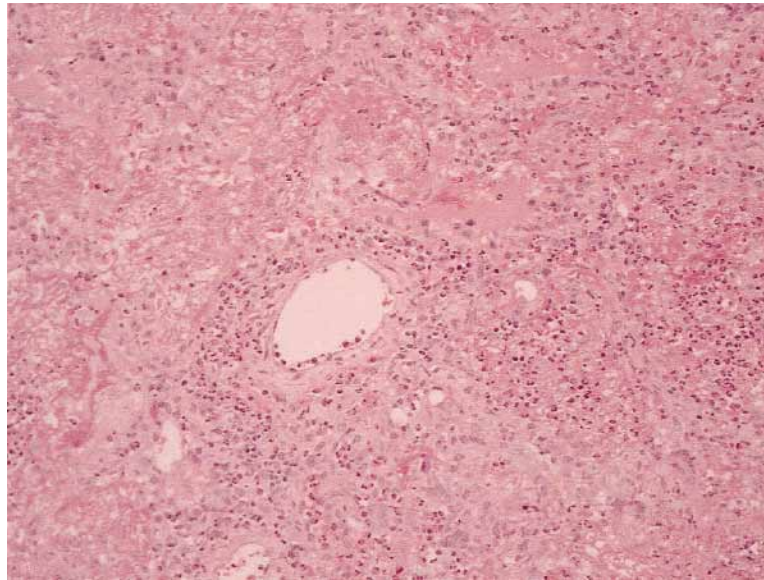


**FIG 1.** Biopsied lung tissue shows eosinophilic perivascular infiltration that is typical of evolving CSS lesions and in this case similar to eosinophilic pneumonia. There is a prominent infiltrate of eosinophils and macrophages, but the vessel in the center of the field is largely unaffected. This finding is fully supportive of the diagnosis of CSS and demonstrates that extravascular granulomas need not be detectable to make the pathologic diagnosis of CSS. (Courtesy of Dr Andrew Churg)

**TABLE I.** Definitions of the Churg-Strauss syndrome

| Study                                          | Criteria                                                                                                                                                                                                                                                                | Purpose and limitations                                                                                                                                                                      |
|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Churg and Strauss <sup>1</sup>                 | (1) Necrotizing vasculitis of small and medium-sized arteries and veins; (2) eosinophil infiltration around involved vessels and in tissues; and (3) extravascular granulomas                                                                                           | Identified CSS as a pathologically distinct form of vasculitis, but was based on autopsy examination of multiple organs of those with end-stage disease                                      |
| Hammersmith <sup>2</sup>                       | (1) History of asthma; (2) peak blood eosinophilia >1500 eosinophils/mm <sup>3</sup> ; and (3) systemic vasculitis involving 2 or more extrapulmonary organs                                                                                                            | Expanded the defining features of CSS beyond pathologic criteria by including clinical criteria— notably, a history of asthma. Would not identify those with CSS without asthma              |
| American College of Rheumatology <sup>15</sup> | Four or more of the following 6 criteria: (1) asthma; (2) >10% blood eosinophilia; (3) mononeuropathy (including multiplex) or polyneuropathy; (4) nonfixed pulmonary infiltrates on chest radiograph; (5) paranasal sinus abnormalities; (6) extravascular eosinophils | Was designed and validated solely to distinguish and classify forms of vasculitis in patients with documented vasculitis; was intended for studies of vasculitis, not for clinical diagnosis |

### Hammersmith criteria

In 1984, another major contribution to defining CSS was made at the Hammersmith Hospital by Lanham et al,<sup>2</sup> who analyzed 16 of their own patients and another 138 reported in the literature. They noted that CSS was in part felt to be rare because of “an undue orthodox reliance” on meeting pathologic criteria and because the clinical components of CSS were not often recognized as being consistent with CSS. Their report and literature analysis was instrumental in helping emphasize a clinical approach to CSS.<sup>2</sup> To identify cases of probable CSS, the Hammersmith analysis of CSS-compatible illness was based on the coexistence of 3 defining criteria: (1) a history of asthma, (2) peak blood eosinophilia >1500 eosinophils/mm<sup>3</sup>, and (3) systemic vasculitis involving 2 or more extrapulmonary organs.<sup>2</sup> With application of these 3 criteria, Lanham et al helped to define CSS and emphasized not only

the fallibility associated with relying solely on “classic” pathologic diagnoses but also the need for clinicians to recognize this distinct vasculitic syndrome.

If the Hammersmith criteria are to be applied to future studies, a contemporary examination of each criterion is warranted. Blood eosinophilia can fluctuate, and patients with CSS have occasionally been given the diagnosis of CSS without blood eosinophilia. Nevertheless, eosinophilia in CSS is usually in excess of that found with extrinsic asthma. Requiring proof of vasculitis at 2 or more extrapulmonary sites is often difficult to achieve in a patient presenting with evolving CSS in whom one wants to render a diagnosis and initiate appropriate corticosteroid therapy as swiftly as possible. Finally, the requirement of a history of asthma might have implications both for clinicians needing to diagnose CSS and for investigators needing to understand the underlying pathophysiology of CSS

and its relationship to asthma. It is now recognized that though asthma is often antecedent to the development of CSS vasculitis, asthma can develop later, even among series that require asthma as a diagnostic criterion.<sup>6</sup> CSS presenting without asthma<sup>3,4,7-11</sup> and asthma developing 3 years after the onset of gastrointestinal manifestations of CSS<sup>12</sup> are well documented.

In clinical practice, the diagnosis of asthma—by documentation of reversible airway obstruction with pulmonary function testing—is not always formally established. Moreover, for the clinician, if preexisting asthma is required for a diagnosis of CSS, some patients presenting with CSS without antecedent or recognized asthma might be denied the diagnosis of CSS and put at risk for developing potentially fatal vasculitic complications.<sup>3</sup>

For investigators interested in delineating the pathophysiology of CSS and its interrelationships with asthma, the universe of patients with typical and limited<sup>13,14</sup> CSS—whether they develop asthma before, concomitantly with, or after their vasculitis (or even never)—needs to be identified and analyzed. If asthma is required for the diagnosis of this ill-understood syndrome, then the unknown portion of patients who might develop asthma late or never will be excluded, potentially skewing the opportunities to evaluate the full natural history and pathophysiology of the syndrome. Thus, a rigid application of the Hammersmith criteria requiring documented asthma for the diagnosis of CSS might be unwarranted both clinically and investigatively.

### **The American College of Rheumatology criteria**

To develop classification (ie, notably not diagnostic) criteria for vasculitides, the American College of Rheumatology (ACR) in 1990 analyzed 20 patients with biopsy-proven CSS vasculitis and compared them with 787 control patients with other forms of documented vasculitis. For those with CSS vasculitis, 6 criteria were identified: (1) asthma, (2) >10% eosinophils on differential blood leukocyte counts, (3) mononeuropathy (including multiplex) or polyneuropathy, (4) nonfixed pulmonary infiltrates on chest radiographs, (5) paranasal sinus abnormalities, and (6) extravascular eosinophils.<sup>15</sup> The presence of 4 or more of these 6 criteria yielded a sensitivity of 85% and a specificity of 99.7%. It must be recalled that this classification of CSS, like that of other vasculitides analyzed by ACR classification criteria, was validated specifically for patients with established vasculitis and was intended to standardize clinical definitions for use in research studies. For other, more common forms of vasculitis, the ACR classification criteria have been shown to function poorly when used as diagnostic criteria in identifying individual patients with specific forms of vasculitis.<sup>16,17</sup> The same would likely be true for CSS; consequently, reliance on the ACR classification criteria might pose difficulties for clinicians in making the appropriate diagnosis of CSS. This might be pertinent both to the patient with CSS and to the recorded identification of CSS for its later analytic detection in

medical records. Nevertheless, the ACR criteria are less constraining in not mandating an established presence of asthma to make the CSS diagnosis.

### **Chapel Hill criteria**

In 1994, an international conference proposed classification criteria for varied forms of vasculitis.<sup>18</sup> CSS was defined as “eosinophil-rich and granulomatous inflammation involving respiratory tract and necrotizing vasculitis affecting small-medium sized vessels and associated with asthma and eosinophilia.”<sup>18</sup> This definition requires biopsy evidence of specific findings, but requisite biopsy specimens often are not available in patients with evolving CSS, and biopsied respiratory tract tissues, especially from transbronchial biopsies, often do not uniformly exhibit diagnostic findings of granulomatous inflammation.<sup>2</sup> As for the ACR classification criteria for vasculitides, the Chapel Hill criteria perform poorly when used as diagnostic criteria for other forms of vasculitis<sup>19</sup> and are the least sensitive of the 4 sets of potential defining criteria for CSS.<sup>4</sup>

The limitations of currently used criteria have implications for potential research studies of CSS, in addition to those mentioned above. CSS can be difficult to identify clinically; pathologically, it can be underdiagnosed even when biopsy specimens are available, because evolving lesions might exhibit only perivascular eosinophil infiltration without nominally “classic” findings and because vasculitic changes might be spotty and not uniformly sampled in biopsies. Even when the diagnosis of CSS is rendered, there are no specific ICD9 codes for CSS or for other distinct forms of vasculitis. Retrospective medical record reviews will therefore encounter difficulties in identifying patients with CSS, even independent of the diagnostic limitations that are inherent in applying any of the 4 sets of potential diagnostic criteria.

### **CSS: THE SPECTRUM OF DISEASE AND ISSUES OF DIFFERENTIAL DIAGNOSIS**

Although limited forms of CSS have been recognized previously,<sup>12,14</sup> the spectrum of the syndrome has been expanded in part by the recognition of forme frustes of CSS. Churg et al<sup>20</sup> reported 4 patients weaned from corticosteroid therapy for asthma in whom CSS developed either as obvious vasculitis (2 patients) or as suggestive vasculitis, eosinophilic lymphadenopathy, and eosinophilia. These cases were believed to represent long-smoldering CSS that was unrecognized while corticosteroids were being used to treat asthma. Other, analogous presentations of CSS have been reported in patients with asthma on tapering oral steroids or inhaled steroids.<sup>21,22</sup> These reports, pertinent to considerations of antiasthmatic medication-associated CSS, might suggest that CSS underlies or is developing in some corticosteroid-treated patients with asthma and that at least incipient CSS might be more prevalent than currently recognized.

Although asthma and paranasal sinusitis might be cardinal features of CSS, asthma and allergic sinusitis fre-

quently coexist in those without CSS. Blood eosinophilia is usually of a greater magnitude in CSS than in asthma. In contrast to asthma, acute-phase reactants, including the erythrocyte sedimentation rate, are frequently, but not uniformly, increased in CSS.<sup>6</sup> Antineutrophil cytoplasmic antibodies are present in approximately one half of patients with CSS<sup>23</sup> and are absent in common asthma. Chest radiographic studies in asthma do not reveal parenchymal abnormalities, whereas infiltrates, nodules, and other changes are common in CSS.<sup>2,24</sup>

In addition to asthma, the differential diagnosis of CSS includes eosinophilic syndromes, including the umbrella diagnosis of the idiopathic HES.<sup>25</sup> Some manifestations of HES and CSS (eg, mononeuritis multiplex) might be common to both, though asthma is uncommon in HES and vasculitis is usually not demonstrable in HES.

## THE INCIDENCE OF CSS

In considering the relationship of CSS to asthma and its treatments, it is reasonable to consider not only whether our diagnostic awareness of CSS might be increasing but also whether there is an increasing incidence of CSS, especially relative to the documented increases in the incidence of asthma.<sup>26</sup> Data on the prevalence or incidence of CSS are limited. In a 10-year study of vasculitis in a defined, ethnically homogeneous population of approximately 500,000 in an eastern coastal region of the United Kingdom, the incidence of CSS was 2.7 cases per million patient-years according to the ACR criteria and 3.4 cases per million patient-years according to the Hammersmith criteria.<sup>27</sup> Rates of CSS increased approximately 2.5-fold over the 10-year period, somewhat more than for other forms of vasculitis.<sup>27</sup> Whether these temporal trends represent increasing physician awareness or true increases in CSS incidence is uncertain.<sup>28</sup> Others have reported annual incidences of CSS in the United Kingdom of 6 to 18 per million<sup>29</sup> and of 1.8 and 64.4 per million in the general population and in patients with asthma, respectively.<sup>30</sup> In the United States, annual incidence rates of approximately 60 per million have been estimated among patients with asthma using both zafirlukast and montelukast.<sup>29</sup> As reported at the workshop, a retrospective study of patient records by AstraZeneca and Ingenix Pharmaceutical Services, using surrogate ICD9 codes for CSS-associated conditions reported on UnitedHealthcare claims, estimated the incidence of CSS among asthma patients to range from 0 to 67 per million, depending on the criteria applied to define CSS. Thus, at the present time there are limited data on the incidence of CSS in both the general and the asthmatic populations. Whether CSS incidence is changing as a result of greater diagnostic recognition or whether it is affected by specific antiasthmatic treatment modalities is unknown.

## ASSOCIATIONS OF CSS WITH SPECIFIC ASTHMA THERAPIES

In 1998, 8 patients with asthma were reported to have developed CSS while receiving zafirlukast<sup>31</sup>; however,

other treatment modalities for asthma have been associated with CSS. When cromolyn was introduced as an asthma treatment, drug-associated eosinophilic pulmonary infiltrates were recognized.<sup>32</sup> At that time, CSS was underappreciated, and whether some of the eosinophilic reactions associated with cromolyn treatment might have been due to CSS remains conjectural. The French Vasculitis Study Group evaluated many patients with CSS from 1963 to 1995. According to their analyses of 80 patients for putative triggering factors for CSS, 14 of the patients had received recent allergen desensitization treatments, 8 had discontinued corticosteroid therapy, and 4 had received vaccinations.<sup>6</sup> The issue of whether these possible triggering factors were causal or were simply associated with severity of asthma and CSS is central to the consideration of whether and how specific asthma therapies contribute to CSS development.

CSS has been associated with several asthma medications. Many reports have suggested that the efficacy of the CysLT1 antagonists zafirlukast,<sup>31,33</sup> montelukast,<sup>29,34</sup> and pranlukast<sup>35</sup> in controlling symptomatic asthma has enabled tapering of corticosteroid therapy for asthma, thereby unmasking incipient CSS. Such a mechanism might also explain the development of CSS in patients receiving inhaled corticosteroids, including fluticasone and budesonide, either alone or with salmeterol.<sup>29,36</sup> Such unmasking of latent CSS in other patients with asthma might also account for the development of CSS, at times months later, in those who had steroids tapered without receiving CysLT1 antagonists.<sup>20-22</sup> In contrast, there have been cases of CSS developing in asthmatic patients who had received the CysLT1 antagonists zafirlukast<sup>37,38</sup> and montelukast<sup>39</sup> without recent tapering of corticosteroids. Other drugs associated with the development of CSS include macrolide antibiotics,<sup>40</sup> estrogens,<sup>41</sup> and cocaine.<sup>42</sup>

At the workshop, representatives from the FDA presented preliminary findings based on analyses of data from its Adverse Events Reporting System (AERS) for cases of CSS, eosinophilic pneumonia, and other systemic eosinophilic conditions associated with 5 asthma drug products. AERS is a computerized database of spontaneously reported adverse events suspected to have occurred in association with drugs and biologics. Reports of adverse events come from manufacturers, health professionals, and consumers and vary in completeness and quality of information. Cases reported to the FDA are generally recognized to be a very small percentage of actual cases and are subject to considerable reporting biases.

The 5 drug products examined were zafirlukast, montelukast, zileuton, fluticasone dipropionate (oral inhalation forms), and salmeterol xinafoate. A total of 180 US cases with adequate quality data were identified and coded into an analytic database. Of 165 patients who met 2 or more of the ACR criteria for CSS, features of CSS had developed in 83 patients in association with zafirlukast (52 also received fluticasone), in 63 with montelukast (41 with concomitant fluticasone), in 12 with fluticasone (2 with concomitant zafirlukast and/or mon-

telukast use), in 5 with the 5-lipoxygenase inhibitor, zileuton, (2 with fluticasone use), and in 2 with salmeterol alone. In all, 126 of the patients had histories of prior systemic corticosteroid use; of the 94 of these with adequate information, 88% had developed CSS during decreasing corticosteroid usage whereas 12% had developed CSS with no prior use or with distant (>1 year) prior use of corticosteroids. Six patients died from their CSS. (A more extensive publication containing these data is in preparation by Anne Trontell, Claudia Karwoski, and members of the FDA Office of Postmarketing Drug Risk Assessment Churg-Strauss Project Team.)

Thus no single compound or class of antiasthmatic agents was associated with CSS. Each of the 3 structurally distinct CysLT1 inhibitors was associated with CSS, but so too was the 5-lipoxygenase inhibitor zileuton (whose lower frequency of CSS illness might reflect its smaller market share) as well as inhaled corticosteroids and salmeterol. Systemic corticosteroids constitute the principal therapy of CSS, so use of these various antiasthmatic medications might, in those who tapered systemic corticosteroids, have allowed incipient CSS to become manifest. In those who were not receiving corticosteroids, the use of these various antiasthmatic medications might have helped treat the asthmatic symptoms but not the developing CSS. Overall, CSS is an uncommon form of vasculitis, probably one third less prevalent than Wegener's granulomatosis,<sup>27</sup> and the antiasthmatic medications associated with CSS are generally safe.<sup>43</sup>

### Cysteinyl leukotrienes in CSS

Although the available data associating specific CysLT1 antagonists, 5-lipoxygenase inhibitors, and inhaled corticosteroids with CSS do not identify a single candidate mechanism contributory to the development of CSS in those with asthma, roles for cysteinyl leukotrienes in the pathophysiology of CSS should not be dismissed. Asthma is recognized to be a heterogeneous and multifactorial disease,<sup>44</sup> and genetic polymorphisms might contribute to the development, manifestations, and therapeutic responses among those with asthma.

The cysteinyl leukotrienes are well recognized as mediators important to asthma.<sup>45</sup> CysLT1 is present in human eosinophils and lung smooth muscle cells but is also found in other cells, including some B cells and monocytes<sup>46</sup>; mRNA for CysLT1 is found in other organs, including the spleen, small intestine, heart, and thymus.<sup>47,48</sup> In the latter sites, the functions of cysteinyl leukotrienes are less certain, but they likely have actions beyond those conventionally recognized as mediators of asthma. As an example potentially pertinent to endothelial involvement in vasculitis, cysteinyl leukotrienes enhance endothelial cell expression of P selectin, an action not inhibited by CysLT1 inhibitors and likely mediated by other cysteinyl leukotriene receptors.<sup>49</sup> In addition to CysLT1, at least one other such receptor exists. CysLT2 has been identified, and the CysLT1 antagonists noted above do not antagonize CysLT2. CysLT2 mRNA is found in various organs, including the

heart, spleen, lymph nodes, and adrenals.<sup>50-52</sup> Thus there is the potential for cysteinyl leukotrienes to exert a broader range of activities in different organs and via different receptors than heretofore known. Because the molecular bases of corticosteroid actions are still not defined, even steroids and leukotriene modifying therapeutics might have roles in altering differential activities mediated by cysteinyl leukotrienes or other eicosanoids.

Not only do CysLT1 antagonists block the actions of cysteinyl leukotrienes at CysLT1; they might also, as evidenced by studies with MK-571, a prototypical CysLT1 antagonist, exert broader actions by inhibiting specific organic anion transporters, including the multidrug resistance-associated protein.<sup>53</sup> The roles of these channels in immune responses are not yet fully known, but they might (for instance) modulate inflammatory reactions,<sup>54</sup> regulate dendritic cell migration to lymph nodes,<sup>55</sup> and be differentially expressed on T<sub>H</sub>1 and T<sub>H</sub>2 lymphocytes.<sup>56</sup> Thus therapeutic CysLT1 antagonists that inhibit the functions of specific organic anion transporters might affect broader immune responses and be pertinent to the development of CSS within some subsets of patients with asthma.

### POTENTIAL PATHOPHYSIOLOGY OF CSS

As is true for several other forms of vasculitis, the pathogenesis of CSS is not at all clear, but it probably derives from autoimmune mechanisms involving endothelial cells and leukocytes.<sup>57</sup> In CSS, in contrast to other forms of vasculitis, eosinophils are the predominant and signature leukocytes, but the roles of eosinophils in driving the pathogenesis of CSS are virtually unknown. Remarkably few studies have addressed the potential pathophysiologic mechanisms of CSS. Recently, an impairment of CD95 ligand-mediated apoptosis of lymphocytes and eosinophils in CSS has been reported, associated with altered expression of a soluble CD95 splice variant and with oligoclonal T-cell expansions.<sup>58</sup> Increases in serum levels of soluble thrombomodulin, indicative of endothelial cell damage; soluble IL-2 receptor, indicative of T cell activation (although possibly also derived from eosinophils); and eosinophil cationic protein, indicative of eosinophil activation, have been reported in CSS.<sup>59</sup> Little pathophysiologic information is available from studies of lesional tissues in CSS. A study of neuronal biopsy specimens has shown rare deposition of eosinophil granule major basic protein and indicated that CD8<sup>+</sup> and CD4<sup>+</sup> T cells outnumber eosinophils in sites of CSS neuropathy.<sup>60</sup> Unanswered and understudied questions include whether CSS and its vasculitic complications are a T cell-driven process, how eosinophils are participatory in the pathophysiology of CSS, and, most importantly, what the underlying pathophysiologic processes are in CSS.

### FUTURE RESEARCH DIRECTIONS

There was a consensus among the workshop participants that CSS is a distinct form of vasculitis—notable for its eosinophilia and frequent association with asthma and

sinusitis—whose underlying pathophysiology and relationship to asthma are very poorly understood. The workshop was organized in response to the increase in reports of CSS among patients with asthma treated with newer therapeutic agents. Potential explanations for this increased reporting include the following: (1) there might be an increase in the true incidence of CSS, independent of therapies; (2) increased reporting might be attributable to increasing physician awareness and diagnosis of CSS; (3) there might be increased reporting, especially to the FDA, of CSS associated with the use of newer leukotriene modifying and other antiasthma medications; (4) patients with incipient CSS might be more likely to receive newer asthma therapeutics because of the severity or refractoriness of their asthma; (5) newer asthma therapeutics, by enabling a reduction in systemic corticosteroid therapy, might have unmasked underlying CSS; and (6) newer agents might be directly eliciting or promoting the development of CSS. Future research is necessary to clarify the relative importance of these alternative hypotheses.

Studies of CSS should address 2 distinct, interrelated, but not identical goals: (1) defining the underlying pathophysiologic processes of CSS and (2) establishing the relationship of asthma and its therapies to CSS. The approaches to addressing these 2 issues might be different. To address the underlying pathophysiology of CSS, all patients with CSS should be studied, including patients who present initially with nonpulmonary vasculitic complications, such as those involving the gastrointestinal, cardiac, or neurologic systems. Definitions of CSS should not necessarily mandate asthma as a defining feature; in this way, those patients in whom asthma is not recognized, not prominent, or not present are available for investigational considerations. Likewise, patients presenting to physicians other than those with a focus on asthma, whether they are primary care providers or subspecialists such as rheumatologists and neurologists should be sought and included. Because blood and lesional eosinophilia is a hallmark of CSS, parallel investigations of patients with idiopathic eosinophilic syndromes, including HES and chronic eosinophilic pneumonia, are warranted. HES shares some features with CSS, including peripheral neuropathies, and chronic eosinophilic pneumonia has at times been premonitory to or complicated by the later development of CSS.<sup>61,62</sup> These comparative studies would aim to delineate whether CSS and other eosinophilic syndromes arise from common or distinct pathobiologic mechanisms and whether better diagnostic discriminators for these individual eosinophil-associated syndromes can be identified. Although an understanding of the epidemiologic character of CSS would be of interest for this overall goal, the primary focus of these studies would be on delineating underlying mechanisms, potentially identifying new diagnostic markers for CSS and differentiating CSS from related eosinophilic diseases.

For investigations establishing the relationship of asthma and its therapies to CSS, definitions of CSS requiring asthma as a defining feature would be acceptable, appropriate, and practically necessary, given the inadequacies

of current diagnostic coding for CSS. These studies might include record-based reviews to evaluate the epidemiology of CSS among those with asthma and the relationships of antiasthmatic therapies to the development of CSS. Attention should be paid to whether leukotriene-modifying drugs or inhaled steroids are associated with CSS and related eosinophilic syndromes when the use of these agents is expanded to treat milder asthma or chronic obstructive pulmonary disease.

The workshop participants recognized that there are many practical impediments to investigating CSS. As noted above, there are limitations to each of the 4 sets of potential diagnostic criteria for CSS. For studies related to the goal of investigating the pathophysiology of CSS, definitions of CSS will likely be based on contemporary combinations of available pathologic findings (not requiring the “classic” triad) and clinical findings and judgment. Some studies of the interrelationships of asthma and CSS might use different criteria, such as requiring asthma as an identifier. For both goals, there might be 2 levels of CSS definition: definite and probable. Another impediment is the difficulty of identifying patients with CSS, both retrospectively (in chart reviews), because of uncertainties in diagnosis and absence of specific identifying ICD9 codes, and prospectively, because of potential ambiguities in making the diagnosis of CSS and because of the absence of a central reporting system. Given that CSS is uncommon, it might be difficult for single centers to encounter sufficient numbers of patients for needed investigations. There are no animal models of CSS, and human studies of CSS pathophysiology have been very limited to date.

Despite the difficulties inherent in investigations of CSS, the workshop participants believed that investigations aimed at the goals of defining the pathophysiology of CSS and ascertaining the interrelationships among CSS, asthma, and asthmatic therapies are fully warranted. CSS appears to be uncommon, but it is probably underdiagnosed. Moreover, CSS is a potentially fatal disease. Because patients with asthma might have incipient CSS, it becomes important to identify which patients with an asthma phenotype are at risk for serious CSS and what roles antiasthma therapies might play in CSS development. If newer antiasthma therapeutics, by enabling the tapering of systemic corticosteroids, are unmasking CSS, what underlying mechanisms of CSS are being unmasked and how might incipient CSS be identified?

## RECOMMENDATIONS FOR RESEARCH STUDIES

Research to define the underlying pathophysiologic processes of CSS and establishing the relationship of asthma and its therapies to CSS should be encouraged. Investigations of the potential pathophysiology might include studies of the following: (1) lymphocyte populations active in CSS and the question of whether they overexpress particular cytokines (eg, IL-5); (2) the expression of chemokines, cytokines, or other mediators potentially active in recruiting and activating eosinophils

or other leukocytes at sites of CSS inflammation; (3) local endothelial cell activation and damage; and (4) altered apoptosis of lymphocytes and eosinophils. With evolving knowledge of cysteinyl leukotriene receptor diversity and cysteinyl leukotriene activities, studies evaluating roles for cysteinyl leukotrienes in CSS pathophysiology are appropriate. As a corollary to studies of underlying mechanisms of CSS, novel markers of CSS disease activity, perhaps related to underlying endothelial cell damage, should be sought and evaluated as potentially clinically pertinent tools for identifying patients at risk for incipient CSS. These studies would also aim to evaluate whether the basic pathophysiology of CSS is distinct from that of asthma or is rather an evolution of that of asthma and whether CSS differs from other hyper-eosinophilic diseases. Studies could be performed both on blood cells and lesional biopsies.

To facilitate these studies, 4 organizational arrangements should be considered, in part to overcome the infrequency with which single investigative centers might encounter patients with CSS:

1. Consider establishing a repository of CSS tissues and blood samples, with each patient's samples accompanied by information about the clinical status of the patient that is as standardized as possible. In contrast to a central CSS registry that would be time- and resource-intensive to maintain, a repository of samples from patients with CSS and related eosinophilic diseases would provide an efficient means of making samples available for studies.
2. Encourage investigators to work together, perhaps through a consortium arrangement, to begin to prospectively evaluate potential candidate pathophysiologic mechanisms in CSS and related eosinophilic syndromes. With common protocols and investigative plans, blood or biopsy samples could be studied as they become available and the results from a number of centers could be pooled.
3. Consider establishing a mechanism for reporting all cases of CSS whether they are associated with newer therapeutics or not. Both primary care providers and physicians likely to encounter CSS patients would be encouraged, in part through their professional societies (eg, the ACR; the American Thoracic Society; the American Academy of Allergy, Asthma and Immunology; the American College of Chest Physicians; and the American Society of Internal Medicine), to report new CSS cases. Although it is recognized that a patient registry that tracks patient data over time would be difficult and expensive to maintain, a Web-based reporting mechanism might be used to facilitate efficient collection of data on patients suspected to have CSS.
4. Encourage partnerships with pharmaceutical concerns to support studies based on large patient databases (eg, from health maintenance organizations) that could further evaluate the development of CSS and related eosinophilic syndromes among patients with asthma and relationships to asthma therapies.

## APPENDIX: Workshop participants

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