

Churg Strauss Syndrome and Leukotriene antagonist use: A respiratory perspective
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(Word count 3500)

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Keywords: Churg Strauss syndrome, asthma, Leukotriene Antagonists, Eosinophilia, Vasculitis

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ABSTRACT (Word count: 224)

Background: Churg Strauss Syndrome (CSS) is a rare granulomatous small vessel vasculitis that occurs against a background of long-standing asthma. Leukotriene antagonists (LTAs) are used in the management of asthma and may facilitate a reduction in steroid dosage. Reports of the development of CSS in asthmatic patients following the initiation of LTA therapy suggest either a causal association or an unmasking of latent CSS as steroid doses fall. We have undertaken a systematic review to establish whether evidence of a drug induced syndrome exists.

Methods: Systematic review searching Medline from database inception to August 2007 to identify cases with a possible association between LTAs and CSS. Hill's criteria of causation were used to assess strength of causality.

Results: 62 cases in which CSS developed after the introduction of LTA therapy were identified. Patients were divided into three groups: Group 1 had received no previous steroid therapy, group 2 had been treated with oral and / or inhaled corticosteroids, but had no change in steroid therapy following LTA introduction and group 3 had a clear reduction in steroid therapy following introduction of LTA therapy. The majority of patients from each group exhibited a clear temporal relationship between initiation of LTA and development of CSS with no evidence of pre-existing disease.

Conclusions: Currently available evidence suggests an association between LTA and CSS that may be causal.

INTRODUCTION:

Churg Strauss Syndrome (CSS) is an uncommon disease with an unclear cause with an estimated annual incidence of 2.7 per million patient-years[1]. In 1990, the American College of Rheumatology (ACR) suggested that patients should have 4 out of 6 criteria (asthma, eosinophilia >10%, mono or polyneuropathy, nonfixed pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophilia.) for diagnosis of CSS [2] (see Table 1 in online supplement).

Churg Strauss Syndrome has characteristic histological findings and the association with asthma distinguishes it from other vasculitides. It has been recognized that, in many but not all patients, the disease follows a characteristic 3-stage course [3](see Fig. 1 in online supplement). Asthma and/or allergic rhinitis, with or without nasal polyposis, precedes full development of the syndrome, often by many years. Differentiating CSS from other disorders with eosinophilic tissue infiltration is difficult and, in the absence of histopathologically demonstrable small-vessel vasculitis, the clinical context (particularly the presence of a history of asthma) is highly relevant for a diagnosis of CSS. Antineutrophil cytoplasmic antibodies (ANCA) are not generally viewed as the primary cause of the disease, since up to 50% of patients with CSS do not express these antibodies [4, 5].

Leukotriene antagonists (LTAs) are a relatively recent addition to the treatment options in asthma. These drugs include one enzyme inhibitor of 5-lipoxygenase (Zileuton) and chemically distinct cysteinyl leukotriene type I (cys-LT1) receptor antagonists such as zafirlukast, pranlukast and montelukast. These agents neutralise the effects of the cysteinyl leukotrienes (LTC₄, LTD₄ and LTE₄) by selectively antagonising cys-LT1 receptors.

A number of case series and reports in the recent literature suggest an association between LTAs and CSS with a number of patients developing CSS following the introduction of LTA therapy. The low incidence of CSS following treatment with LTAs makes investigation of this issue with controlled studies of sufficient power difficult and to date there are no systematic reviews collating this evidence. We have therefore undertaken a systematic review to explore further the possibility of a causal association.

METHOD:

Identification of potential studies

We conducted a systematic literature review to identify studies that reported an association between CSS and LTA use. Studies were identified using MEDLINE: (1950 to August 2007) limiting study selection to citations in English language. The search term combinations used were: Leukotriene antagonists and Churg Strauss syndrome, Montelukast and Churg Strauss syndrome, Zafirlukast and Churg Strauss Syndrome, Pranlukast and Churg Strauss Syndrome, Zileuton and Churg Strauss syndrome. The search revealed 212 citations that underwent subsequent review (see figure 1).

Assessment of CSS and LTA use

Data were collected on the age and gender of patients, history of asthma, present and past treatment, nature of corticosteroid treatment, type of LTA used, duration of LTA therapy prior to the development of CSS, organ involvement and ANCA status.. The presence of dormant, suppressed or *forme fruste* disease [6] before the introduction of LTA therapy was assessed according to pre-determined criteria

((see online supplement table 1). Where possible the duration, route and timing of steroid therapy in relation to LTA introduction were recorded.

Assessment of potential causal relationship between LTA use and CSS

The cases were divided into 3 groups depending on steroid usage prior to LTA introduction (see Box 1 below).

Box: 1

- Group 1: 9 cases of CSS post LTA – without antecedent continuous oral steroid therapy. Seven cases were entirely steroid naïve before initiation of LTA.
- Group 2: 30 cases - patients on stable doses of ICS (n=27), inhaled and oral corticosteroids (2) and OCS (n=3) therapy only. Here LTA was added to improve asthma control.
- Group 3: 23 cases where LTA therapy led to improved control of symptoms and facilitated tapering or withdrawal of ICS (1 case), OCS (18 cases) or OCS plus ICS (2 cases).

Correct Identification of the causative drug

To our knowledge, we could not identify any additional drug that was started during the time period studied preceding the development of CSS in the patients who received LTRA.

Considering Hill's criteria of causation, clinical evidence of CSS should follow (not predate) the onset of treatment with the LTA [7]. Generally, in drug induced adverse reactions, this "latency period" may be as short as a few seconds (in patients with anaphylaxis or acute bronchospasm), a few hours (in transfusion-related acute lung injury), or weeks to years in treatment with chemotherapeutic agents, or radiation therapy. As such, there is no clear latency that proves or disproves drug causality

STATISTICAL METHODS:

Organ involvement following exposure to each LTA was compared by cross-tabulation using the Chi square test. The univariate odds ratio for each organ was calculated using logistic regression. The time from LTA exposure to CSS / number of organs involved with the Kruskal-Wallis test (with use of Dunn's multiple comparison post hoc test to examine the interval between LTA use and CSS onset in individual groups). Associations between ANCA status and LTA agent and organ involvement was compared by cross-tabulation using the Chi square test. Univariate odds ratio for ANCA positive / negative was calculated using logistic regression..

To assess for independent predictors of organ pattern / ANCA status, we performed logistic regression analysis. To assess for independent predictors of the interval between LTA and CSS occurrence, we

generated a general linear model. The predictor variables included in the multivariate model examining predictors of ANCA status were the LTA type, group (1,2 or 3), and the number and pattern of organs involved (heart, lung, nerve, skin). The variables included when examining independent predictors of the organ involvement were the LTA type, group (1, 2 or 3) and the ANCA status, with the fraction of cases with a given organ affected used as the dependent variable. Statistical analysis was performed using SPSS 9.0.

RESULTS:

Patient demographics

Reports of 63 cases in which CSS followed LTA therapy were identified. The mean age at presentation was 47 (range 7 to 79) and 33 (55%) were female. The mean duration of asthma prior to presentation was 7.5 years (range 4 months to 20 years).

One reported case following Zileuton administration was excluded as it did not meet the ACR criteria for CSS [8]. The remaining 62 cases had based their diagnosis on at least 4 out of 6 ACR criteria. 32 of these included data on histological confirmation of diagnosis (nasal mucosa: 1, heart: 4, nerve: 6, skin: 10, lung: 10, liver: 1). There were no major variations in the diagnostic criteria used in the diagnosis of CSS for the majority of reported patients.

Exclusion of Other Causes of Drug Induced CSS

CSS associated with drugs other than LTA is a rare occurrence and only a few cases have been reported in the literature [9-15]. Only one of our reported cases had been on receiving simultaneous macrolide (rokitamicin) [16]. Thus we could not find significant evidence to suggest confounding associations with drugs previously reported to cause CSS.

Organ involvement and LTA use

Different LTAs implicated in the cases of CSS were Montelukast (29 cases), Zafirlukast (17 cases), Pranlukast (16 cases). Lung was the most common organ involved at presentation of CSS (n=48) followed by nerve (n=37) and skin (n=24). 16 patients had cardiac involvement, 8 of which belonged to a single series. [17]

We used univariate Chi square analysis to investigate the association between use of the three LTA agents and the occurrence of vasculitis in each of the organs (lung, heart, nerve and skin). The LTA used was significantly associated with the occurrence of cardiac disease ($p=0.001$), but not with other organs (see online supplemental Table 2). Thus, Zafirlukast tended to be associated with lung and cardiac involvement, whereas Pranlukast tended to be associated with neurological CSS, but not cardiac disease, with Montelukast associated with intermediate risk.

To assess for independent predictors of the pattern of organ involvement, we developed a multivariate logistic regression model for each organ using patient group (1, 2 or 3), ANCA status, and LTA type as predictor variables (Table 1). Using this approach, there were no significant independent predictors of lung, nerve or skin involvement, whereas LTA type was independently associated with cardiac involvement ($p<0.05$). These findings are summarised in Figure 2).

Table 1. **Association between LTA use and pattern of organ involvement.** We performed univariate and multivariate logistic regression examining predictors of the pattern of organ expression (dependent variable), the latter controlling for ANCA status and patient group. *Compared to Montelukast

	Lung		Cardiac		Nerve		Skin	
	P value	Odds ratio (95% C.I.)	P value	Odds ratio (95% C.I.)	P value	Odds ratio (95% C.I.)	P value	Odds ratio (95% C.I.)
LTA type								
<i>Univariate analysis</i>								
Pranlukast	0.14	0.2 (0.02 to 1.8)*	0.006	0.15 (0.03 to 0.6)*	0.09	2.9 (0.8 to 10.6)*	0.71	0.8 (0.2 to 2.6)*
Zafirlukast	0.15	1.9 (0.5 to 7.1)*	0.32	3.1 (0.3 to 29.3)*	0.71	0.001 (0 to 1×10^{17})*	0.28	2.1 (0.5 to 8.1)*
Montelukast	0.35	1.0	0.003	1.0	0.23	1.0	0.41	1.0
<i>Multivariate analysis</i>								
Pranlukast	0.43	0.5 (0.1 to 3.2)*	0.01	0.1 (0.03 to 0.7)*	0.05	5.6 (0.97 to 32)*	0.1	0.9 (0.2 to 3.5)
Zafirlukast	0.09	8.3 (0.8 to 59)*	0.6	2.0 (0.2 to 24)*	0.8	0.6 (0.01 to 246)*	0.9	5.6 (0.8 to 40)
Montelukast	0.11	1.0	0.03	1.0	0.15	1.0	0.2	1.0

ANCA positivity and disease manifestation

ANCA measurements were reported in 48 cases; it is unclear whether the remainder had ANCA measured and not reported, or not measured at all. Of these 48 cases, 22 (46%) were ANCA negative. 17 cases were p-ANCA positive, one was c-ANCA positive (1:640) [18] and in 8 the positive ANCA pattern was not specified. In 18 cases anti-MPO ELISA was positive, in 22 it was negative and in 26 this was not reported.

ANCA positivity was associated with LTA type on univariate analysis, with a higher probability of this in those treated with Pranlukast (80%) and Zafirlukast (56%) ($p < 0.05$), and with advanced age (mean age 58, range 21 to 79, versus 41, range 17 to 72, $p < 0.05$). The association of organ involvement with ANCA status is summarised in Table 2.

Using multivariate logistic regression (Table 2), ANCA positivity was independently associated with a low incidence of lung disease (odds ratio 0.1, 95% confidence interval 0.01 to 0.98, $p < 0.05$) and a high incidence of skin involvement (odds ratio 14.3, 95% confidence interval 1.8 to 110, $p < 0.05$), but not with the number of organs involved, the LTA used or the group. In addition, 12 of 22 (54%) ANCA – negative cases had evidence of vasculitis with extravascular eosinophilic infiltration on histological analysis. Thus, ANCA status does not appear to influence eosinophilic infiltration.

Table: 2 Association between CSS phenotype and ANCA status (dependent variable). Univariate analysis was performed using the Chi square test with logistic regression (with a single predictor variable) used to generate odds ratios; ^refers to all three drugs. Using multivariate logistic regression analysis, lung involvement was independently associated with a negative ANCA test and skin involvement with a positive ANCA, but the association with LTA type and neurological involvement was lost. *relative to Montelukast

		ANCA positive (n=26)	ANCA negative (n=22)	ANCA not recorded	P value (univariate analysis)	Odds ratio (logistic regression analysis, 95% C.I.)	P value (multivariate logistic regression)	Odds ratio (multivariate logistic regression, 95% C.I.)
LTA type	Pranlukast	12 (80%)	3 (20%)	1	0.04^	6.7 (1.5 to 30)*	0.33	4.6 (0.4 to 48)*
	Zafirlukast	5 (56%)	4 (44%)	8		2.1 (0.4 to 9.8)*	0.20	4.5 (0.1 to 194)*
	Montelukast	9 (38%)	15 (62%)	5		1.0	0.43	1.0
Organ	Lung	17 (46%)	20 (54%)	11	0.05	0.2 (0.04 to 0.99)	0.04	0.12 (0.01 to 0.98)
	Heart	3 (38%)	5 (62%)	8	0.3	0.4 (0.09 to 2.1)	0.29	0.12 (0.003 to 5.8)
	Nerves	19 (68%)	9 (32%)	9	0.02	3.9 (1.1 to 13.2)	0.19	8.6 (0.3 to 225)
	Skin	13 (72%)	5 (28%)	6	0.05	3.4 (1.05 to 12.0)	0.01	14.3 (1.8 to 110)
Interval between LTA use and CSS (mean+/-SEM)		6.7 +/- 2.3	5.9 +/- 1.0		0.8			
Number of organs affected (mean+/-SEM)		2.2 +/- 0.2	2.2 +/- 0.1		0.95		0.11	

Influence of confounding drug therapy with Oral (OCS) or Inhaled corticosteroids (ICS): (Groups 1, 2 and 3)

The characteristics of the patients in the different groups are outlined in online supplementary table 3

Group 1 cases (n=9) - no continuous oral / inhaled steroid therapy when developed CSS

Seven cases were not on inhaled corticosteroids (ICS) or oral corticosteroids (OCS) when they started LTA. None of them met our criteria for suppressed or *forme fruste* disease.

Group 2 Cases – (n=30) - patients on continuous ICS or OCS therapy prior to developing CSS

None of the group 2 cases had any alteration of either OCS or ICS therapy prior to developing CSS. 28 (93%) of them developed CSS within 12 months of LTA therapy. It could be argued that the disease in these cases may have progressed with or without the introduction of LTA. It should be noted, however, that there was no change in steroid after LTA initiation.

Group 3- (n=23) - patients started on LTA with subsequent reduction in OCS or ICS therapy.

In 23 cases LTA led to better control of asthma symptoms thus facilitating tapering or withdrawal of ICS (2 case), OCS (19 cases) and OCS plus ICS (2 cases) respectively. In these cases it is difficult to be sure that withdrawal of drug therapy did not bring about a relapse of a grumbling pre-existing CSS.

Relationship between onset of CSS and starting LTA

In our review, CSS was reported later than 12 months following LTA introduction in only 5 of 62 patients (8.5%), [19-23] 8 out of 9 cases in group 1 (89%), 22 out of 31 cases in group 2 (71%) and 18 out of 22 cases in group 3 (83%) presented within 6 months of initiating LTA therapy. (Fig 3)

Recurrence of CSS on rechallenge with LTA

Re-challenge followed by disease recurrence is an essential determinant of drug-induced respiratory disease. Two cases suffered a relapse of CSS following re-introduction of LTA. One had been on LTA for 18 months before developing CSS. This was treated with OCS and withdrawal of LTA. Reintroduction of LTA caused a recurrence of blood eosinophilia and worsening symptoms despite a fixed continued dose of corticosteroids. [24]. In the second case, previously diagnosed CSS not related to LTA therapy had been controlled with OCS. A one week trial of Montelukast resulted in relapse of CSS within 2 weeks [25].

Remission of Signs and Symptoms with Removal of the Drug

In 52 of the 62 cases reported in this review (84%), the LTA therapy was stopped following development of CSS. Cessation of LTA was accompanied in most cases by escalation of treatment (summarised in online table 4). In one case series, [26] CSS resolved following Montelukast withdrawal despite no change in the steroid dose. In the other two cases, Montelukast was stopped and prednisolone dose was transiently increased, but was brought down rapidly within one week suggesting that Montelukast was the driving factor for ongoing vasculitis. In two other reported cases, disease manifestations resolved following stopping the LTA therapy alone. These patients did not receive any steroid or other immunosuppressive therapy [8, 27]. In ten cases, it was not clear whether the LTA therapy was stopped or not when the CSS was treated.

The presence of “form fruste” disease and the influence of Steroid withdrawal

It could be argued that patients who develop CSS but had evidence of pre-existing disease were either in the final phase of developing CSS prior to adding LTA therapy, or in a suppressed state where oral steroid withdrawal may have provoked progression to CSS. This pattern was identified in 4 of patients [28-31] in groups 1-2 (10%) and 7 (30%) of patients in group 3, suggesting that in the majority of cases there is no evidence to substantiate steroid withdrawal as a trigger for the development of CSS.

DISCUSSION:

The cases in this review cover a spectrum from patients with CSS without any preceding corticosteroid use, those where a suppressed CSS may have been precipitated by an abrupt withdrawal / tapering of the corticosteroids, and patients with clear evidence of disease before the introduction of LTA- i.e. those who may have progressed naturally. A significant number of patients who developed CSS did not have any suggestion of dormant disease or existing disease and showed a clear temporal relationship between LTA initiation and onset of CSS. In 2 cases, LTA treatment appears to have caused a relapse of CSS[24, 25] The published evidence in case series and reports therefore suggests an association between LTA and CSS that merits further consideration and may be causal

The cases in this review cover a broad ethnic population and the full range of LTA available worldwide. There is a suggestion that Zafirlukast might have a greater predilection for cardiac involvement, but we cannot exclude reporting bias due to the limited number of reports. Clearly, the manifestations of the disease might also be under immunological / pharmacogenetic influences. Several case control studies have suggested that CSS patients with ANCA positive disease differ from those without ANCA. Sinico et al found that ANCA positive cases had higher frequencies of renal involvement, alveolar haemorrhage, purpura, and mononeuritis multiplex. ANCA negative cases had more cardiomyopathy and pulmonary infiltrates. In the French vasculitis study group, ANCA positive patients had greater renal involvement, sinusitis, neuropathy and purpura. ANCA positive patients also had greater evidence of vasculitic lesions on biopsy. In this context it is interesting to note that there is an apparently equal distribution of organ involvement other than lung and skin involvement in both positive and negative ANCA cases in the reported drug induced / associated cases[4, 5].

Our Group 1 patients, who were not on continuous steroid therapy, present the most convincing evidence of causation of CSS by LTA as none of these patients had any evidence of dormant or form fruste disease. A temporal relationship between initiation of LTA and the development of CSS is apparent since more than half of cases present within 6 months of therapy.

Our Group 2 patients- who had no alteration of any steroid therapy following introduction of LTA- represent the largest group of cases with CSS. Again there was an apparent temporal relationship between the initiation of LTA therapy and the development of CSS within 12 months in 28 out of 31 cases.

Our group 3 patients who had steroid therapy altered after the introduction of LTA represent cases where attributing their CSS to the initiation of LTA alone is difficult. Nevertheless, overall, this review suggests a temporal relationship of LTA therapy and CSS in 58 out of 62 cases reported in the English literature

This study has limitations. Although this review was limited to English language papers upon the MEDLINE database, sufficient numbers of studies were available to perform meaningful data syntheses. It is also important to recognise that due to the publicity on a possible link between LTA exposure and CSS, most publications will have focussed on this association. It is interesting to note that associations have been reported for both omalizumab, high dose combination treatment with salmeterol and fluticasone, and disodium cromoglycate[32-34]. We cannot therefore exclude the possibility of reporting bias in these publications. In view of the low incidence of CSS following treatment with LTAs there are currently no controlled studies of sufficient power available to formally analyse the

possible interaction between any drug exposure and CSS. As a result, our review was limited to case reports / series, and consequently no formal assessment of the quality of evidence was possible

Health care database analysis has been used to assess any relationships between LTA use and the development of CSS. Using postmarketing surveillance DuMouchel et al. concluded that differences based on relative reporting were observed in the patterns of association of AGA (allergic granulomatous angitiis) with LTRA, ICS, and beta (2)-agonist therapies. A strong association between LTRA use and AGA was present regardless of the use of other asthma drugs.[35] Alternatively a recent report utilising pooled data from two nested case-control studies found no association between CSS and leukotriene modifiers after controlling for asthma drug use[36]

A workshop in 2001 was sponsored by the National Heart, Lung, and Blood Institute, to consider interrelationships among CSS, asthma, and asthma therapeutics and to assess what is known about underlying mechanisms of CSS. It concluded that treatment of patients with asthma with any of leukotriene receptor antagonists, a 5-lipoxygenase inhibitor, and inhaled corticosteroids have been associated with CSS development but it was unknown whether these agents were eliciting CSS.[37]

If LTA induce CSS, what is the mechanism? None of the case reports or case series have provided any clear mechanistic insight into the pathogenesis of LTA induced CSS. An imbalance in leukotriene receptor stimulation in patients with an underlying eosinophilic disorder has previously been suggested [38-40] and remains a potential cause of sustained eosinophilic stimulation which could promote the development of CSS. Unfortunately there is little human data to suggest how LTA could induce CSS both with and without ANCA production or why ANCA status and organ involvement varies with the drug used. Clearly further research focussing upon the clinical phenotypic differences between ANCA positive and ANCA may provide insights into this dilemma.

CONCLUSIONS:

Based on the available clinical evidence there is a suggestion of a causal relationship between LTA and CSS. Respiratory physicians need to be aware of the risk of CSS when treating asthmatic patients with LTAs. Patients should be made aware of the signs and symptoms of CSS after initiation of LTA therapy and they should be regularly monitored for complications. The presence of >2 ACR criteria should make one explore the possibility of vasculitis before LTA therapy is introduced.[28, 29, 31]

Acknowledgments: University of Birmingham

Competing interests: None

Funding: Dr Thickett is funded by a Wellcome research grant. Dr Little is funded by the HEFCE Senior Lecturer scheme. Dr Nathani was funded by UHB Charities.

Figure legends:

Figure 1: Summary of studies assessed and included in this review

Fig 2 Pattern of organ involvement according to the LTA used. For each of the four organs (lung, cardiac, neurological and skin) the number of cases with involvement (black shading) is compared with the number without that particular organ involvement (clear shading). * $p < 0.05$ as assessed by multivariate logistic regression analysis, controlling for patient group and ANCA status.

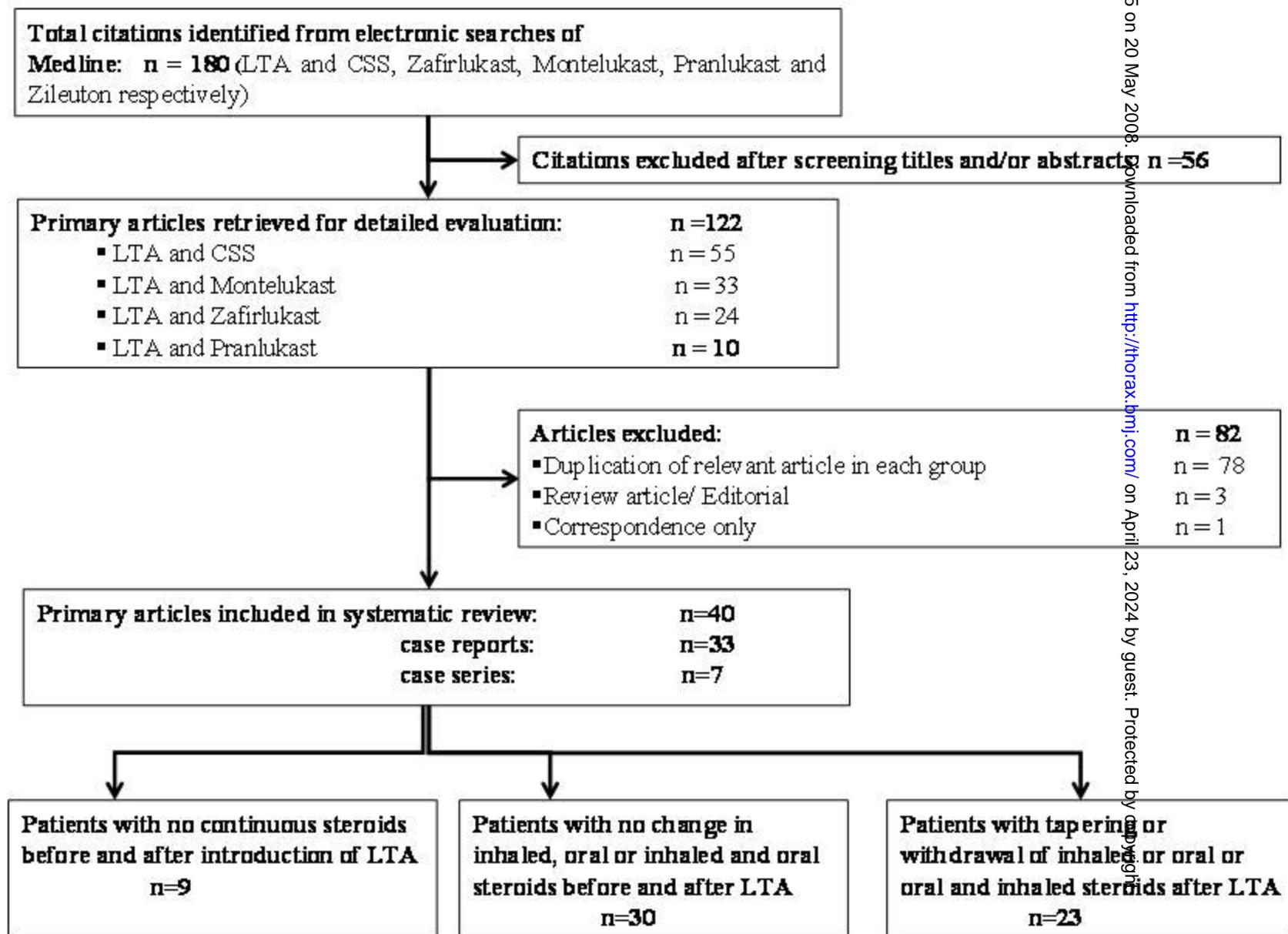
Figure 3: Interval between LTA use and onset of CSS. The percentages refer to the fraction of each group developing CSS within the time scale specified

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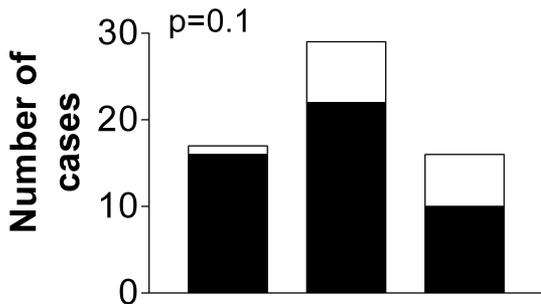
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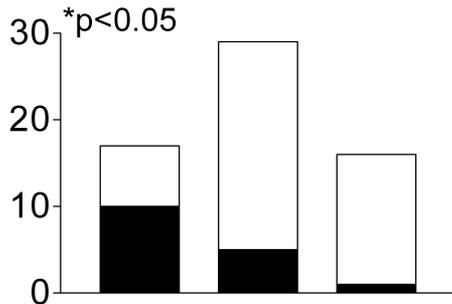
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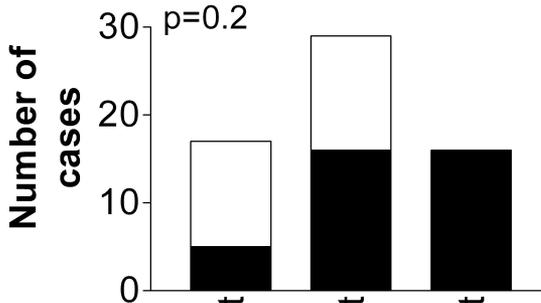
Lung



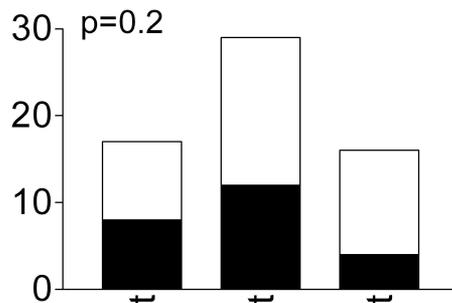
Cardiac



Neurological



Skin



Zafirlukast

Montelukast

Pranlukast

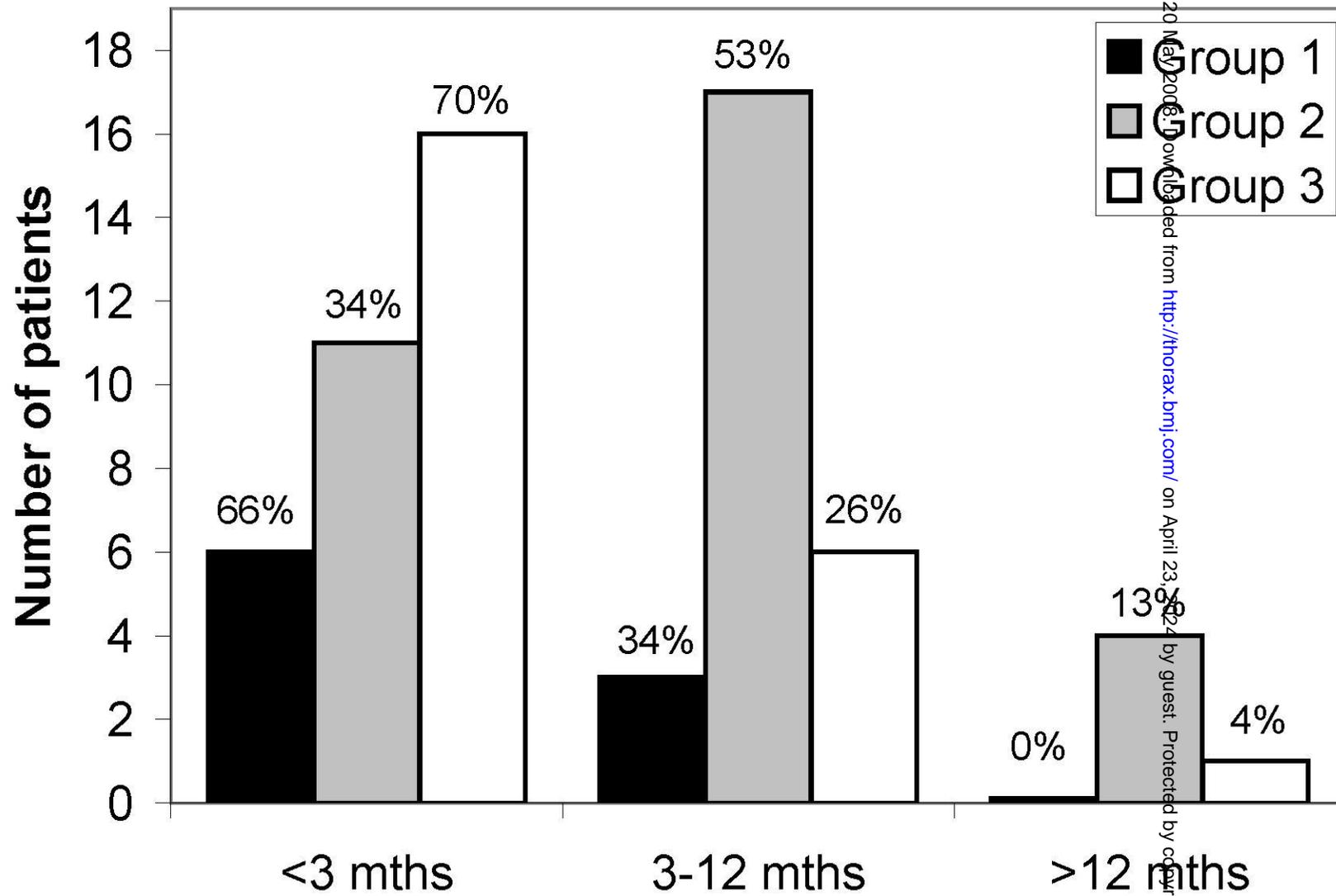
Agent

Zafirlukast

Montelukast

Pranlukast

Agent



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Online supplement:

Supplementary Table 1

Churg-Strauss Syndrome Definitions ACR 1990
criteria: 4 out of 6 required:

Asthma

Eosinophilia >10%

Neuropathy, mono or poly

Pulmonary infiltrates, non-fixed

Paranasal sinus abnormality

Extravascular eosinophils

[dt1]

Forme Fruste Churg Strauss syndrome for this review

Asthma plus at least two other criteria from the ACR criteria above.

Supplementary table 2. Multivariate logistic regression examining independent predictors of the pattern of organ expression (dependent variable). *Compared to Montelukast

	Lung		Cardiac		Nerve		Skin	
	P value	Odds ratio (95% C.I.)	P value	Odds ratio (95% C.I.)	P value	Odds ratio (95% C.I.)	P value	Odds ratio (95% C.I.)
LTA type								
Pranlukast	0.43	0.5 (0.1 to 3.2)*	0.01	0.1 (0.03 to 0.7)*	0.05	5.6 (0.97 to 32)*	0.1	0.9 (0.2 to 3.5)
Zafirlukast	0.09	8.3 (0.8 to 59)*	0.6	2.0 (0.2 to 24)*	0.8	0.6 (0.01 to 246)*	0.9	5.6 (0.8 to 40)
Montelukast	0.11	1.0	0.03	1.0	0.15	1.0	0.2	1.0

Supplementary Table 3: Characteristics of studies and patients included in the systematic review of Churg-Strauss- Syndrome (CSS) following treatment with LTA in asthma. *p<0.05 comparing the 3 groups with respect to interval from LTA to CSS using the Kruskal Wallis test; the interval in group 2 patients was significantly longer than group 3 (p<0.05) using Dunn's multiple comparison post hoc test.

Study group	Steroid therapy	N	Median interval from LTA to CSS (interquartile range)*	Type of evidence	LTA used	Occult disease prior to LTA	ANCA status	Organs involved
<u>Group 1</u> (Not on continuous steroids, n=9)	Entirely steroid naïve	7	3 months (1.5 to 8.5)	Case report: 3 Case series: 1	Zafirlukast (2) Pranlukast (6)	0 cases	5 positive 2 negative	Lung 4 Cardiac 1 Skin 3
	Intermittent oral steroids	2		Case report: 2 Case series: 1	Montelukast (1)	0 cases	2 positive	Nerve 3
<u>Group 2</u> (On continuous inhaled, inhaled and oral steroids or oral steroids alone, n= 30)	Inhaled steroids +/- intermittent oral steroids	25	4.5 months (3.0 to 9.0)	Case report: 13 Case series: 5	Zafirlukast (6)	2 cases	11 positive 10 negative 1 unknown	Lung 22 Cardiac 2 Nerve 14
	Oral and inhaled steroids	2		Case report: 2 Case series: 0	Pranlukast (7)	2 cases	5 negative 1 unknown	Skin 12 Renal 1
	Oral Steroids only	3		Case series 1	Montelukast (17)	0 cases	1 positive 1 unknown	Liver 1 Joint 1
<u>Group 3</u> (Withdrawal of oral or inhaled steroids following LTA, n=23)	Withdrawal of inhaled steroids	2	3 months (1.75 to 4.0)	Case report: 1	Zafirlukast (9) Pranlukast (3) Montelukast (11)	1 case	1 unknown	Lung 16 Cardiac 10 Nerve 14 Skin 10 Renal 2

Supplementary Table 4 Treatment Instigated after onset of CSS.

Modification of treatment	Numbers of patients (%)	Data incomplete (25.4%)
Stopped leukotriene	45 (71)	16
Increased steroids	55 (87)	6
Second line agent	14 (22)	0
Stopped leukotriene alone	2 (3)	0
CSS recurred after rechallenge	2 (3)	0

Figure 1

Churg Strauss Syndrome – The disease evolution (8-10 years)			
Phase 1 Prodromal and evolution into tissue eosinophilia	Phase 2 Tissue Eosinophilia		Evolution into Vasculitic phase
Asthma Allergic Rhinitis Nasal Obstruction	Nasal Polyposis	Infiltrative Eosinophilic Pneumonia Eosinophilia Reversible Exophthalmos Chronic Otitis media	Hearing Loss Skull Base Infiltration with granulomas Skin Nodules, palpable purpura, petechiae Eosinophilic Gastroenteritis Heart failure, Acute Pericarditis, Myocardial infarction Mononeuritis Multiplex Symmetric or asymmetric polyneuropathy Cerebral haemorrhage and infarction Focal segmental glomerulonephritis

LTA triggering prodromal to eosinophilic and vasculitic phases: \uparrow LTB₄, \uparrow Leukotrienes acting on unidentified receptors, Endothelial cell activation