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Leukotriene Receptor Antagonists and Churg-Strauss Syndrome

Cause, Trigger or Merely an Association?

Karina A. Keogh

Division of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Abstract

Concern has been raised in the medical literature that the use of leukotriene receptor antagonists for the treatment of asthma may be associated with an increased incidence of Churg-Strauss syndrome, a rare small-vessel vasculitic syndrome. This review provides a critical appraisal of the literature to address this question. The incidence of Churg-Strauss syndrome in the general population is one to four cases per million. In patients with asthma it is 20–60 cases per million patient-years, which is similar to that seen in a population receiving leukotriene receptor antagonists. There is no evidence for a direct causative role of leukotriene receptor antagonists in the development of Churg-Strauss syndrome. There may be multiple other non-causative reasons for an association, including the fact that these agents may be initiated in patients who are already in the process of developing Churg-Strauss syndrome, or that the use of leukotriene receptor antagonists leads to a reduction in corticosteroid use, which in turn allows the Churg-Strauss syndrome to be 'unmasked'.

Cysteinyl leukotrienes are inflammatory mediators formed from arachidonic acid by the action of 5-lipoxygenase. In asthma, leukotrienes produced in eosinophils, mast cells and alveolar macrophages cause marked bronchoconstriction, airway oedema and mucous hypersecretion.[1] Leukotriene receptor antagonists (montelukast, pranlukast, zafirlukast) were developed to target the cysteinyl leukotriene receptor 1 ($CysLT_1$),[2] and have been used widely in patients with asthma since their introduction in the mid-1990s. They are generally very well tolerated; however, a possible association has been raised between their use and the development of a rare vasculitic disorder, Churg-Strauss syndrome.[3-8]

The association of Churg-Strauss syndrome with a leukotriene receptor antagonist zafirlukast was first reported in a case series of eight patients with asthma by Weschsler and colleagues.[5] Since then, Churg-Strauss syndrome has also been linked with montelukast and pranlukast, as well as zileuton, a 5-lipoxygenase inhibitor that, although not a leukotriene receptor antagonist, acts on the same pathway.[7-10] Therefore, it has been suggested that in some patients with asthma, leukotriene receptor antagonists may precipitate the development of hypereosinophilia and vasculitis. Following this, warnings have been attached to the product labels for montelukast, zafirlukast and pranlukast. In this review, the data surrounding leukotriene receptor antagonist use in asthmatics and the possible association with Churg-Strauss syndrome is discussed.

1. What is Churg-Strauss Syndrome?

Churg-Strauss syndrome is a rare disorder of unknown aetiology, consisting of asthma, peripheral and tissue eosinophilia, and systemic small vessel vasculitis.[11,12] It classically progresses through three stages. The first stage is the development of asthma, most typically adult-onset asthma. Asthma precedes other manifestations in the majority of patients and typically by a number of years.[13] This disease phase may be associated with peripheral blood eosinophilia (typically >10% of the total white blood cell count), often accompanied by allergic rhinitis and sinusitis. The second phase is one of tissue eosinophilia: eosinophilic pneumonia (often characterised by 'transient pulmonary infiltrates'); eosinophilic gastroenteritis; eosinophilic myocarditis or eosinophilic involvement of the pleura or pericardium (table I). Apart from the associated asthma, it can be difficult to distinguish the disease from other systemic hypereosinophilic syndromes. Ultimately, the diagnosis of classic Churg-Strauss syndrome requires the development of systemic vasculitis, the third stage. These three stages do not always develop in this specific order, they may occur simultaneously or years apart, and do not have to occur in this stepwise fashion. Yet, patients with classic Churg-Strauss syndrome will ultimately have disease features fulfilling all three stages. The features that separate Churg-Strauss syndrome from other forms of small-vessel vasculitis are the presence of asthma and systemic and tissue eosinophilia, all relatively uncommon in other vasculitic states.[14] The mean age at diagnosis is 40–55 years.

Table I. Clinical manifestations of Churg-Strauss syndrome[11,13,15-18]

Characteristic	Prevalence of manifestation (%)
Asthma	95–100
Peripheral eosinophilia (>10%)	90–100
Organ involvement	
peripheral nerve	65–80
paranasal sinus	50–75
skin	50–70
lung	50–70
gastrointestinal	30–50
joints	30–40
kidney	20–40
endomyocardial	10–20
pericardial	10–20
central nervous system	5–20

Major sites of involvement include the entire respiratory tract (sinuses, nose, lungs) and skin, with a particular predilection for the peripheral nerves, classically presenting as mononeuritis multiplex. Other organs affected include the gastrointestinal tract, heart and kidneys (table I). The syndrome is often associated, particularly in the vasculitic phase, with the presence of perinuclear antineutrophilic cytoplasmic antibodies (P-ANCA) in 50–80%, which target primarily myeloperoxidase.[13,15,19,20] P-ANCA also appears to correlate with vasculitic disease activity,[13,20,21] as it does in Wegnener's granulomatosis and microscopic polyangiitis,[22] which may have implications for the treatment and need for cytotoxic agents.

When first described in 1951, the diagnosis of Churg-Strauss syndrome was based on three pathological findings in an individual with asthma: necrotising small vessel vasculitis, perivascular eosinophilic inflammation and extravascular granulomas. Now we know that it is very uncommon to find all three findings in a single biopsy specimen, and biopsy proof is not required to make the diagnosis. Recently, the spectrum of Churg-Strauss syndrome has also been expanded. Patients with many but not all of the features (typically lacking evidence of vasculitis) have been described as having the so called forme fruste Churg-Strauss syndrome. It is likely that in our current era of more aggressive treatment of asthma and eosinophilic infiltrative disease, the natural disease course may be modified.[12,23]

As in all very rare diseases, it is hard to know the precise incidence of Churg-Strauss syndrome; however, an incidence of one to four cases per million patient years has been reported, with an apparent increase in recent years.[10,24,25] Paralleling this potential rise in the incidence of Churg-Strauss syndrome has been the emergence of novel asthma therapies, specifically antagonists of the leukotriene

receptor, with three separate agents available in 12 countries by 1998.[1] Since many patients diagnosed with Churg-Strauss syndrome have a history of recent leukotriene receptor antagonist use, there has been concern that use of these agents may either trigger the onset of the full manifestations of Churg-Strauss syndrome or, in fact, play a direct causative role, perhaps in a subset of the asthmatic population with an underlying predisposition to developing the syndrome. Indeed, part of the difficulty with regards to establishing a causative link between leukotriene receptor antagonists and Churg-Strauss syndrome is the fact that there may be confounding by indication. Epidemiological studies evaluating the association are limited because, potentially, those at a greater risk for the development of Churg-Strauss syndrome (i.e. those with more severe asthma) are more frequently prescribed leukotriene receptor antagonists. In addition, very little is known about the pathophysiology that underlies Churg-Strauss syndrome.

To try to answer the question 'is there a causal relationship between leukotriene inhibitors and Churg-Strauss syndrome?', a literature review was performed using the PubMed database. The search included all English language articles from the first published trials on leukotriene receptor antagonists in 1990 to December 2006. Specific search terms included 'Churg Strauss syndrome', 'vasculitis', 'leukotriene receptor antagonists', 'lipoxygenase inhibitors', 'montelukast', 'pranlukast', 'zafirlukast', 'zileuton', and 'hypereosinophilia'. In addition, the reference lists of articles identified in the initial search were evaluated.

2. Is the Incidence of Churg-Strauss Syndrome Changing?

The first question to address is whether or not the incidence of Churg-Strauss syndrome is truly increasing. There is not one agreed-upon set of diagnostic criteria for Churg-Strauss syndrome. Of the three major diagnostic classification schemes, the American College of Rheumatology (ACR) criteria (table II) has been found to be the most inclusive because of less-strict requirements (eosinophilia and vasculitis in only one extrapulmonary organ).[13]

Table II. The American College of Rheumatology criteria for the classification of Churg-Strauss syndrome.[31] At least four of the following six criteria must be fulfilled, in the setting of vasculitis

Asthma
Peak peripheral eosinophilia >10% (of total white blood cell count)
Peripheral neuropathy attributable to a systemic vasculitis
Transient pulmonary infiltrates on chest roentgenogram
Paranasal sinus abnormality
Biopsy specimen of a blood vessel with extravascular eosinophils

Applying the ACR criteria, Watts et al.[24] estimated the incidence of Churg-Strauss syndrome to be 2.7 cases per million in the general population in eastern England. This estimate is in keeping with other values in western European populations of one to four cases per million.[25-28] In at least one population there has been an apparent 2- to 3-fold increase in the incidence of Churg-Strauss syndrome over a 10-year period of study (1988–97).[24] However, given the low overall incidence of Churg-Strauss syndrome, any small numerical difference in incident cases has a large impact on incidence rates. One further possible explanation for apparent increasing incidences in Churg-Strauss syndrome is greater diagnostic awareness of the condition. The fact that the diagnosis is now less reliant on pathological findings may also be leading to a greater number of diagnoses. Not surprisingly, estimates of Churg-Strauss syndrome incidence in an asthmatic population are 10–20 times higher than in the general population, between 20 and 60 cases per million patient-years,[29,30] which is similar to the incidence of 60 per million patient-years in patients using leukotriene receptor antagonists.[7] Therefore, it is unclear that there has been an increase in the true incidence of Churg-Strauss syndrome and it is equally unclear whether or not it is associated with the introduction of these agents.

A recent paper by DuMouchel et al.[32] suggested a relationship between leukotriene receptor antagonist use and Churg-Strauss syndrome, based on a review of postmarketing surveillance data utilising the public release version of the Adverse Event Reporting System (AERS) database. AERS is a US FDA database that collects information worldwide

on serious postmarketing adverse-event reports. During the study period 1997 to 31 March 2002, the authors found a strong association between leukotriene receptor antagonist use and Churg-Strauss syndrome, with 337 cases of Churg-Strauss syndrome in patients on leukotriene receptor antagonists reported, whereas the other agents that were studied (inhaled corticosteroids, long- and short-acting β_2-adrenoceptor agonists), after correcting for leukotriene receptor antagonist use, appeared to have little or no association with Churg-Strauss syndrome. However, the AERS data are based on voluntary reporting, with only a minority of cases thought to have been captured. There may also have been an over-reporting bias. Concern regarding leukotriene receptor antagonists and Churg-Strauss syndrome was first raised in 1998, which was the second year of analysis in the study; therefore, in subsequent years, physicians may have been more likely to report Churg-Strauss syndrome in patients on these agents. Furthermore, an association does not necessarily imply a causal relationship. It may be that sicker, more corticosteroid-dependent individuals are more likely to be tried on leukotriene receptor antagonists[33,34] and that vasculitis then develops after leukotriene receptor antagonists allow for a reduction in oral corticosteroids or evolves following the natural disease progression of Churg-Strauss syndrome.

3. Potential for a Pathogenic Role of Leukotriene Receptor Antagonists in Churg-Strauss Syndrome

There are several theoretical mechanisms by which leukotriene receptor antagonists could potentially cause Churg-Strauss syndrome. Firstly, there may be a pharmacological effect. Leukotriene receptor antagonists target $CysLT_1$ in the lung, blocking the effects of the cysteinyl-leukotrienes C_4, D_4 and E_4 (figure 1). However, $CysLT_1$ is also found in extra-pulmonary sites, including the vasculature[35] where, unlike in the lung, the results of antagonism are less clear. There are also other leukotriene receptors, not blocked by these agents, most prominently $CysLT_2$, found in the vascular endothelium, activation of which has been linked to pro-inflammatory and pro-thrombotic signalling.[36,37] Thus, $CysLT_1$ inhibition by leukotriene receptor antagonists may increase circulating levels of leukotrienes, which in turn could promote the development of Churg-Strauss syndrome through pro-inflammatory effects on non-inhibited receptors. Leukotriene B_4, a dihydroxy leukotriene, which mediates chemotaxis, acts on different receptors that are not antagonised by leukotriene receptor antagonists. However, the formation of leukotriene B_4 would be prevented by the 5-lipoxygenase inhibitor zileuton, which has also been associated with the development of Churg-Strauss syndrome, suggesting against a leukotriene B_4-mediated association of these agents and Churg-Strauss syndrome.

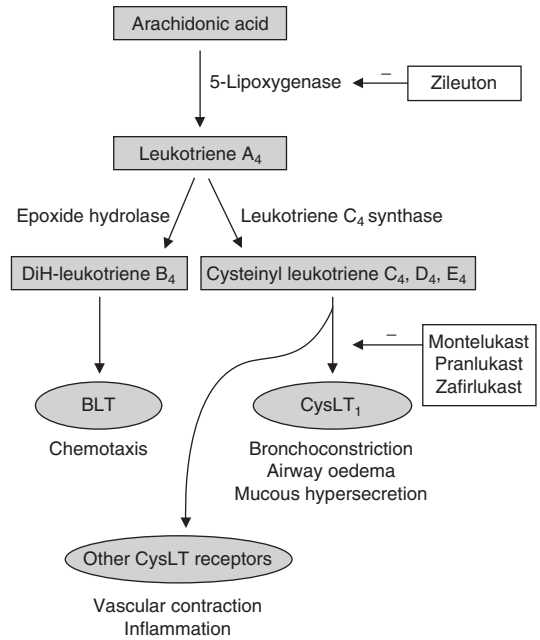

Fig. 1. Modulators of the leukotriene system. Leukotriene receptor antagonists (montelukast, pranlukast and zafirlukast) target the cysteinyl leukotriene receptor 1 ($CysLT_1$) in the lung, blocking the effects of the cysteinyl leukotrienes (CysLT) C_4, D_4 and E_4, thereby producing their therapeutic effects. Other CysLT receptors, not blocked by these agents, most prominently $CysLT_2$, which is found in the vascular endothelium, are linked to pro-inflammatory and pro-thrombotic signalling. Leukotriene B_4, a dihydroxy leukotriene that mediates chemotaxis, acts on different receptors, which are not antagonised by leukotriene receptor antagonists; however, the formation of leukotriene B_4 is prevented by the 5-lipoxygenase, zileuton. **BLT** = B leukotriene receptor; **DiH** = dihydroxy.

Although the mechanism of action of leukotriene receptor antagonists are similar, their chemical structures are quite different, including the sites responsible for their pharmacological action, thus making the occurrence of a common hypersensitivity or immunologically mediated reaction quite unlikely.[38,39] Furthermore, the development of Churg-Strauss syndrome has also been associated with the introduction of multiple other agents with different sites of action including fluticasone propionate, erythromycin and sodium cromoglicate.[10] The similarity in disease manifestations reported in the recent case series of Churg-Strauss syndrome, when compared with older series, would also argue against the emergence of a separate drug-induced form of Churg-Strauss syndrome.[13,40]

4. Unmasking Effect of Corticosteroid Reduction

Leukotriene receptor antagonists are an effective treatment for certain forms of asthma[41] and, as such, often reduce airway inflammation to allow for the tapering of oral or inhaled corticosteroids, and may "unmask pre-existing Churg-Strauss syndrome through relative corticosteroid dose reduction".[42] A similar mechanism has been postulated for other agents linked with Churg-Strauss syndrome such as sodium cromoglicate and inhaled glucocorticoids and macrolide antibacterials, which also allow for a reduction in glucocorticoid use.[43,44] It appears that the cessation or reduction in glucocorticoid treatment of asthma is a significant risk factor for the development of Churg-Strauss syndrome.

5. Natural Progression of Disease

Concern about the increased incidence of Churg-Strauss syndrome and the knowledge that Churg-Strauss syndrome can develop in patients with asthma led to a workshop held by the US National Heart, Lung, and Blood Institute, the National Institute of Allergy and Infectious diseases, the Office of Rare Diseases, the National Institutes of Health and the FDA in 2001. The particular aim of this workshop was to assess the relationship between different asthma therapies and the development of Churg-Strauss syndrome. In association with this workshop, the FDA reported their investigation of 165 patients with probable Churg-Strauss syndrome reported in association with anti-asthmatic treatments.[10] A total of 146 of these 165 patients developed Churg-Strauss syndrome in association with the use of one of the leukotriene receptor antagonists.[10] The majority (88%) of these patients developed systemic features of Churg-Strauss syndrome while the dose of their systemic corticosteroids was being tapered.[10] The taskforce concluded that on the balance of evidence, the introduction of these agents allows the tapering of systemic glucocorticoids, thus unmasking rather than directly causing Churg-Strauss syndrome.[10]

In our review of the Churg-Strauss syndrome experience at the Mayo Clinic, 23 patients received leukotriene receptor antagonists, of whom 16 (70%) began treatment before diagnosis, although in retrospect three patients were already developing vasculitis when treatment with a leukotriene receptor antagonist was begun. Six patients (26%) began leukotriene receptor antagonists during remission.[13] Only two of those treated after diagnosis relapsed. Moreover, the use of leukotriene receptor antagonists did not affect the time between the onset of asthma and the onset of vasculitic manifestations, which would suggest the that development of Churg-Strauss syndrome was following its natural time-line.[13]

We also found that leukotriene receptor antagonist use was not correlated with the frequency or distribution of eosinophilic or vasculitic organ manifestations, except for a more frequent prevalence of paranasal sinus involvement in those patients with a history of leukotriene receptor antagonist use, which is not generally a vasculitic manifestation.[13]

Most recently, Harrold and colleagues[33] report an evaluation of asthma drug use and the association of Churg-Strauss syndrome from pooled data from two nested case-control studies, with 45 cases of possible or definite Churg-Strauss syndrome and 4700 control patients with asthma. While they found a strong crude association between leukotriene receptor antagonists and Churg-Strauss syndrome,

there was no significant association found between Churg-Strauss syndrome and leukotriene receptor antagonists when multivariate analysis adjusted for the use of other anti-asthmatic agents (particularly oral and inhaled corticosteroid agents).[33] Leukotriene receptor antagonists tend to be prescribed for patients with more severe asthma;[34] this more severe manifestation may merely be a precursor to the development of Churg-Strauss syndrome rather than an effect of the treating agents.

6. Conclusion

As leukotriene receptor antagonists continue to increasingly be used in the management of patients with severe asthma, cases of Churg-Strauss syndrome will continue to be diagnosed in a very small minority of asthmatic patients treated with these agents. Although data have suggested that leukotriene receptor antagonists may play a causative role in the development of Churg-Strauss syndrome, ultimately the literature to date does not appear to support this hypothesis. Until the aetiology and pathophysiological pathways behind the development of Churg-Strauss syndrome are fully understood, a causal aetiology cannot be definitively excluded. While this is the case, I personally favour discontinuing leukotriene receptor antagonists in patients who develop Churg-Strauss syndrome and avoiding them in patients with known Churg-Strauss syndrome.

However, the current level of evidence appears to support the conclusion that leukotriene receptor antagonists, by reducing the need for oral corticosteroids, allow the eosinophilic and particularly the vasculitic manifestations of Churg-Strauss syndrome to be 'unmasked'. Therefore, leukotriene antagonists continue to be recommended as generally safe and very well tolerated agents used in the treatment of asthma. Patients on these agents, along with all patients with moderate to severe asthma who are being tapered off corticosteroids, should be carefully monitored for signs and symptoms suggestive of an underlying process such as Churg-Strauss syndrome.

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Correspondence: Dr *Karina A. Keogh*, Division of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, MN 55905, USA.
E-mail: keogh.karina@mayo.edu