Leukotriene antagonists and Churg-Strauss syndrome: the smoking gun

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The cysteinyl leukotrienes, leukotriene C4 (LTC4), LTD4, and LTE4 are pro-inflammatory agents previously known as the "slow reacting substances of anaphylaxis". These arachidonic acid derivatives have broad ranging pro-inflammatory actions including airway smooth muscle contraction and bronchoconstriction, increase in vascular permeability, increase in mucus secretion, and inflammatory cell infiltration of lung tissue.[1] The leukotriene receptor antagonists (LTRAs) zafirlukast, pranlukast, and montelukast block the effects of these mediators and are the most recently released agents with potential anti-inflammatory action for use in asthma.[2] They are antagonists of LTC4, LTD4, and LTE4 and act as selective competitive antagonists of the cysteinyl leukotriene ($CysLT_1$) receptor, as distinct from the 5-lipoxygenase inhibitor zileuton.

An association between LTRAs and Churg-Strauss syndrome (CSS) has recently been suggested by a series of published case reports. CSS is a rare systemic vasculitis whose characteristic features include extravascular eosinophil infiltration/vasculitis, peripheral eosinophilia, and asthma. The case reports published to date describe 15 subjects, 13 of whom were being treated with zafirlukast[3–7] and one with pranlukast[8]; a single case of pulmonary eosinophilia following treatment with montelukast[9] has also been reported although this case may reasonably be reclassified as CSS. The Medicines Control Agency (UK) has received five reports of CSS associated with the use of montelukast and notes 35 such foreign reports associated with montelukast and 15 with zafirlukast.[10] No causal relationship has yet been determined between LTRA drugs and CSS.

The onset of this condition has been reported to range from two days to 10 months after starting treatment with an LTRA at both standard and subtherapeutic doses.[3] Extrapulmonary manifestations (table 1) appeared in all subjects. Nine had evidence of cardiomyopathy, five of peripheral neuropathy, one had CNS involvement, and six had skin manifestations. All subjects had asthma, upper respiratory tract involvement (sinusitis/polyposis/rhinitis), and infiltrates on the chest radiograph. Consistent biopsy evidence was found in 12 of the 15 cases. Remission was induced quickly with systemic corticosteroids alone in 13 cases and with added cyclophosphamide in two. Cyclophosphamide was continued as maintenance treatment in two cases and methotrexate was added in one case.

Much of the literature has suggested that the introduction of leukotriene antagonists allowed significant steroid dose reduction, thereby unmasking previously controlled CSS.[5] Indeed, three of the subjects described[5 7] had three of four requisite diagnostic criteria of the American College of Rheumatology for CSS[11] before the introduction of zafirlukast and a further nine had two of the four requisite criteria at the start of treatment with anti-leukotrienes. All of the 15 cases had received at least intermittent treatment with prednisolone during the previous year and in 10 cases the steroid dose had been reduced within two months of the onset of CSS. No change in steroid dose occurred in the remaining five cases.[5 7 9]

Commercial postmarketing surveillance (Zeneca, UK) has identified 44 cases of systemic hypereosinophilia following zafirlukast treatment, from which 13 cases of CSS could be identified using standardised (ACR) criteria.[11] This represents experience with some 770 000 patients treated with zafirlukast. Such details for other LTRAs are not yet available. An attempt to distinguish the natural prevalence of CSS in asthma sufferers suggests a background of 36–80 cases of CSS per million asthmatics per year.[12] The Drug Safety Research Unit at Southampton, UK estimates that patients treated with salmeterol have a prevalence of CSS of 43 per million per year, those treated with nedocromil have a prevalence of 62 per million per year, while the prevalence of CSS in those treated with zafirlukast approximates 44–118 per million per year.

Table 1 Details of 15 published cases of Churg-Strauss syndrome (CSS) following treatment with a leukotriene receptor antagonist (LTRA)

Age	*Sex*	*Steroid reduction (change)*	*LTRA to onset (months)*	*ACR CSS criteria pre-diagnosis*	*Manifestations*						*Treatment*		*Ref*
					Cardio	*Skin*	*Neuro*	*CXR*	*Sinus*	*Biopsy*	*CS*	*Immunosuppressant*	
47	M	+	1	2		+		+	+	Skin	+		3
67	M	−	8	2			PNS	+	+	Nerve	NA	NA	7
60	F	−	10	2				+	+	Lung	NA	NA	7
52	F	+	1	2	−		PNS	+	+	Nerve	+		8
53	F	+	2	2	+	+	CNS	+	+	Lung	+		5
45	F	−	2	2	+	+	PNS	+	+	Lung	+	Cyclophosphamide	5
43	F	+	3 days	3	+	+	PNS	+	+	−	+		5
59	F	+	4	2	+			+	+	Heart	+		5
36	F	+	3	4	+			+	+	Lung	+	Cyclophosphamide	5
21	M	−	2	2	+	+		+	+	Lung	+		5
43	F	+	3	1	+			+		Heart	+		5
48	F	+	3	2	+			+	+	−	+		5
23	F	+	2	1	+			+		Heart	+		5
44	F	+	2 days	3		+	PNS	+	+	Lung	+	Methotrexate	6
26	M	−	4	2		−	−	+	+	−	+		9
45.9 (13.4)*	11F/4M	10	3.1 (2.8)*	2.0 (0.7)*	9	6	6	15	13	12	13	3	

ACR = American College of Rheumatology; Cardio = cardiomyopathy; Neuro = neuropathy; PNS = peripheral nervous system; CNS = central nervous system; CXR = chest radiographic infiltrate; sinus = sinus disease; biopsy = biopsy evidence of vasculitis; CS = corticosteroids; NA = not available.
*Mean (SD).

A number of factors may explain the possible association between LTRA use and CSS. Firstly, these subjects may all have manifested a subclinical or forme fruste[13] of CSS before starting treatment with the LTRA, the disease then becoming manifest coincidentally. Certainly the natural history of this condition is thought to pass through successive phases of asthma and rhinosinusitis, peripheral eosinophilia with radiographic pulmonary infiltrates, and, finally, systemic vasculitis,[14] and these cases may represent the coincidental passage from the second to the third phase in this progression. Lanham *et al*[15] have suggested that patients with CSS may have a decreased dependency on steroids before the onset of the systemic vasculitic phase, perhaps foreshadowing progression. This proposal, however, is somewhat contradicted in this group by the fact that all of these subjects underwent escalation of asthma treatment (LTRA introduction) prior to the development of this syndrome.

A reduction in the steroid dose certainly provides a feasible causal link although this is not supported by the occurrence of this syndrome in those in whom oral steroid dose reduction did not temporally precede the onset of CSS. Systemic steroid therapy was, however, used by all subjects within 6–12 months before the onset of CSS. More forcefully, there have been very few reports of CSS following the introduction of other asthma treatments including inhaled corticosteroids,[16] theophylline, and cromolyns,[17–19] all of which have shown some steroid sparing effect.[20–23]

Notably, no cases of CSS have been reported in association with the use of the 5-lipoxygenase inhibitor zileuton. It can therefore be postulated that a state of eosinophilic activation occurs, perhaps in response to the unopposed activity of LTB4. Certainly, LTB4 is an eosinophil chemoattractant[24] although this activity is limited and, indeed, blocked by zileuton.[25] The failure of an LTB4 antagonist to exert any beneficial physiological effect in asthma[26] further tends to diminish any likely clinical significance of LTB4 activity in asthma, if not CSS.

Finally, CSS may represent an idiosyncratic or hypersensitivity reaction to LTRA exposure. CSS has, indeed, been described following treatment with azithromycin, roxithromycin and erythromycin,[27] oestrogen replacement,[28] and carbamazepine.[29]

The factors underlying eosinophil activation and proliferation in CSS remain poorly understood and no clear mechanistic link between CSS and LTRA agents has yet been found. Steroid dose reduction facilitated by LTRA use may well be responsible for unmasking steroid suppressed CSS previously categorised as asthma.

To date there is insufficient compelling evidence with which to impeach LTRAs as a direct cause of CSS. It seems prudent, however, to be vigilant to the emergence of CSS in moderate to severe asthmatics with upper respiratory symptoms following the introduction of LTRAs. Marked peripheral eosinophilia and abnormal chest radiographs, which are unusual in atopic asthma, may help in the early identification of subjects developing CSS.

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