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Leukotriene Modifiers and Churg-Strauss Syndrome

Adverse Effect or Response to Corticosteroid Withdrawal?

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Abstract

Zafirlukast, montelukast and pranlukast are all cysteinyl leukotriene receptor antagonists that have recently been approved for the treatment of asthma. Within 6 months of zafirlukast being made available on the market, 8 patients who received the agent for moderate to severe asthma developed eosinophilia, pulmonary infiltrates, cardiomyopathy and other signs of vasculitis; the syndrome that these patients developed was characteristic of the Churg-Strauss syndrome. All of the patients had discontinued systemic corticosteroid use within 3 months of presentation and all developed the syndrome within 4 months of zafirlukast initiation. The syndrome dramatically improved in each patient upon reinitiation of corticosteroid therapy.

Since the initial report, there have been multiple similar cases reported to the relevant pharmaceutical companies and to federal drug regulatory agencies in association with zafirlukast as well as with pranlukast, montelukast, and with use of high doses of inhaled corticosteroids, thus leading to an increased incidence rate of the Churg-Strauss syndrome. Many potential mechanisms for the association between these drugs and the Churg-Strauss syndrome have been postulated including: increased syndrome reporting due to bias; potential for allergic drug reaction; and leukotriene imbalance resulting from leukotriene receptor blockade. However, careful analysis of all reported cases suggests that the Churg-Strauss syndrome develops primarily in those patients taking these asthma medications who had an underlying eosinophilic disorder that was being masked by corticosteroid treatment and unmasked by novel asthma medication-mediated corticosteroid withdrawal, similar to the forme fruste of the Churg-Strauss syndrome.

It remains unclear what the exact mechanism for this syndrome is and whether this represents an absolute increase in cases of vasculitis, but it appears that none of the asthma medications implicated in leading to the development of Churg-Strauss syndrome was directly causative of the syndrome. These agents remain well tolerated and effective medications for the treatment of asthma, although physicians must be wary for the signs and symptoms of the Churg-Strauss syndrome, particularly in patients with moderate to severe asthma in whom corticosteroids are tapered.

Leukotriene modifiers are a new class of medications that have recently been approved for the treatment of asthma. They include cysteinyl leukotriene receptor antagonists such as zafirlukast, montelukast and pranlukast, as well as the 5-lipoxygenase (5-LO) inhibitor, zileuton. Although the clinical trials leading to the approval of these drugs concluded that these drugs were effective and well tolerated, several adverse events were noted when these drugs were approved for use in larger population samples. For instance, several cases of liver function abnormalities were reported with zileuton,[1] and several cases of Churg-Strauss syndrome were reported in association with zafirlukast.[2]

In 1996, zafirlukast was the first cysteinyl leukotriene receptor antagonist to be approved by the US Food and Drug Administration (FDA) and 6243 patients had received the drug in clinical trials accounting for 2479 patient-years of exposure prior to the drug's approval. In all of these participants, there were minimal adverse events and adverse effect rates were similar to those of placebo. However, within 6 months of zafirlukast becoming available, and with more than 40 000 patient-years of exposure, a report on 8 patients receiving zafirlukast for asthma who developed a syndrome consisting of pulmonary infiltrates, cardiomyopathy and eosinophilia consistent with the Churg-Strauss syndrome was published.[2]

Since that time, several other case reports of Churg-Strauss syndrome have been reported in the literature, to the relevant pharmaceutical companies and to the FDA, not only in association with zafirlukast, but also, in association with montelukast, pranlukast and with other novel asthma medications such as salmeterol, sodium cromoglycate (cromolyn) and several inhaled corticosteroids. As all these new cases arise, it is important to question the pathogenesis of this syndrome. Is a direct adverse effect of these otherwise effective asthma medications? Is it a result of corticosteroid withdrawal in these patients? Or is some other mechanism responsible for the syndrome?

In this article, we present 3 case reports, review what has been reported in the literature regarding leukotriene modifiers and Churg-Strauss syndrome and finally, postulate a mechanism to explain the association between these drugs and Churg-Strauss syndrome.

Table I. Sensitivity and specificity of 1990 American College of Rheumatology criteria for classification of Churg-Strauss syndrome[2]

Criterion	Sensitivity (%)	Specificity (%)
Asthma	100	96
Eosinophilia >10%	95	97
Neuropathy (mono or poly)	75	80
Pulmonary infiltrates	40	92
Paranasal sinus abnormality	86	79
Extravascular eosinophils	81	84

1. Churg-Strauss Syndrome

Churg-Strauss syndrome, also known as allergic angiitis and granulomatosis, is a vasculitis of unknown aetiology that was first described by Churg and Strauss in 1951.[3] The 1990 American College of Rheumatology has since promulgated specific diagnostic criteria for the syndrome. For a diagnosis of Churg-Strauss syndrome to be made patients must present with at least 4 of the following 6 features: (i) moderate to severe asthma; (ii) peripheral blood eosinophilia (>10%); (iii) mononeuropathy or polyneuropathy; (iv) pulmonary infiltrates; (v) paranasal sinus abnormality; and, (vi) extravascular eosinophils[4] (table I).

2. Case Reports

The following case reports have been highlighted as they represent samples of the different circumstances in which Churg-Strauss syndrome has been seen to occur. The details of case 1 have been previously published;[2] the other reports are unpublished.

2.1 Case 1

A 45 year-old woman with a history of recurrent asthma and sinusitis that required therapy with systemic corticosteroids for control began therapy with zafirlukast.[2] This resulted in a dramatic im-

provement in her asthma symptoms. For the first time in several years, she was able to taper her prednisone dose and within 2 months, was able to discontinue systemic corticosteroid therapy altogether.

Two weeks later, the woman developed a vasculitic rash on her arm and her flank, accompanied by fever, nausea, anorexia and loose stools. She was admitted to hospital and was noted to have 36% eosinophilia, fever with temperature 38.7°C, and diffuse pulmonary infiltrates (see fig. 1). After developing unilateral foot drop suggestive of mononeuritis multiplex, and worsening shortness of breath (an echocardiogram revealed a depressed ejection fraction of 0.35) she underwent skin and lung biopsies, both of which were consistent with necrotising eosinophilic vasculitis with granuloma formation consistent with the Churg-Strauss syndrome (fig. 2).

The woman was treated with prednisone and cyclophosphamide and experienced a return to baseline lung function, resolution of eosinophilia, rash, neuropathy and cardiomyopathy. She continued to do well over the next 12 months but with each attempt at corticosteroid withdrawal, her asthma worsened and she once developed recurrence of rash. Therapy with systemic corticosteroid therapy was maintained and she was stable 24 months later.

2.2 Case 2

A 51-year-old woman with a 25-year history of moderate to severe aspirin-sensitive asthma received multiple courses of corticosteroids over the last few years, at least 3 to 4 times per year and the courses often lasted for several months at a time. She also had chronic sinusitis, had received several courses of antibacterials and had undergone prior sinus operations. She had a history of low grade eosinophilia of 9% in the past while receiving corticosteroids. Since her last course of systemic corticosteroids 3 months earlier, she had been maintained on high doses of fluticasone propionate and montelukast with good control of her asthma symptoms.

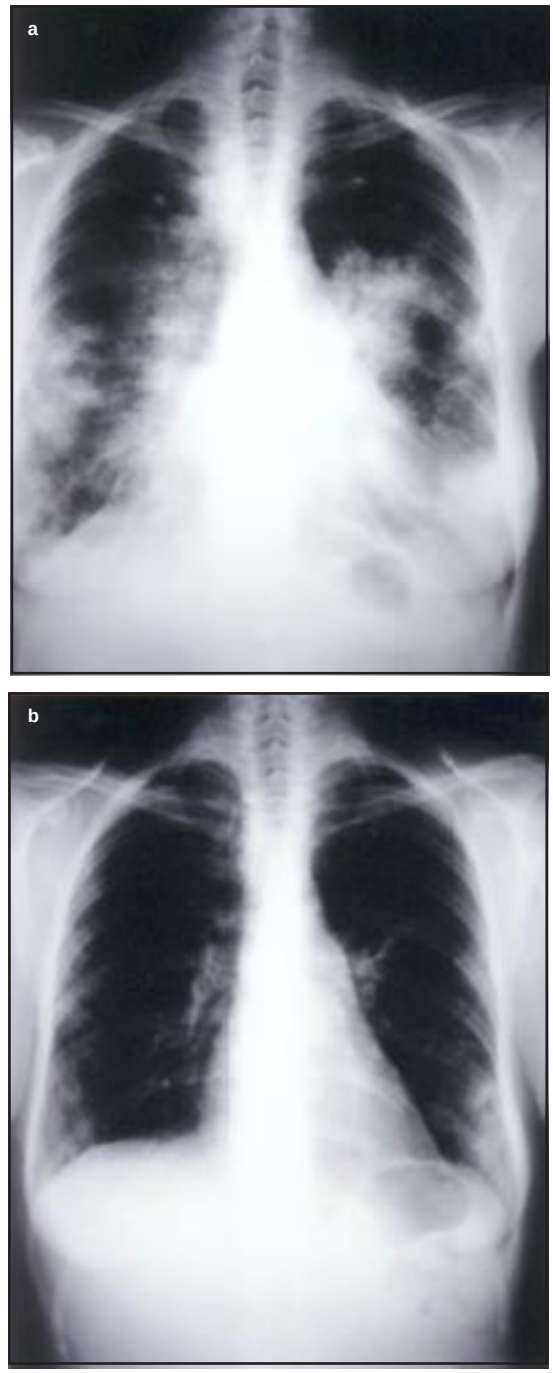

Fig. 1. Posteroanterior chest x-ray showing extensive confluent airspace disease in patient 1 upon admission to hospital (a), with interval resolution of pulmonary infiltrates following 1 month of treatment with corticosteroids and cyclophosphamide (b).

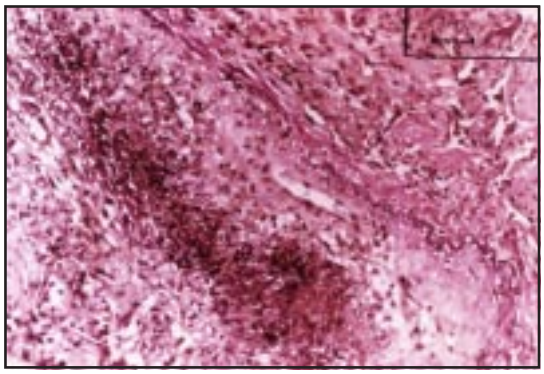

Fig. 2. Pathology specimen of lung biopsy from patient 1 with elastin stain demonstrating a necrotising vasculitis with destruction of elastic lamina (bar = 40μm).

The woman presented to her physician with a 2-week history of dyspnoea, myalgias, malaise and worsening sinus symptoms that were refractory to a recent 2 week course of antibacterials. Examination revealed bibasilar coarse râles, but no skin lesions nor focal neuropathy. A complete blood count revealed a white blood cell count of $14\,500 \times 10^6$/L with 45% eosinophilia and chest x-ray revealed new bilateral lower lobe infiltrates. Her echocardiogram was within normal limits. Systemic corticosteroids were resumed with rapid resolution of her eosinophilia, pulmonary infiltrates and dyspnoea. Montelukast was continued throughout the episode and thereafter.

2.3 Case 3

A 53 year-old woman with a long history of asthma had received asthma maintenance therapy with ß-agonists, theophylline and methylprednisolone until 2 years prior to presentation when systemic corticosteroid therapy was stopped and high dose fluticasone propionate (1100 μg/day) was begun. After the patient required two courses of systemic corticosteroid therapy to control of worsening asthma, salmeterol was initiated and the dosage of fluticasone propionate was increased to 2200 μg/day.

A few months later, the woman was admitted to hospital because of fever, malaise, dyspnoea, haemoptysis and arthralgias. An examination was notable for ecchymoses and palpable purpura on her arms and legs. Chest x-ray revealed cardiomegaly, basilar infiltrates and pleural effusion. Her white blood cell count was $22\,500 \times 10^6$/L with 59% eosinophilia. Open lung biopsy was consistent with Churg-Strauss syndrome and the patient received treatment with systemic corticosteroids and cyclophosphamide and her condition improved.

3. Discussion

These cases of Churg-Strauss syndrome which occurred in association with zafirlukast (case 1), montelukast (case 2), and high doses of fluticasone propionate and salmeterol (case 3) are representative of the many cases of Churg-Strauss syndrome that have been reported over the last few years as new asthma therapies have been introduced. In each of the above cases there is a long history of asthma and sinusitis, a long history of multiple courses of systemic corticosteroids, and the initiation of new asthma therapy in conjunction with systemic corticosteroid withdrawal prior to the manifestation of Churg-Strauss syndrome symptoms. Although the individuals in the 3 case reports described in section 2 were all middle-aged women, the syndrome has been reported in a spectrum of patients, both male and female, of all ages. Before postulating a mechanism for this syndrome in these patients, let us review the cases that have previously been reported in the literature to date.

3.1 Zafirlukast and Churg-Strauss Syndrome

The first case series published[2] involved 7 women and 1 man who received zafirlukast therapy for asthma. All patients (whose ages ranged from 21 to 59 years) had corticosteroid-dependent asthma, and all developed a syndrome that consisted of pulmonary infiltrates, myocarditis or cardiomyopathy, and significant eosinophilia (that ranged from 19 to 71% of total white blood cell count). In addition, 2 of the 8 patients developed neuropathy, 6 had sinusitis, 3 developed rash, 6 de-

veloped fevers greater than 38.5°C, 7 developed muscle pains and 6 had erythrocyte sedimentation rates greater than 40 mm/h on presentation. Of the 8 patients, 6 had biopsies that documented eosinophilic tissue invasion.

Interestingly, these 8 cases occurred within 6 months of zafirlukast approval, after only 50 000 patient-years of exposure to the agent, representing an annualised incidence of approximately 160 cases per million patients with asthma, which is several times the previously reported incidence of Churg-Strauss syndrome[5] (estimated to be 2 to 3 cases per million patients per year). Of note, however, is the fact that all the patients had discontinued high dose corticosteroid use within 3 months of presentation, and all developed the syndrome within 4 months of zafirlukast initiation. While 2 patients were also treated with cyclophosphamide, all of these patients improved dramatically with reinstitution of corticosteroid therapy. In each of these patients, eosinophil counts returned to normal, chest x-ray abnormalities resolved, and other symptoms abated. However, several months later, after treatment of the initial manifestations of the syndrome, all patients remained clinically stable, but all except one still required corticosteroids for the control of asthma and vasculitis-related symptoms. When these patients tried to taper corticosteroid therapy, 1 patient developed a recurrence of rash and eosinophilia, 2 others developed flares of their asthma and 1 patient had recrudescence of her neuropathy. Unfortunately 3 patients were lost to follow-up.

Since publication of this report, additional cases of eosinophilic syndromes associated with zafirlukast were reported to Zeneca, the manufacturer of zafirlukast, and to the FDA. Up to November 1, 1998, after approximately 1 300 000 patient-years of zafirlukast exposure, an annualised incidence of approximately 60 cases of Churg-Strauss syndrome per million patients with asthma treated with zafirlukast has been reported to Zeneca and the FDA.[6] Of these patients, all had been receiving long term corticosteroid therapy or had multiple corticosteroid tapers. Although this incidence of 60 cases per million patients per year is lower than the initial estimates, it still represents a significantly higher incidence than that previously reported for Churg-Strauss syndrome. Furthermore, several other patients with systemic eosinophilia and with clinical end-organ involvement, but without biopsy-proven vasculitis have also been reported to the FDA and to the drug companies (none have been published). Most of these patients, too, had been treated with systemic corticosteroids within 1 year or had previously been receiving high doses of inhaled corticosteroids.

3.2 Hypotheses for Increased Incidence of Churg-Strauss Syndrome with Zafirlukast

As one of the primary manifestations of Churg-Strauss syndrome is marked eosinophilia, it is clear that this is a disorder of eosinophil recruitment and dysfunction. Eosinophils synthesise mediators with bronchoconstrictor potential, especially the leukotrienes which mediate airway obstruction; but eosinophils also release cationic proteins that have the potential to mediate organ dysfunction which each of the patients has exhibited. Each of the patients who developed Churg-Strauss syndrome in association with a leukotriene modifier developed airway obstruction that was initially diagnosed as asthma and then eventually developed other systemic manifestations.

Several hypotheses have been proposed to account for what seems to be an increased incidence of the Churg-Strauss syndrome in the setting of leukotriene modifier use. It has been postulated that this constellation of findings would have developed independently of leukotriene modifier use and that these new cases have only been reported due to reporting bias that has resulted from the introduction of a new drug. However, the fact that the incidence of this syndrome in the zafirlukast-treated population represents at least a several-fold increase in Churg-Strauss syndrome incidence makes this hypothesis less plausible. While no cases occurred in the trials leading up to either the

approval of either zafirlukast or montelukast, this syndrome is a rare enough entity that not enough patients were exposed to exceed the background incidence of the syndrome.

Another theory is that Churg-Strauss syndrome represents an allergic reaction to zafirlukast in a population of patients with asthma that is already predisposed to allergic diathesis. While it is difficult to absolutely dismiss this theory in all cases of zafirlukast-associated eosinophilic disorders – in fact, a case of drug-induced lupus in a child after treatment with zafirlukast has recently been reported[7] – many features of these patients make this scenario less likely. First, granulomatous vasculitis is an extremely rare occurrence in association with drug therapy: only 8 cases have previously been reported in the literature. Secondly, the time course of the development of the syndrome (more than 2 to 3 months from drug initiation in most cases) is a relatively long lag time for a drug reaction to occur. Furthermore, the syndrome has developed not only with zafirlukast but also, 2 other leukotriene receptor antagonists with different chemical structures, montelukast[8] and pranlukast,[9] and in patients who were taking neither of these drugs but rather, high dose inhaled corticosteroids and salmeterol (section 2.3, case 3). Other compelling arguments against this theory are the fact that after 1 year off zafirlukast, many patients with Churg-Strauss syndrome developed recurrent symptoms after further attempts were made at corticosteroid withdrawal, and some of the patients in the initial study[1] developed symptoms prior to initiation of zafirlukast therapy.[2]

Yet another theory that has been proposed is that this syndrome results from an imbalance in leukotrienes.[10] While the effects of zafirlukast are believed to result from blockade of the *cysteinyl-LT1* receptor which transduces the effects of leukotriene (LT) C4, LTD4 and LTE4, the drug has no effect on the receptors for LTB4, which has been shown to be chemoattractant for eosinophils and neutrophils (see fig. 3). However, there has been 1 report to the FDA of a similar systemic eosinophilic condition in association with use of zileuton,[11] the 5-LO inhibitor that blocks synthesis of all of the leukotrienes, including LTB4. Furthermore, eosinophil chemotaxis has been shown *in vitro* to be inhibited by both 5-LO blockade as well as leukotriene receptor antagonism,[12] and eosinophil reduction has been demonstrated in human participants receiving leukotriene receptor antagonists as well.[13] Thus, while unopposed LTB4 activity remains a theoretical mechanism, there is

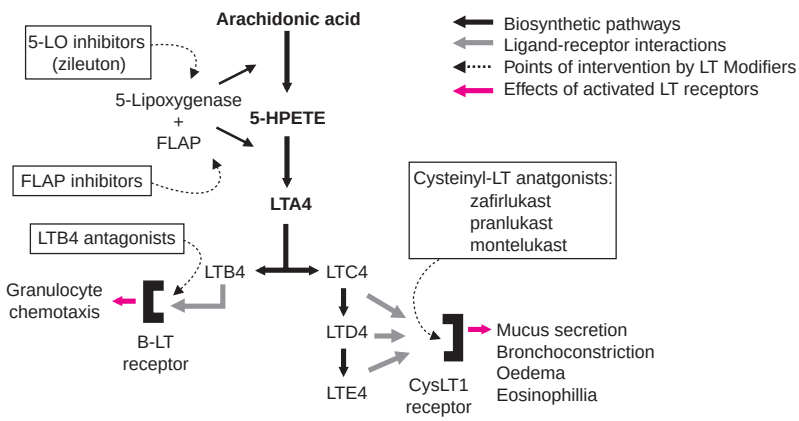

Fig. 3. Schematic representation of the leukotriene pathway and the sites of action of the leukotriene modifiers. **B-LT** = leukotriene B4 receptor; **FLAP** = 5-lipoxygenase activating protein; **LT** = leukotriene; **5-HPETE** = 5-hydro(per)oxy-eicosatetraenoic acid; **5-LO** = 5-lipoxygenase.

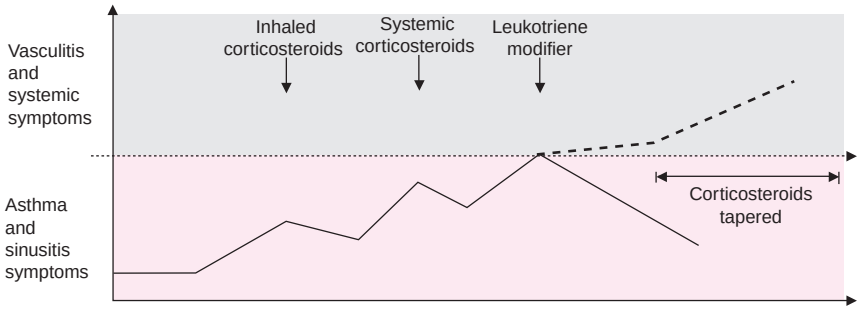

Fig. 4. Potential mechanism and time-line for development of Churg-Strauss syndrome in patients receiving leukotriene modifiers. Churg-Strauss syndrome is an indolent disease that is initially characterised by many years of mild asthma and sinusitis, symptoms of which may improve with both inhaled or systemic corticosteroids. When asthma symptoms progress and leukotriene modifiers are added as therapy, airway symptoms may improve to the point that corticosteroid therapy can be tapered, allowing for an unmasking of other systemic manifestations of the vasculitic syndrome. Alternatively, the syndrome may progress despite corticosteroid therapy.

little evidence to support this theory for the syndrome in these patients as leukotriene receptor blockade would lead to similar aetiological activities that inhibition of 5-LO synthesis might yield.

The most likely explanation for the development of Churg-Strauss syndrome in patients taking leukotriene modifiers is that these individuals have an underlying eosinophilic disorder that was being masked by corticosteroid treatment and that is unmasked by zafirlukast-mediated corticosteroid withdrawal. We believe that these patients had the forme fruste of Churg-Strauss syndrome.[14,15] This is initially manifested as airway obstruction and is therefore clinically recognised as asthma. It is likely that this is the heralding event of the underlying systemic eosinophilic disorder that eventually produces systemic manifestations. However, in patients who develop Churg-Strauss syndrome, recurrent episodes of airway obstruction were considered to be asthma exacerbations and were treated with systemic corticosteroids which, we postulate, also quelled any systemic end-organ eosinophilic sequelae. This was the case in all of the patients described in the report from our group[2] as well as in the other cases reported in section 3.1. Each patient had been treated with multiple courses of corticosteroids before the introduction of zafirlukast treatment, and it was not until leukotriene receptor antagonism therapy with zafirlukast was initiated that the airway obstruction symptoms improved enough to allow a reduction in corticosteroid dosage. It is likely that this reduction in corticosteroid dosage enabled the previously suppressed eosinophilia to demonstrate its protean symptoms (fig. 4).

There have been several other reports in the literature of Churg-Strauss syndrome in association with zafirlukast use. Katz and Papernik[16] described the case of a 53 year-old woman with asthma and chronic sinusitis who had received intermittent pulse therapy with methylprednisolone. Ten days after her last oral corticosteroid taper, she was prescribed zafirlukast. Less than 2 months later, she developed arthralgias, amaurosis fugax, rash, eosinophilia, pericardial effusion and multiple pulmonary nodules, whose biopsy revealed eosinophilic infiltrates and granulomas, suggestive of Churg-Strauss syndrome. Prompt resolution occurred with reinitiation of high dose corticosteroid therapy. The authors contested that this case represented zafirlukast-induced Churg-Strauss syndrome independent of corticosteroid therapy and postulated that zafirlukast could directly provoke this eosinophilic systemic inflammatory syndrome. While they claimed that there was no association between corticosteroid use or withdrawal and the development of Churg-Strauss syndrome in this patient, the patient had been receiving sys-

temic corticosteroids just 10 days prior to zafirlukast initiation, which was approximately 2 months before Churg-Strauss syndrome became manifest. The time course, although different from those reported in the series from our institution[2] is entirely consistent with the indolent nature of the forme fruste of Churg-Strauss syndrome. It may take a few months following corticosteroids withdrawal in a person who has had multiple suppressive corticosteroid tapers (i.e. corticosteroid treatment courses that suppressed both asthma and vasculitis symptoms) for the disease to become manifest.

Another reported case of Churg-Strauss syndrome in association with zafirlukast involved a 47-year-old man with moderate persistent asthma with eosinophilia that required frequent courses of prednisone.[17] Two months after starting therapy with zafirlukast, he developed a syndrome consisting of worsening asthma, progressive vasculitic rash, and biopsy-proven eosinophilic invasion of lung tissue with infiltrates on chest x-ray. The authors implied a 'possible causal relationship' for zafirlukast, and contrasted their report with the cases reported by our institution[2] by saying that the patient had not tapered corticosteroids after zafirlukast use. This patient, however, had 'experienced multiple asthma exacerbations that required treatment with prednisone' and subsequently had been maintained on inhaled doses of corticosteroids when the syndrome occurred. Green and Vayonis[18] described 2 more cases of Churg-Strauss syndrome in patients treated for asthma with zafirlukast who had not been receiving systemic corticosteroids. They contrasted their patients with the cases reported by our institution[2] by stating that their patients had not been withdrawn from corticosteroids and hence did not have the forme fruste of Churg-Strauss syndrome. They too implied a causative role for zafirlukast.

It is our contention that the severe asthma and sinusitis experienced by these patients,[16-18] as well as that of all other patients with Churg-Strauss syndrome that have been reported, was the heralding event of incipient Churg-Strauss syndrome. We believe again that the corticosteroids that were given to treat the patients' severe asthma likely masked the development of other systemic eosinophilic manifestations that occurred subsequently. As Churg et al.[14] have reported, even inhaled corticosteroids could mask the forme fruste of Churg-Strauss syndrome, but they may not mask Churg-Strauss syndrome as the syndrome progresses and higher doses of corticosteroids are required. While there was an association with zafirlukast use, there still has yet to be any convincing evidence that the medication is causally linked; each of these patients' courses could be consistent with the natural course of the Churg-Strauss syndrome i.e. 'indolent allergic disease that evolves into asthma with multiple exacerbations that may progress to eosinophilia and finally, multi-organ eosinophilic vasculitis'.[19]

3.3 Churg-Strauss Syndrome and Other Leucotriene Modifiers

This theory was able to be tested with the availability on the market and increased use of 2 other cysteinyl leukotriene receptor antagonists, montelukast and pranlukast. Several case reports of Churg-Strauss syndrome have been reported to the FDA and drug companies with these leukotriene modifiers that have different chemical structures from zafirlukast. Kinoshita et al.[9] described a 52-year-old woman with asthma and sinusitis who developed eosinophilia, mononeuritis multiplex, pulmonary infiltrates and biopsy-proven vasculitis 4 months after starting prankulast and 2 months following tapering of prednisone.[9] The symptoms resolved following corticosteroid re-initiation and the authors postulated that pranlukast also permitted corticosteroid withdrawal and led to the unmasking of Churg-Strauss syndrome.

Furthermore, similar to case 2 outlined earlier (see section 2.2) several other cases of Churg-Strauss syndrome have been reported in association with montelukast. In the recently reported case by Franco and Artes,[8] and in those by Haranath et al.[20] and Wechsler et al.,[21] montelukast again fa-

cilitated corticosteroid withdrawal and in each case, Churg-Strauss syndrome developed. In the 8 months following its release on the US market in early 1998, an incidence of approximately 60 cases of Churg-Strauss syndrome per million individuals with asthma treated with montelukast per year was reported to Merck and the FDA;[22] this is strikingly similar to the incidence associated with zafirlukast. Although not precisely known and difficult to accurately calculate, this could theoretically represent the incidence of Churg-Strauss syndrome in a corticosteroid-naive asthma population. A good way to assess the incidence of Churg-Strauss syndrome and to perhaps better understand the pathophysiology involved might entail observing new cases that develop in children with asthma, a population that may receive these drugs as an alternative to corticosteroids.

4. Conclusions

What can we thus conclude about the relationship between the Churg-Strauss syndrome and leukotriene modifiers? As all reported cases of Churg-Strauss syndrome in the setting of leukotriene receptor blockade have occurred after patients had tapered either systemic or high doses of inhaled corticosteroids, it appears in these cases that blockade of leukotriene receptors modulates the asthmatic component of hypereosinophilia, but not the systemic effects which require the previously tapered corticosteroids for control. While most apparent in this class of drugs, it is not exclusively a leukotriene modifier phenomenon, as many other medications that modulate airway obstruction and allow the dosages of systemic corticosteroids to be reduced carry warnings stating that vasculitis or pulmonary infiltrates with eosinophilia may occur during their use. This is the case for beclomethasone, flunisolide, sodium cromoglycate and others.[23] As is the case for the patient described by D'Cruz et al.[24] who developed Churg-Strauss syndrome during fluticasone propionate use, this is likely the mechanism of Churg-Strauss syndrome in the patient described in case 3 (see section 2.3) who developed Churg-Strauss syndrome following corticosteroid withdrawal in association with the use of high doses of inhaled corticosteroids, i.e. fluticasone propionate, and the long-acting ß-agonist, salmeterol. Glaxo Wellcome has recently issued a warning to healthcare professionals of the potential for eosinophilia in association with fluticasone propionate. Therefore, any drug that allows a patient's asthma to be improved to the point that corticosteroids are able to be tapered or such that corticosteroids are not initiated as soon as they might have been in the past has the potential to be associated with Churg-Strauss syndrome.

Why have so many new cases of Churg-Strauss syndrome arisen? While it appears that there has been a disproportionate number of cases of Churg-Strauss syndrome reported in the last 2 years since the leukotriene modifiers have been introduced, it remains unclear whether or not this actually represents an increase in the number of cases, or whether previous reports of incidence underestimated the incidence due to poor understanding of the disease by physicians. Furthermore, the population-based incidence of Churg-Strauss syndrome for the general population is known but there are no studies examining the incidence specifically in the population of individuals with asthma. Regardless, the apparent increased incidence could be due to increased reporting in the setting of a potential relationship with a new drug, and due to increased awareness of the disease since the initial reports.

Another explanation, however, is it is only now that there are medications available that are able to specifically treat the asthmatic airway obstruction in patients with poorly controlled asthma, requiring corticosteroid therapy. In the past, each time the patient's asthma flared, treatment with corticosteroids, drugs with multiple target actions, would be reinitiated. In the leukotriene modifiers there exists a nonsteroidal medication that prevents leukotriene driven airway obstruction. In patients who still require corticosteroids, but who receive a leukotriene modifier instead, these medications do

not block other eosinophil effects (as corticosteroids do) and thus, systemic eosinophilic manifestions are unmasked.

Further evidence that the increased incidence of Churg-Strauss syndrome is not exclusive to nor directly related to the use of leukotriene modifiers is the fact that several cases have also reported with other asthma medications such as inhaled corticosteroids.

With the use of high dose inhaled corticosteroids, there may often be sufficient systemic absorption to allow for masking of the underlying vasculitis. However, as the disease progresses, inhaled doses may not be high enough to allow for maximal treatment of the disease.

Leukotriene modifiers, long-acting ß-agonists and high dose inhaled corticosteroids are important novel medications for the treatment of asthma. They are relatively well tolerated drugs, with only rare adverse effects. Nevertheless, while the Churg-Strauss syndrome does not appear to be a direct result of leukotriene modifier use, the syndrome is potentially life-threatening and hence, physicians must be especially wary of it in high risk patients[25] (i.e. patients with late-onset asthma that is difficult to control, with features of multisystem vasculitic involvement) in whom the beneficial effects of treatment with new asthma medications allow corticosteroids to be tapered; chest x-rays and eosinophil levels should be monitored in these individuals prior to corticosteroid tapering and at the first hint of systemic sequelae. In order to better evaluate whether this could be an idiosyncratic drug reaction and whether underlying vasculitis may be present, careful consideration of assessment of baseline eosinophil levels should also be carefully considered prior to therapy in corticosteroid-naïve individuals.

In patients who do develop the syndrome, corticosteroid therapy should be reinitiated, treatment with cyclophosphamide should be considered and eosinophil counts and symptoms should be closely monitored. Finally, to better understand the mechanism and pathogenesis of this syndrome, it is imperative that medical personnel report all new cases of Churg-Strauss syndrome to the pharmaceutical companies and to drug regulatory agencies.

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