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THE LEUKOTRIENE-RECEPTOR ANTAGONIST MONTELUKAST AND THE RISK OF CHURG–STRAUSS SYNDROME: A CASE–CROSSOVER STUDY

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ABSTRACT

Background: There has been some concern that leukotriene-receptor antagonists might precipitate the onset of Churg–Strauss syndrome (CSS). **Objective:** To investigate the relationship between the leukotriene-receptor antagonist montelukast and CSS onset. **Methods:** Medication histories of 78 CSS patients from France and Germany were retraced by questioning the patients, treating physicians and dispensing pharmacists, and from medical records. Using a case–crossover research design, we compared exposures to montelukast and other asthma medications during the 3-month 'index' period immediately preceding CSS onset with those of 4 previous 3-month 'control' periods. Odds ratios (OR) were computed by conditional logistic regression. **Results:** OR (95% confidence interval) for CSS onset were 4.5 (1.5–13.9) for montelukast, 3.0 (0.8–10.5) for inhaled long-acting β_2-agonists, 1.7 (0.5–5.4) for inhaled corticosteroids and 4.0 (1.3–12.5) for oral corticosteroids. Montelukast exposure during control periods increased temporally over 3 consecutive calendar periods of CSS onset from 1999 to 2003 (P_{trend} <.0001). **Conclusion:** Montelukast use was associated with a 4.5-fold higher risk of CSS onset within 3 months. However, the positive estimates obtained for other long-term asthma-control medications suggest that this link might be confounded by a general escalation of asthma therapy before CSS onset. The montelukast–CSS association observed herein is likely also explained by the increasing use of this medication over time.

INTRODUCTION

Churg–Strauss syndrome (CSS) is a small-vessel vasculitis that occurs in the context of asthma and eosinophilia. The etiology of this rare and potentially life-threatening disease is unknown [1, 2]. Over the last decade [3–6], more than a hundred cases of CSS, published or registered in post-marketing monitoring systems, had occurred in individuals receiving asthma therapy with a leukotriene-receptor antagonist (LTRA) – montelukast, zafirlukast or pranlukast [7, 8]. Those reports raised public health concerns that LTRA might precipitate the onset of CSS and even more so since the possibility of CSS being triggered or caused by drugs had been suspected previously [1, 2].

It was thought that LTRA could induce CSS via drug hypersusceptibility [9] or a collateral effect of these agents on eosinophil chemoattraction [10]. Based on clinical observations, the most widely favored hypothesis put forth so far to explain the potential link between LTRA and CSS stipulated that LTRA administration allows tapering of corticosteroids needed to treat the asthma, thereby coincidentally unmasking a latent form of CSS [6, 8]. However, that theory conflicted with reports of LTRA-associated CSS occurring in the absence of concomitant corticosteroid reduction [3, 11–15], the overall modest corticosteroid-sparing effect of LTRA [16] and the few similar observations made for drugs more potent at reducing oral corticosteroid doses, such as inhaled corticosteroids [17–21]. Most importantly, only rare observational studies sought to determine whether a real association exists between LTRA and CSS [22].

We conducted a case–crossover study, a research design in which the cases act as their own controls, to explore the possible relationship of exposure to montelukast, the only LTRA available in the study area, and CSS development.

PATIENTS AND METHODS

Study population

Study participants were retrospectively recruited through the FVSG and the Interdisciplinary Vasculitis Center Bad Bramstedt in Germany. Candidates for study participation from France were identified among patients enrolled in a prospective clinical

trial conducted by the FVSG from 1995 to 2005. That trial evaluated therapeutic strategies for newly diagnosed CSS and included 140 patients from 55 French and a few other European medical centers [23, 24]; for legal reasons, only patients enrolled in that trial by French centers were considered for this study. The Interdisciplinary Vasculitis Center Bad Bramstedt, a specialized tertiary referral center, identified potential participants for this study from a prospective registry of all vasculitis patients followed in their facility since 1991.

In both countries, montelukast was first approved in March/April 1998 [25, 26]. Because the study assessed exposures during the 15-month period preceding CSS onset (see below), we searched the databases for all individuals diagnosed with CSS between July 1999 and the time this study was launched in April 2004. Individuals for whom the investigation revealed that CSS onset predated July 1999 were subsequently excluded from the analyses. The final analysis also retained only subjects meeting the American College of Rheumatology (ACR) classification criteria [27] or those proposed by Lanham et al. [28] (table 1). To avoid the possibility of incomplete data, we considered that the ACR criterion of 'eosinophilia >10%' was also met by an absolute peripheral eosinophil count >1500/mm^3.

Table 1. Classification criteria for Churg–Strauss syndrome.

Criteria of the American College of Rheumatology [27]*
Asthma
Eosinophilia >10% (on differential white blood cell count)
Mono- or polyneuropathy
Non-fixed pulmonary infiltrates
Paranasal sinus abnormality
Extravascular eosinophils on biopsy
Criteria of Lanham et al. [28]†
Asthma
Peak peripheral blood eosinophil count >1500/mm^3
Systemic vasculitis involving ≥2 extrapulmonary organs

*≥4 of 6 items required.
†All 3 items required.

Data collection

The time of CSS onset and prior asthma-treatment exposures relevant to this study were examined using 3 information sources: 1) study participants, 2) their local treating physicians and hospital medical records, and 3) their pharmacists. We retained exposures for the 4 following classes of long-term asthma-control medications (with respective active principles): LTRA (montelukast), inhaled long-acting β_2-agonists (formoterol, salmeterol), inhaled corticosteroids (beclomethasone, budenoside, fluticasone) and oral corticosteroids (betamethasone, dexamethasone, methylprednisolone, prednisolone, prednisone). Furthermore, information on immunotherapy prescribed for allergies and vaccinations were collected to identify a potential confounding effect of these putative triggers of CSS [29]. Throughout the investigation, participants, their physicians and pharmacists were informed that this study's purpose was to examine risk determinants of CSS without revealing its specific focus on montelukast.

Interviews with study participants

First, all study participants underwent a 40–60-minute telephone interview using a detailed standardized questionnaire. To prepare for the interviews, participants received the questionnaire beforehand. To facilitate recall of previously used medications, the 8- and 10-page questionnaires listed by brand name the 36 and 62 medications (grouped in drug classes

and sorted alphabetically), which are commonly available for asthma treatment in France and Germany, respectively. The questionnaires also included labeled color photographs (showing pharmaceutical formulations and devices with original packages) of all listed medications. In France and Germany, drugs are delivered exclusively in their original distinctive packages as provided by the manufacturers. In addition, patients were encouraged to track down duplicates of their doctor's prescriptions they may have kept.

During the interviews, we recorded the histories of asthma, sinusitis and allergy, and detailed information on the initial symptoms, date of CSS onset and all subsequent manifestations until its diagnosis. Then, based on the list of medications provided in the questionnaires, the patients were asked to name all the anti-asthmatic medications taken during the 2-year period prior to CSS onset. Periods of exposures were recorded as months and years of initiation and withdrawal. Ultimately, we asked for the identity and contact information of local treating physicians, mainly general practitioners, pulmonologists, allergists and otorhinolaryngologists, and the dispensing pharmacists they had consulted during the 2-year period of interest. In addition to the information given orally during the interviews, the patients also returned the filled-out questionnaires by mail.

Survey among treating physicians and review of medical records

For each participant, we attempted to contact his/her general practitioner and, when applicable, at least 1 local treating specialist able to provide reliable information regarding the use of asthma therapies. Treating physicians were either asked to reply by mail (Germany) or questioned by telephone (France); in the latter case, the investigator making the phone call was unaware of the information collected during patients' interviews. The physicians were asked for detailed information on initial CSS manifestations and all anti-asthmatic treatments prescribed during a period spanning from 2 years before CSS onset until its diagnosis, based on the dates initially provided by the patients during the telephone interviews.

Furthermore, hospital medical records, including trial report forms and/or hospital discharge letters were reviewed with respect to date and signs of CSS onset, and drug histories.

Survey among dispensing pharmacists

All pharmacists indicated by the participants were asked by mail to provide us with printouts of electronic records on any medications they had dispensed to those clients during the entire period under investigation, as defined above. In France and Germany, drug deliveries are limited to a 30-day maximum supply and, therefore, patients receiving long-term medications must return to the pharmacy every month.

Definition of CSS onset and prior exposures

We then collated all the collected information to define each patient's date of CSS onset, which was defined as the very first occurrence of any manifestations attributable to CSS. Symptoms attributed to asthma, sinusitis and/or allergic conditions, and exposures to medications were not considered to determine CSS onset. Unless a precise day or week of onset could be cited, the date was set at the 15^{th} day of the respective month.

Using this date, we then established the individual exposure histories for the 15-month period preceding CSS onset. Exposure times to drugs of the same pharmacological category were cumulated; for inhaled combination therapies with long-acting β_2-agonists and corticosteroids, exposures were assigned to both classes. The precise beginning and end of exposure were primarily determined using information given by treating physicians and/or pharmacists; when unavailable, exposure periods were defined using the dates mentioned by the patient and/or hospital records.

Case–crossover analysis

The risk of CSS onset associated with the investigated drug classes was assessed by a case–crossover analysis [30]. This variant of a traditional case–control study compares exposures to a potential risk factor during the 'index' period immediately preceding the event, e.g. disease onset, with those during several prior 'control' periods. Based on putative pathogenic mechanisms [9, 31], we considered for our primary analysis that CSS onset would occur within 3 months after first exposure to montelukast or another pharmaceutical trigger. Accordingly, for each patient, the 4 consecutive 3-month periods immediately preceding the 3-month index period served as control periods. An index- or control-effect period was defined as being exposed to a medication class as soon as a drug belonging to that class had been used for at least 1 day during the period. When for a given medication class the period of use could not be precisely determined, we treated the corresponding effect periods as missing data. In addition, sensitivity analyses, e.g. by using 2-month (1 index and 6 control periods) and 4-month effect periods (1 index and 2 control periods), and subgroup analyses were performed to test for the robustness of the results of the primary analysis. The assumption that there is no linear trend in the probability of exposure to each of the medication classes considered over time was verified by first comparing the levels of exposure across the 4 control periods preceding CSS onset and then by comparing the pooled levels of exposure during 4 control periods analyzed by year of CSS onset.

Statistical analyses

For the case–crossover analysis, we used conditional logistic regression to estimate matched odds ratios (OR) [32]. Categorical variables were compared using χ^2 and, when appropriate, Fisher's exact tests, and continuous variables using Student's t-test or Kruskal–Wallis tests. For all statistical analyses, a 2-tailed $P < .05$ was considered significant.

Ethical aspects

The study protocol was reviewed and approved by the Commission Nationale de l'Informatique et des Libertés in France and the Ethics Committee of the University of Lübeck in Germany. All patients gave written informed consent to participate in the study.

RESULTS

Patient selection and responses to surveys

Among a total of 110 screened files, 78 (71%) patients were identified who fulfilled all selection criteria and consented to participate in the study (fig 1).

Information from at least 1 community physician was obtained for 71 (91%) participants. Printouts of the medications dispensed by pharmacists covering the entire 15-month period investigated were obtained for 40 (51%) participants and covering part of this period for 11 (14%) participants. No information was obtained from either treating physicians or dispensing pharmacists for only 3 (4%) patients.

Clinical data

The main characteristics of the 78 subjects are listed in table 2. The majority (96%) of patients satisfied ACR classification criteria for CSS; only 3 (4%) were included based solely on Lanham's criteria. In addition, all but 1 subject fulfilled at least 1 of the following items: 1) histological proof of vasculitis, granulomatosis and/or extravascular eosinophilia; 2) positive antineutrophil cytoplasm antibody (ANCA) testing; 3) peripheral eosinophilia $>1500/mm^3$ and/or >10% of the white blood cell count.

Table 2. Characteristics at CSS diagnosis of the 78 subjects.

Criteria	All	Exposure to montelukast	
		Yes	No
Subjects, n	78	20	58
Mean age (± SD), yr	53.9 ± 13.8	51.3 ± 13.0	54.8 ± 13.9
Sex (males/females), n	43/35	9/11	34/24
Prior asthma, n (%)	76/78 (97)	20/20 (100)	56/58 (97)
Disease presentation, n (%)			
Polyposis	48/77 (62)	13/20 (65)	35/57 (61)
Sinusitis	67/78 (86)	19/20 (95)	48/58 (83)
Pulmonary infiltrate	49/78 (63)	12/20 (60)	37/58 (64)
Eosinophilic alveolitis	28/77 (36)	7/20 (35)	21/57 (37)
Alveolar hemorrhage	3/78 (4)	1/20 (5)	2/58 (3)
Peripheral nerve involvement	50/78 (64)	13/20 (65)	37/58 (64)
Cardiac involvement	30/78 (38)	6/20 (30)	24/58 (41)
Cutaneous involvement	26/78 (33)	7/20 (35)	19/58 (33)
Arthritis	12/78 (15)	3/20 (15)	9/58 (16)
Glomerulonephritis	8/78 (10)	3/20 (15)	5/58 (9)
ANCA positivity, n (%)	30/74 (41)	6/19 (32)	24/55 (44)
C-ANCA or anti-PR3*	6/74 (8)	0	6/55 (11)
Anti-MPO*	20/74 (27)	5/19 (26)	15/55 (27)
Histological proof, n (%)	45/78 (58)	11/20 (55)	34/58 (59)
Peripheral eosinophilia†, n (%)	72/78 (92)	18/20 (90)	54/58 (93)
Classification criteria satisfied, n (%)			
ACR	75/78 (96)	19/20 (95)	56/58 (97)
Lanham	44/78 (56)	12/20 (60)	32/58 (55)
Both	41/78 (53)	11/20 (55)	30/58 (52)

ACR: American College of Rheumatology, ANCA: anti-neutrophil cytoplasm antibodies, C-ANCA: diffuse cytoplasm-labeling pattern; MPO: myeloperoxidase, PR3: proteinase 3, SD: standard deviation.

*1 patient with C-ANCA and anti-MPO specificity.

†Defined as either absolute count >1500/mm^3 or relative count >10% of white blood cells.

The mean time (± standard deviation) between CSS onset and diagnosis was 3.8 ± 4.0 (median: 2.4) months. Among the 76 (97%) individuals with prior asthma, the mean interval between asthma onset and that of CSS was 92.8 ± 120.3 (median: 42.8) months. Seventeen (22%) individuals developed asthma <15 months before CSS onset.

Drug exposures

Table 3 shows the exposure rates to montelukast and the other investigated classes of asthma medications during the 15 months before CSS onset, either as total or stratified by 3-month index and control periods. Overall, the mean number of these anti-asthmatic drug classes used was 2.2 ± 1.3 (median: 2.5). Exposure rates to all 4 asthma-medication classes increased from the earliest to the latest control periods, although not in a statistically significant manner (table 3).

To investigate whether there was a secular trend in drug intake, we compared the pooled exposure frequencies during control periods stratified by time tertiles of CSS onset (July 1999–December 2000, January–December 2001 and January 2002–December 2003). This analysis demonstrated a statistically significant increase for exposure to montelukast over time (P <.0001) (table 3).

Table 3. Exposure rates for montelukast or other anti-asthmatics during the 15 months preceding CSS onset (total and individual 3-month effect periods, and stratified for the year of CSS onset).

		Montelukast		LABA		Inhaled CS		Oral CS	
		No./total (%)	P_{trend}	No./total (%)	P_{trend}	No./total (%)	P_{trend}	No./total (%)	P_{trend}
Total		20/78 (26)		51/78 (65)		57/78 (73)		43/78 (55)	
Control 4	(–12/–15 months before onset)	6/78 (8)	⎫	37/72 (51)	⎫	46/74 (62)	⎫	28/73 (38)	⎫
Control 3	(–9/–12 months before onset)	8/78 (10)		40/71 (56)		46/74 (62)		29/72 (40)	
Control 2	(–6/–9 months before onset)	9/78 (12)	.13	42/71 (59)	.09	48/74 (65)	.45	31/72 (43)	.33
Control 1	(–3/–6 months before onset)	12/78 (15)	⎭	47/72 (65)	⎭	50/74 (68)	⎭	33/72 (46)	⎭
Index	(0/–3 months before onset)	15/78 (19)		45/71 (63)		49/73 (67)		35/70 (50)	
Control exposure according to year of CSS onset									
Years 1999/2000		1/112 (1)	⎫	60/105 (57)	⎫	65/112 (58)	⎫	48/108 (44)	⎫
Year 2001		10/88 (11)	<.0001	45/81 (56)	.58	54/80 (68)	.11	39/84 (46)	.18
Years 2002/2003		24/112 (21)	⎭	61/100 (61)	⎭	71/104 (68)	⎭	34/97 (35)	⎭

CS: corticosteroids, LABA: inhaled long-acting β_2-agonists.
No./total: numbers of periods exposed/total periods.

Twenty (26%) individuals were exposed to montelukast within the 15 months before CSS onset. For 16 (80%) of them, information on montelukast intake was obtained from at least 2 sources. The average interval from starting of montelukast to CSS onset was 11.3 ± 13.8 (median: 8.4) months; the individual durations of montelukast intake against time of CSS onset are plotted in figure 2. Pertinently, 7 of these 20 individuals were not taking oral corticosteroids during the 3-month period of montelukast initiation. In addition, 7 (9%) individuals received montelukast either before the 15-month period under study (n = 3) or after CSS onset (n = 4).

Comparisons of baseline characteristics, such as organ manifestations of CSS and ANCA positivity, did not reveal any statistically significant differences between montelukast-exposed and -unexposed patients during the 15 months preceding CSS onset (table 2).

During the 3-month 'index period', immunotherapy against allergies was identified in 2 and flu vaccinations in 3 other patients; none of the 5 patients had been exposed to montelukast. Immunotherapy had been started >2 years before CSS onset.

Case–crossover analysis

Results of the case–crossover analysis are reported in table 4. In the primary analysis, exposure to montelukast and CSS onset within 3 months yielded an odds ratio (OR) of 4.5 (95% confidence interval [CI]: 1.5–13.9). Positive OR were also obtained for the other investigated classes of anti-asthmatic drugs, and, in the sensitivity analyses, for 2- or 4-month index and control periods (table 4). In a multivariate model including all 4 asthma-medication classes as covariates, the OR for 3-month periods were 6.7 (95% CI: 1.3–34.1) for montelukast, 2.9 (95% CI: 0.6–13.3) for inhaled long-acting β_2-agonists, 1.0 (95% CI: 0.2–4.8) for inhaled corticosteroids and 4.2 (95% CI: 1.2–14.6) for oral corticosteroids.

To evaluate the effect of overall long-term increased exposure to montelukast with calendar year, we calculated the OR for montelukast for 3 periods of CSS onset, as defined above. This subgroup analysis yielded an infinite OR for the earliest period (July 1999–December 2000), and OR of 2.2 (95% CI 0.5–10.9) and 2.3 (95% CI 0.3–16.7) for the 2 following periods (January–December 2001 and January 2002–December 2003), respectively. A further subgroup analysis that was restricted to the 59 (76%) subjects with a history of asthma lasting at least 15 months yielded the following OR for 3-month risk periods: montelukast 4.5 (95% CI 1.5–13.7), long-acting β_2-agonists 3.7 (95% CI 0.7–19.5), inhaled corticosteroids 0.3 (95% CI 0.05–1.8) and oral corticosteroids 5.0 (95% CI 1.4–17.4).

DISCUSSION

The results of this case–crossover analysis on 79 subjects with CSS indicate that montelukast therapy is associated with a statistically significant 4.5-fold increased risk of developing CSS within 3 months. However, use of inhaled long-acting β_2-agonists and oral corticosteroids also incurred increased risk ratios of comparable strengths for developing CSS, although only the latter reached statistical significance. Consistent effect-size estimates were obtained by sensitivity analyses for varied effect-period lengths and for the subgroup of patients whose asthma had been diagnosed at least 15 months before CSS onset. Taken together, these findings might suggest that the association with CSS onset is not specific to montelukast but a phenomenon possibly associated with the group of medications prescribed for long-term control of severe asthma.

Table 4. Risk of CSS associated with exposure to montelukast or other anti-asthmatic agents (according to a case–crossover analysis) within the 3 months preceding vasculitis onset (primary analysis) and 2- or 4-month risk-periods (sensitivity analyses).

Drug category	**3-month periods**			**2-month periods**			**4-month periods**		
	Periods Exposed, %		OR (95% CI)	Periods Exposed, %		OR (95% CI)	Periods Exposed, %		OR (95% CI)
	Index	Controls		Index	Controls		Index	Controls	
Montelukast	19	11	4.5 (1.5–13.9)	17	11	3.6 (1.2–10.5)	19	13	2.8 (0.9–8.7)
LABA	63	57	3.0 (0.8–10.5)	64	58	4.1 (1.0–16.6)	66	62	3.6 (0.7–19.0)
Inhaled corticosteroids	67	64	1.7 (0.5–5.4)	67	64	1.7 (0.5–5.7)	68	67	1.3 (0.4–4.9)
Oral corticosteroids	50	42	4.0 (1.3–12.5)	50	42	8.6 (2.2–33.3)	50	43	4.0 (1.0–15.6)

LABA: inhaled long-acting β_2-agonists, OR: odds ratio; CI: confidence interval.

The case–crossover design, as implemented here, has become widely used in pharmacoepidemiology [33]. This technique was initially devised to analyze the effect of transient exposures on acute events, but has also proved useful in the setting of prolonged exposures and events with more subtle onset [34, 35]. Because this method uses self-matching, it eliminates the risk of between-person confounding due to differences in unmeasured or unknown factors that might exist between cases and controls. However, because the case–crossover design implicitly assumes that the exposure to the risk factor under study is constant across control periods, bias could occur when there is a time trend for exposure [36].

We think that the case–crossover design enabled a more adequate assessment of a possible LTRA-associated risk of developing CSS than a traditional case–control study, especially because it avoided the difficult task of selecting a valid control group. As demonstrated by the high exposure to inhaled long-acting β_2-agonists (65%), oral (56%) and inhaled corticosteroids (73%) within the 15 months prior to CSS onset, the asthma associated with CSS is typically severe [1, 2] and that montelukast had been given to 26% of the subjects might also highlight this severity. Therefore, a traditional case–control design would run the risk of bias due to imperfect or absent matching of controls for the asthma phenotype or other unmeasured factors that may differ between asthmatics that developed CSS and asthmatic controls. Notably, this possibility of inappropriate selection of controls hampers the interpretation of a previously conducted case–control study examining the potential impact of LTRA on CSS [22]. Although that study also found an association between CSS and the use of LTRA and other anti-asthmatics, their results might be attributable to the likely milder asthma of controls that had been selected from a general asthma population.

Our results point to a different mechanism of the LTRA–CSS association than those previously proposed. In light of the sustained and general escalation of asthma therapy prior to CSS onset (table 2), the most plausible explanation for linking montelukast to it appears to be confounding by indication due to gradually worsening asthma. Albeit poorly documented, this scenario fits the concept of a prodromal phase, characterized by increasing frequency and severity of asthma attacks, before vasculitis emerges as the hallmark of CSS [28, 37, 38]. Moreover, we confirmed previous observations [7, 9] that the time from montelukast initiation to CSS onset frequently lasted many months. This long interval is indeed difficult to reconcile with the theories of a collateral drug effect, such as eosinophil chemoattraction or corticosteroid tapering ‘unmasking’ CSS, or hypersusceptibility to montelukast, because such adverse events would be expected during the early phase of first exposure [39].

Analysis of prescribing patterns for montelukast also provides insight into the observed association between this agent and CSS. In our study population, montelukast exposure rose markedly for CSS onsets from 1999 to 2003, a finding that certainly reflects the expanded use of montelukast in clinical practice following its approval in 1998. Bearing in mind the vulnerability of the case–crossover design in a situation in which the probability of exposure is time-dependent, this long-term trend may have further contributed to the observed association between montelukast and CSS onset. Indeed, OR stratified by years of CSS onset indicated a more conservative 2-fold risk for the 2 most recent periods, supporting that the overall estimate of 4.5 was inflated by the low prescription rates during the earliest phase after montelukast marketing authorization. As for any new medication, this striking secular increase in montelukast use might also have distorted the general perception of the risk associated with it.

The present study has strengths and limitations. Knowing that CSS is a highly uncommon disorder with an annual incidence of 3 per million [2], its strengths include the large number of well-characterized and *a priori* unselected individuals that credited our analyses with both generalizability of the results and reasonable statistical power. The potential of recall bias was

minimized by meticulous retracing of drug histories of a variety of anti-asthmatic agents from several independent information sources. A possible limitation remains the difficulty of defining and determining exact dates of CSS onset; however, non-differential misclassification should have similarly affected the estimates for montelukast and the other drug classes investigated. Our study must also be viewed keeping in mind its premise that CSS occurs within a definite time period after exposure to a pharmacological risk factor. Another shortcoming is that we focused only on montelukast, as it is the only LTRA approved in France and Germany. Thus, we think that the interpretations of our data could also hold true for observations of CSS development subsequent to zafirlukast and pranlukast exposure, and for those made with other asthma or allergy medications or treatments [4, 17–21, 40–42].

In conclusion, the results of this study demonstrate a close relationship between montelukast intake and acute CSS onset, and led to the hypothesis that montelukast use is a proxy measure for gradually worsening asthma at an individual level and for the important increase of montelukast exposure in general.

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COMPETING INTERESTS

None

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FIGURE LEGENDS

Figure 1. Flow-chart of the study population (numbers in parentheses refer to CSS patients identified from the French Vasculitis Study Group/the Interdisciplinary Vasculitis Center, Bad Bramstedt, respectively).

Figure 2. Timing of montelukast use for the 20/78 subjects exposed to it during the 15 months preceding CSS onset. Horizontal bars represent the exposure period plotted versus the CSS onset date (month 0), the 3-month ‘index’ period (cross-hatched) and the 3-month ‘control’ periods (grey).

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STATEMENT FOR LICENSE TO PUBLICATION

Figure 1

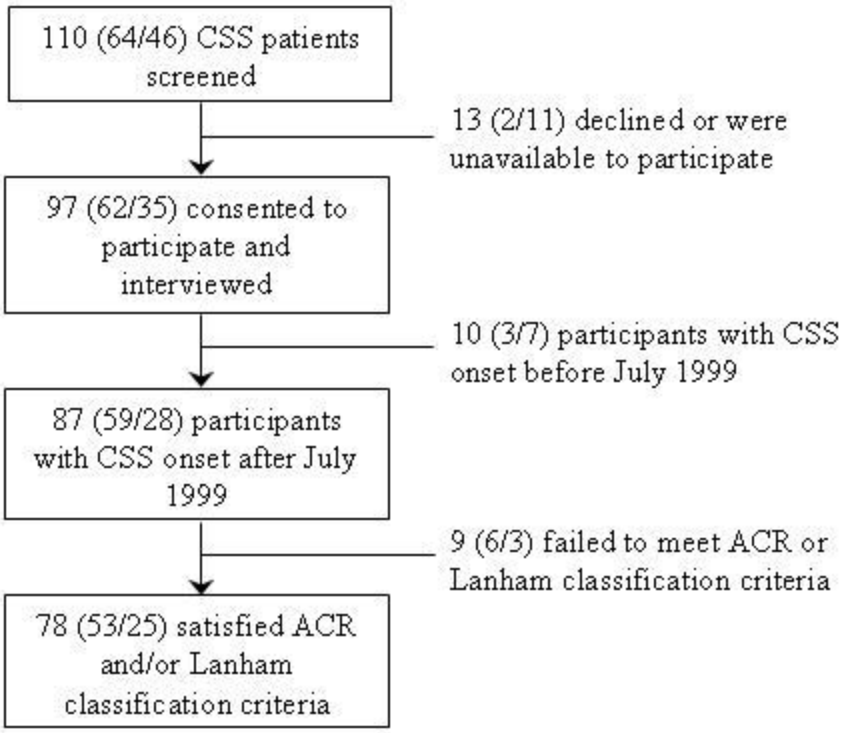
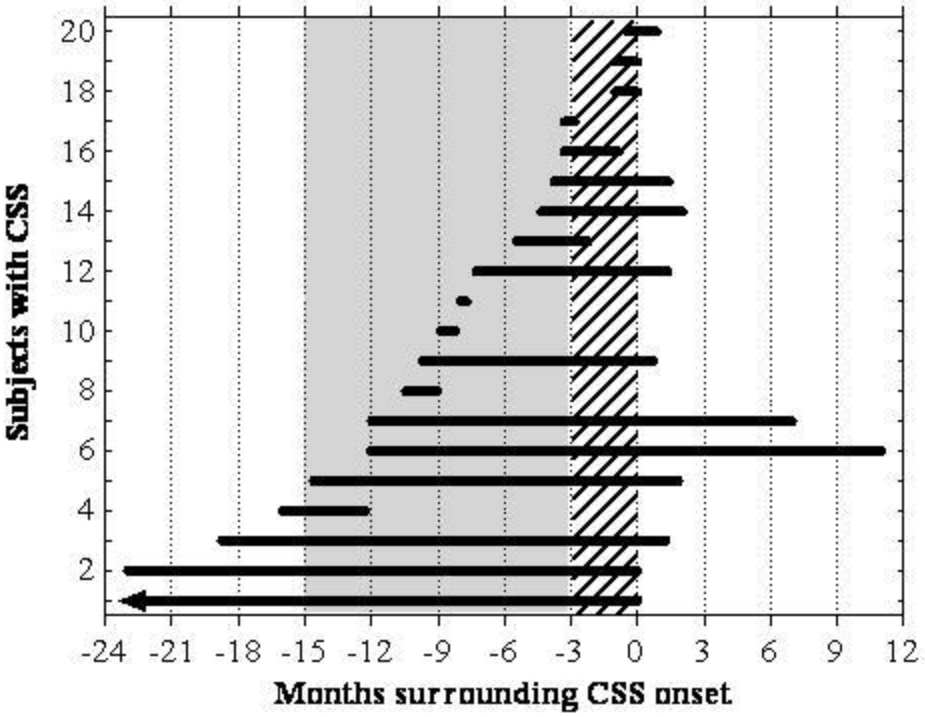

110 (64/46) CSS patients screened
13 (2/11) declined or were unavailable to participate
97 (62/35) consented to participate and interviewed
10 (3/7) participants with CSS onset before July 1999
87 (59/28) participants with CSS onset after July 1999
9 (6/3) failed to meet ACR or Lanham classification criteria
78 (53/25) satisfied ACR and/or Lanham classification criteria

Figure 2


Subjects with CSS
20
18
16
14
12
10
8
6
4
2
-24 -21 -18 -15 -12 -9 -6 -3 0 3 6 9 12
Months surrounding CSS onset