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EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS INDUCED BY MONTELUKAST

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SUMMARY – Leukotriene receptor antagonists are a class of drugs used in maintenance therapy of asthma. Among the adverse effects induced by them, particularly by montelukast, is eosinophilic granulomatosis with polyangiitis (EGPA), which manifests as a form of vasculitis co-occurring with severe asthma and eosinophilia. Our aim was to point to the importance of this particular diagnosis by analyzing the published cases of montelukast induced EGPA and to analyze them in order to identify if this form of EGPA presented some specific characteristics. Leukotriene receptor antagonist induced EGPA is a frequent adverse event compared to EGPA induced by other drugs, and specialists should be aware of it. We observed that more than half of patients were female. Montelukast induced EGPA occurred after a variable period of time. The most common clinical manifestation was neuropathy and most of the patients had a good outcome after immunosuppressant treatment. The present diagnosis should be considered by physicians when patients are prescribed montelukast followed by worsening of symptoms.

Key words: *Eosinophilic granulomatosis with polyangiitis; Eosinophilia; Montelukast; Asthma*

Eosinophilic Granulomatosis with Polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, was first described by Jacob Churg and Lotte Strauss in 1951. They named the affection as "allergic angiitis and granulomatosis", due to the similar histological findings in all the 13 cases they reviewed. EGPA is a rare form of vasculitis, affecting small and medium caliber blood vessels, accompanied by severe asthmatic manifestations and increased eosinophil count in blood and tissue[1].

The incidence of EGPA is between 0.4 and 3.4 cases/million patients yearly[2,3], and the prevalence is between 3.2 and 17.8 cases/million patients[4,5]. The exact cause of EGPA is unknown and the pathogenesis of disease is still unclear. It is supposed that EGPA is a consequence of interaction between environmental and genetic factors, which leads to an inflammatory response. Eosinophils and T and B lymphocytes seem to play a significant role in the pathogenesis of EGPA[6]. Several environmental factors may represent triggers of EGPA, such as foreign antigens or infectious agents such as *Actinomyces* that initiate an inflammatory allergic

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response in genetically predisposed individuals[7]. Other triggers that might induce EGPA are vaccinations and drugs (macrolides, carbamazepine, quinine, omalizumab, and leukotriene receptor antagonists (LTRAs) such as zafirlukast and montelukast)[8]. They contribute to eosinophil attraction and chemotaxis to inflammation sites. Thus, it will result in a notable increase in eosinophil count in blood, followed by tissue eosinophilia, infiltrating the lung or gastrointestinal tract. Vascular inflammation followed by vascular necrosis is usually found in the late stage of the disease, most probably due to the endothelial cell adhesion and activation of leukocytes, along with antineutrophil cytoplasm antibodies (ANCA)[9,10]. In 38% of cases, the presence of ANCA can be associated. Manifestations appear to be different regarding the presence or absence of the antibodies. ANCA positive patients had associated renal involvement or peripheral neuropathy, whereas ANCA negative patients presented heart disorders and fever[6].

Eosinophilic granulomatosis with polyangiitis is a systemic disorder that affects several organs and tissues. Three distinct phases are described in its evolution, i.e., allergic asthma, eosinophilic phase, and vasculitic phase[11]. In most cases, the disease onset is characterized by allergic phase, although in some cases it begins with the eosinophilic one. Both situations end with the vasculitic phase[11]. A synthesis of involvement of different organs is presented in Table 1.

Table 1. Organ involvement in eosinophilic granulomatosis with polyangiitis[11-13]

Organ involvement	Type of disorder	Incidence, %
Upper airways	Nasal polyps, allergic rhinitis, and/or chronic sinusitis	47-93
	Secretory otitis media, hearing loss, facial nerve paralysis, especially in children	
Lower airways	Lung parenchyma	66
	Peripheral migratory infiltrates	70
	Ground glass opacities	83
	Bronchiectasis	66
	Alveolar hemorrhage	3-8
Heart	Endomyocarditis	26
	Pericarditis, valvular defects, and arrhythmias	
Peripheral nerves	Peripheral neuropathy	70
	Neuropathic pain	
Central nervous system	Infarctions or cerebral hemorrhage	Very rare
Gastrointestinal tract	Abdominal pain, gastrointestinal bleeding, perforation	50
Kidney	Variable from isolated abnormalities in urinary sediment to rapid progressive glomerulonephritis	25
Skin	Palpable purpura and nodules	25
	Livedo reticularis, vesicles, aseptic pustules, petechiae, ecchymosis, and urticarial lesions	

Diagnosis is based on the clinical characteristics already described, but certain laboratory findings may permit early identification of organ involvement. Among biological findings, blood eosinophilia is marked, also being one of the main diagnostic criteria. The mean values are between 6.428 and 7.569/mm^3. Most of the patients (±80%) present positive inflammatory response with elevated C-reactive protein (CRP). The levels of both eosinophilia and CRP positively correlate with disease activity[11]. The presence or absence of ANCA is not essential for positive diagnosis as only 33% of patients are ANCA positive[7].

The American College of Rheumatology (ACR) has proposed six criteria to be used to diagnose EGPA, with a minimum of four to be present in order to assume the existence of the disease (Table 2)[14]. A positive diagnosis of EGPA needs to complete the minimum 4 of 6 abovementioned criteria.

Table 2. American College of Rheumatology diagnosis criteria for eosinophilic granulomatosis with polyangiitis, 1990[14]

Asthma
Eosinophilia
History of allergy
Mononeuropathy or polyneuropathy
Pulmonary infiltrates, non-fixed
Paranasal sinusitis

Positive histological findings can also be used in order to state the diagnosis, by an outline made at the International Chapel Hill Consensus Conference 2012[15] revised criteria established in 1990. The diagnosis can be confirmed with high sensitivity by histological samples.

In the early stage of EGPA, differential diagnosis can be a challenge for the physician due to different main manifestations in each patient. Especially before vasculitic phase, eosinophilia might give clues of a parasitic infestation, such as helminthiasis or allergic bronchopulmonary aspergillosis. Also, hypereosinophilic syndrome (ANCA negativity, higher eosinophilia and confirmed vasculitis) and other vasculitides (polyarteritis nodosa, Wegener's granulomatosis) should be excluded[16].

Montelukast Induced EGPA

Montelukast is an LTRA that is used in maintenance therapy of asthma, but also in allergic rhinitis, in both adults and children. It acts by blocking the cysteinyl leukotriene type 1 (CysLT1). Its effect is obtained through inhibition of the inflammatory mediators responsible for bronchoconstriction[17]. Even if considered a safe drug, the most common adverse events according to the summary of product characteristics are upper airway infections (in >10% of all users), fever, rash and gastrointestinal symptoms (nausea, vomiting, diarrhea) in adults, and headaches, abdominal pain and rash in children[18]. Recent studies have also reported neuropsychiatric adverse events (sleeping disorders, especially nightmares, depression and anxiety)[19]. In addition, EGPA (Churg-Strauss syndrome) may also be associated with the use of montelukast[19].

The present review analyzed the reported cases of EGPA induced by montelukast, which were published in the literature between 1999 and 2019, in order to identify if this form of EGPA has specific clinical characteristics or therapeutic outcomes.

Material and Methods

The articles included in the present review were searched using the following databases: PubMed, Web of Science, Science Direct, Scopus and Google Scholar. The search was done using the following key words: "eosinophilic granulomatosis with polyangiitis montelukast" and "Churg Strauss syndrome montelukast". A total of 166 articles were found. The papers were carefully analyzed in order to find data related to the topic of this review based on the following criteria: papers written in English and with on-point content, resulting in 47 relevant articles. Reviews and meeting abstracts were excluded from analysis. The selected articles included 33 cases. A flow chart of the selection process, including reasons for exclusion, is shown in Figure 1.

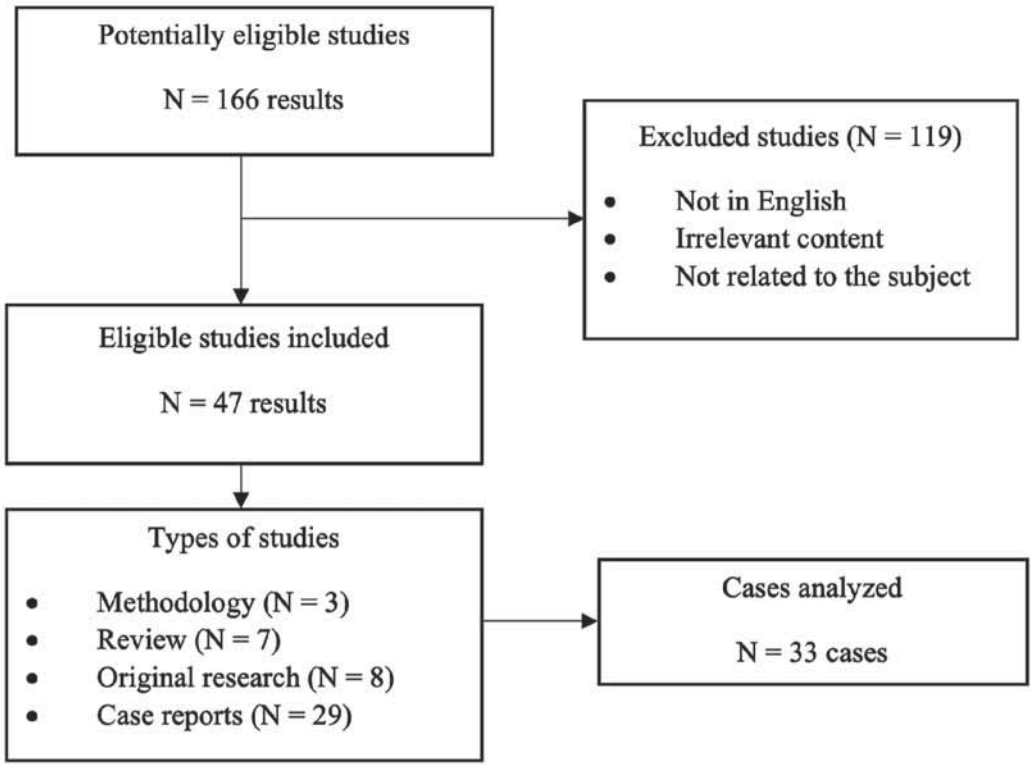

Fig. 1. Selection criteria for eligible studies.

Along with this analysis, the authors performed another one by searching for the reported cases of EGPA induced by montelukast until March 2020 in the European database of adverse events[20] and by analyzing the epidemiological data retrieved.

Results

EGPA induced adverse events reported in EudraVigilance database

Montelukast is one of the drugs involved in drug-induced EGPA[8]. Even if it is considered a safe drug, different side effects are reported in EudraVigilance database. More than eleven thousand reported side effects were correlated with montelukast usage (the exact number is 11,341 reported adverse events until March 18, 2020)[20]. From these reports, 6.58% (746 cases) were montelukast induced EGPA. But, of this number only a small number of case reports published in the literature suggested an association between montelukast use and EGPA.

Most of the reported cases in EudraVigilance[20] were observed in adults aged over 18 years (551 cases, 73.87%). Physicians were responsible for reporting adverse events in 95% of the cases, whereas 5% of the reports were done by patients. EGPA was fatal in 7 (0.95%) cases. In most situations (222 cases), the evolution was unknown, whereas 17.58% of the cases were unsolved. Only 22.55% of the cases were solved without consequences, whereas persistent sequels were reported in 16 cases. A quarter of cases were still active at the time of report[20].

Montelukast induced EGPA published cases

Analyzing the data collected from published cases (Table 3), the mean age at the onset of montelukast induced EGPA is 48.2 years. Only 2 (6.1%) cases of montelukast induced EGPA were reported in children aged below 18 years, a percentage that is lower compared to European database reports. The adverse effect occurred after a mean of 12.7 months of administration. Most of the patients were female (21 cases, 63.63%).

Table 3. Characteristics of the cases of eosinophilic granulomatosis with polyangiitis induced by montelukast

REF	Age	Sex	Months	DG	Card	Fever	ART/MY	Skin	Neuropathy	Sinusitis	EOS x10^9/L	EOS%	ANCA*	Histologic exam	Treatment/Evolution
21	37	F	<1	5	+	+	+	+	-	-	?	24%	?	Lung (+)	Inotropes, diuretics, CS/Good
22	68	M	3	4	-	+	-	-	+	-	32.6	69.8%	-	No	CS/Bad
23	50	M	4	4	-	+	-	-	-	+	6.8	40%	-	Lung (+)	CS + CYC/Good
23	50	M	4	5	+	+	-	-	+	+	9.66	46%	-	No	CS + CYC/Good
24	36	F	36	5	+	+	+	+	+	+	12.8	57%	-	Lung, Bone (+)	CS/Good
25	54	M	<1	3	-	-	+	+	+	-	14.47	57%	+	Skin. Muscle. Nerve (+)	CS + CYC/Good
25	60	F	4	4	-	-	+	+	+	-	13.54	57%	+	Skin. Muscle. Nerve (+)	CS + CYC/Good
25	62	F	<1	5	-	-	+	+	-	+	0.011	10%	+	Skin (+)	CS/Good
26	62	F	3	4	-	-	+	+	+	-	9.97	49%	?	Skin. Muscle (+)	CS + CYC/Good
26	25	M	7	4	+	-	-	+	+	-	13.3	26%	?	No	CS/Good
26	38	F	2	4	-	-	-	-	-	+	18.7	32%	+	Lung (+)	CS/Good
26	63	F	6	4	-	-	-	-	+	+	40	55%	?	No	CS/Good
27	56	M	6	3	-	-	-	+	-	-	40.9	?	-	Skin (+)	CS/Good
28	29	F	12	4	-	-	+	+	+	-	42	58%	+	Skin (+)	CS/Good
29	18	M	<1	4	-	+	-	-	-	+	1.45	15%	-	Lung (+)	CS/Good
30	72	F	<1	5	-	+	+	+	+	-	15.7	54.7%	-	No	CS/Good
31	59	F	36	4	-	+	-	-	-	+	1.95	15.6%	?	Lung (+)	CS/Good
32	61	M	28	4	-	+	+	-	+	-	13.54	61%	-	No	CS + CYC/Good
32	42	F	48	4	+	+	+	-	+	-	7.21	39%	+	Lung. Lymph node (+)	CS + CYC/Good
33	66	F	4	4	-	-	+	-	+	-	0.91	13%	+	No	CS/Good
34	40	M	1	4	-	-	-	+	-	-	11	?	-	Lung (+)	CS/Good
35	46	F	5	3	-	+	+	+	-	-	7.38	42.6%	+	Renal (+). Muscle (-)	CS/Good
36	7	F	15	4	-	-	-	-	-	+	1.18	10%	-	Lung (+)	CS/Good
37	21	F	1	3	-	-	-	+	-	-	5.96	?	+	Skin (+)	CS/Good
38	57	M	9	4	-	-	-	+	-	-	13.56	62%	-	Skin (+)	CS/Good

Table 3, etnd.

39	26	M	4	4	-	+	-	-	-	-	0.14	1%	-	Lung (+)	CS/Good
40	4	F	1	3	-	+	-	-	-	-	3.78	28%	-	Skin (+)	CS + AZA/ Good
41	59	M	24	3	-	-	+	+	+	-	1.5	14%	-	Nerve (+)	CS/Good
42	63	F	36	4	-	-	-	-	+	+	6.3	?	+	No	CS/Good
42	61	F	24	6	-	-	+	-	+	+	10.2	?	+	Skin (+)	CS + CYC + AZA/Good
43	62	F	?	3	-	+	-	+	-	-	6.24	52%	-	Skin (+)	CS + AH/ Good
44	62	F	5	4	-	+	+	-	+	-	5	38%	+	Lung, GI, Nasal (+)	CS/Good
45	77	F	15	3	-	+	-	-	+	-	4.39	30.2%	+	Renal (+)	CS/Good
	48.27%	21 F/ 12 M	12.7%	4	15.15%	48.48%	45.45%	48.48%	54.54%	33.33%	11.62	35%	42.85%*		

REF = reference number; Months = montelukast administration months; DG = diagnostic criteria out of 6; Card = cardiac manifestations; ART/MY = arthralgia and/or myalgia; EOS = eosinophilia in peripheral blood (absolute value, percentage); ANCA = anti-neutrophil cytoplasmic antibody (*level mentioned only in 28 papers); CS = corticosteroids; AZA = azathioprine; CYC = cyclophosphamide; AH = antihistamines; GI = gastrointestinal

The most frequently reported clinical manifestation is neuropathy (54% of cases). Other manifestations are fever and cutaneous manifestations (48% of patients), arthralgia or myalgia (45%), followed by sinusitis (33%) and cardiac symptoms (15%). Surprisingly, in 21.21% of the published cases, positive diagnosis was based on only 3 of the 6 criteria set by ACR in 1990[14]. Eosinophil count in absolute value was absent in one case, but the authors reported their percentage. The mean eosinophil count was 11.6, quantified in $Nx10^9/L$ system, with a mean percentage of 35% from leukocytes (where values were specified or deducitible), but in five (15.15%) cases, we could not estimate the percentage of eosinophils. In most cases (84.84%), ANCA were determined. Of the case reports that mentioned evaluating ANCA, 48.85% of the patients presented positive for this particular antibody. In 8 patients (24.24% of cases), histological examination was not performed and the diagnosis was based on other clinical and biological criteria. In more than half of the patients in whom histological examination was performed, positive results were recorded in one tissue, mainly in the lungs (8 patients), whereas in 10 cases the presence of histological changes was recorded in 2 or more tissues.

All the patients received treatment with corticosteroids, while 9 (27.27%) patients received a combination of corticosteroids and immunosuppressants such as cyclophosphamide or azathioprine. Only one patient received a triple combination consisting of cyclophosphamide, azathioprine and corticosteroids.

Discussion

Montelukast represents one of the major causes of drug induced EGPA. Even if some articles mention other drugs that could produce EGPA[8], such as carbamazepine, omalizumab or macrolides, in EudraVigilance database these cases are not reported[20]. For montelukast, more than 6% of reported adverse effects refer to EGPA, whereas no cases of EGPA are reported for carbamazepine and omalizumab. Considering the group of macrolides, out of a total of 4511 adverse events, only 1 (0.022%) case was reported for erythromycin, while there were 7 (0.038%) cases for clarithromycin and 4 (0.033%) cases for azithromycin. For other LTRAs, we noticed an increased incidence of EGPA cases (n=89, 14.08%) for zafirlukast and 19 (7.39%) EGPA cases for pranlukast[20]. These observations lead to a conclusion that LTRA induced EGPA is a frequent adverse events compared to EGPA induced by other drugs and specialists should be aware of it. Not only montelukast but also other LTRAs might induce EGPA. Given the fact that the incidence of atopic diseases is growing, prescribing montelukast is more frequent, being used mainly for asthma and off-label for atopic dermatitis or chronic urticaria. Due to this increase, the incidence of EGPA could also be increased.

The reported macrolide induced EGPA occurred in adult female patients, and 2 cases in children were only observed with the use of clarithromycin. This sex ratio is actually similar to montelukast induced EGPA, observed in the present analysis. The average duration of therapy with montelukast until the diagnosis of EGPA was 1 year (with a variation from 1 month to 48 months of treatment). In other drug induced EGPA, we noticed a similar variation. Puéchal *et al.*[46] report on the occurrence of EGPA immediately after initiation of omalizumab therapy, while Borekci *et al.*[47] noticed the characteristic symptoms of EGPA after 7 years of omalizumab usage. The specialists who prescribe montelukast for asthma should be aware of this possible side effect that might occur at any moment of evolution. Paradoxically, asthma is also the cause of this disease due to its treatment, and its worsening is an auto amplified effect. Asthma represents actually the first phase of EGPA evolution.

The positive diagnosis of EGPA is based on clinical signs and symptoms, and it is confirmed by laboratory test and histological examination. In the present analysis, the minimal 4 diagnostic criteria were present in only 79% of cases, but in the remaining cases diagnosis was confirmed by histology. Histological examination was performed only in 75.76% of cases. It was not a necessity that should be met to establish the positive diagnosis based on the ACR criteria.

Sinusitis was reported in almost one-third of the cases, while in general, patients with EGPA more frequently reported upper respiratory symptoms. The most frequently observed clinical manifestation was peripheral neuropathy in more than half of the patients, less than in other forms of EGPA. All patients presented asthma as a positive criterion because they received montelukast for asthma treatment. Probably in montelukast induced EGPA, diagnosis is more easily reached because some of the criteria are already

present when therapy with montelukast is initiated (asthma, allergy).

Eosinophilic granulomatosis with polyangiitis is a diagnosis that can have an infaust prognosis if untreated, as the range of manifestations is broad. Most of the patients (97%) had a good outcome after corticosteroid ± immunosuppressive therapy (cyclosporin or azathioprine). Attention should be directed towards neurological symptomatology due to incomplete or absent recovery after treatment. There are no data regarding the percentage of recovery of neurological symptoms. Analysis of data from EudraVigilance database showed that less than a quarter of patients recovered without sequels, but in most cases chronic evolution was unknown.

Among those that used montelukast along with glucocorticoid therapy, EGPA symptomatology was sometimes masked until the corticosteroids were discontinued, probably due to the immunosuppressant effect of this category of drugs.

Conclusion

Montelukast frequently produces EGPA as an adverse reaction. This side effect occurs mainly in adult female patients after a variable period of treatment. Physicians should keep in mind this diagnosis when an asthmatic patient presents sudden worsening of symptoms, especially after being recommended to start treatment with this particular LTRA. Asthma treatment should be established based on the Global Initiative for Asthma (GINA) guideline recommendation last updated in 2019, avoiding large use of LTRAs.

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Sažetak

EOZINOFILNA GRANULOMATOZA S POLIANGIITISOM IZAZVANA MONTELUKASTOM

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Antagonisti leukotrienskih receptora su razred lijekova koji se primjenjuju u terapiji održavanja kontrole astme. Jedna od nuspojava, osobito montelukasta, je eozinofilna granulomatoza s poliangiitisom (EGPA) koja se manifestira kao oblik vaskulitisa koji se pojavljuje zajedno s teškom astmom i eozinofilijom. Naš je cilj bio ukazati na važnost ove dijagnoze te analizirati objavljene slučajeve EGPA izazvane montelukastom kako bismo utvrdili pojavljuje li se ovaj entitet uz neke posebne karakteristike. EGPA izazvana antagonistima leukotrienskih receptora je razmjerno česta u odnosu na EGPA izazvanu drugim lijekovima, čega bi liječnik specijalist trebao biti svjestan. Uočili smo da je više od pola bolesnika ženskog spola, a vrijeme izazivanja EGPA nakon primjene montelukasta je različito. Najčešća klinička manifestacija je neuropatija, a većina bolesnika imala je dobar ishod uz imunosupresivnu terapiju. Liječnici trebaju imati na umu ovu dijagnozu u slučaju pogoršanja simptoma nakon propisivanja montelukasta.

Ključne riječi: *Eozinofilna granulomatoza s poliangiitisom; Eozinofilija; Montelukast; Astma*