Montelukast as a treatment modality for eosinophilic gastroenteritis

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Abstract

Eosinophilic Gastroenteritis (EG) is a rare condition, caused by eosinophilic inflammatory infiltrates in the gastrointestinal tract. It is usually treated successfully with systemic glucocorticoids. Because of frequent relapses, however, there is need for alternatives.

We describe a 38-year old man with steroid-dependent EG, who was successfully treated with montelukast, a leukotriene receptor antagonist. It inhibits leukotriene D4, an important cytokine in the inflammatory cascade. Although montelukast could not replace steroid therapy, it acted as a steroid sparing agent in our patient.

Review of the literature shows that montelukast is efficient in the treatment of EG in a part of the patients. The low cost, the low number of side effects and its efficiency make it an interesting alternative in relapsing or steroid dependent EG. There is need for multicentric studies regarding the treatment of EG. (Acta gastro - enterol. belg., **2011**, 74, **570-575**).

Key words : eosinophilic infiltrates, gastrointestinal tract, inflammation, corticosteroids, treatment, montelukast.

Introduction

Eosinophilic gastroenteritis (EG) is a rare condition, which was first described in 1937 by Kaijser (1). The incidence was estimated to be approximately 1 in 100.000 (2), but this could be an underestimation because the condition is relatively unknown and the diagnosis requires invasive investigation. A recent paper counted 59 patients reported in the literature in the last 20 years in the Mayo clinics (3). Histologically the disease is characterized by eosinophilic infiltrates within the digestive tract. The clinical presentation depends on the anatomical and histological localisation of the infiltrate (see table 1).

Table 1. — **Clinical presentation of esosinophilic gastroenteritis according to histological eosinophilic infiltrate localisation (4)**

Mucosal type :	abdominal pain, nausea and vomiting, diarrhea, gastrointestinal bleeding, malabsorption
Muscularis propria type :	symptoms and signs of obstruction like abdominal pain, abdominal distension, (faecal) vomiting
(Sub)serosal type :	ascites, high peripheral eosinophilia

EG needs to be differentiated from several other conditions, which also involve blood eosinophilia. Talley *et al.* (4) proposed a number of criteria in order to validate the diagnosis : [1] presence of clinical symptoms consistent with EG, [2] a biopsy with eosinophilic infiltrates in one or more sites in the digestive tract or characteristic radiological findings with peripheral eosinophilia, [3] without evidence for other diseases. Table 2 shows a summary of possible differential diagnoses.

In EG, symptoms are caused by inflammation that is propagated by eosinophilic infiltrates. Activated eosinophils release their granules creating a cytotoxic environment and attracting more eosinophils through multiple inflammatory agents.

In this article, we describe a patient with EG who was successfully treated with montelukast. We give a short overview of the current treatment options with the purpose to define the position of montelukast in the therapeutic spectrum.

Case history

A 38-year old man, known with a transmural type of EG for 16 years, presented at the consultation. He was diagnosed with EG on a surgical biopsy of the duodenum, which showed important tissue eosinophilia beginning in the lamina musculosa and extending to the lamina serosa.

He had symptoms consistent with gastric outlet obstruction. He had a medical history of abdominal complaints since the age of 7, relapsing pancreatitis, laparoscopic cholecystectomy, gastro-intestinal reflux disease and auto-immune hypothyroidism (presence of positive TPO- antibodies).

In the past, he was treated with methylprednisolon, in varying doses depending on disease activity. Ten years after the first diagnosis, an attempt was made to

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Submission date : 03/01/2011
Acceptance date : 14/02/2011

Table 2. — **Differential diagnosis of gastrointestinal eosinophilia**

Primary EG :
- idiopathic
- familial

Others (including secondary causes of EG) :
- infections : helminthic, H. Pylori, tuberculosis
- drugs : acetylsalicylic acid, azathioprine, enalapril, carbamazepine, clofazimine, cotrimoxazole, gold salts
- auto-immune disorders :
  - vasculitis : Churg-Strauss syndrome, poly-arteriitis nodosa
  - other : dermatomyositis, polymyositis, sclerodermia, celiac disease
- inflammatory bowel disease : morbus Crohn, ulcerative colitis
- neoplastic disorders : hypereosinophilia syndrome, lymphoma
- eosinophilic oesophagitis or colitis
- intestinal eosinophilia after solid organ transplantation
- food allergy

completely taper off corticosteroid (CS) treatment by associating azathioprine 150 mg and lansoprazol 30 mg. At that time he was taking 4 mg methylprednisolon daily. During one year, several attempts were made to diminish this dose, but the patient relapsed frequently requiring higher doses methylprednisolon with a maximum of 32 mg. Imuran was stopped and the patient continued to take CS during several years, in fluctuating doses according to his symptoms.

Now, again 6 years later, he presented at the consultation and asked for alternatives for his long lasting CS treatment. At that time he was taking methylprednisolon 16 mg, sulpiride 50 mg, levothyroxine 150 µg, omeprazol 40 mg daily and had no complaints. Clinical examination showed no abnormalities. Biochemistry (Table 3) revealed a normal eosinophil count, elevated white blood cell count probably due to steroid treatment and elevated pancreatic tests. Montelukast 10 mg was added to his daily therapy.

During the following months, the patient did not have any serious relapses of EG and could successfully keep the steroid dose at 4 mg methylprednisolon daily. Montelukast 10 mg was continued and the patient attempted to completely taper off CS, which failed.

He then continued on a maintenance treatment with methylprednisolon 4 mg and montelukast 10 mg daily. During the following year, he only had 4 days of abdominal complaints which were effectively treated by doubling montelukast to 20 mg daily.

In our patient, association of montelukast was effective as a steroid-sparing agent, but could not completely replace CS treatment. It was also effective in symptom control since the patient experienced much less exacerbations. Additionally, during exacerbations, doubling of the montelukast dosage was effective, with no need to augment CS.

Table 3. — **Laboratory results**

Test	Result	Units	Reference range
Hemoglobin	15.5	g/dL	14.00 – 18.00
WBC count	10.42	109/L	4.00 -10.00
Neutrophils	80.1	%	38.0 – 77.0
Eosinophils	0.0	%	< 6.0
Lymphocytes	14.0	%	20.0 – 50.0
Basophyls	0.1	%	< 1.0
Monocytes	5.8	%	2.0 – 10.0
Blood platelets	368	109/L	150 – 450
CRP	<1.0	mg/L	<= 5.0
Ureum	41	mg/dL	<= 50
Amylase	124	U/L	28 – 100
Lipase	110	U/L	13 – 60
ALT	34	U/L	<= 41
AST	(16)	U/L	<= 38
Gamma GT	29	U/L	<= 53

Discussion

Corticosteroids

Systemic corticoids are the current standard treatment of EG (4-8). Systemic CS (e.g. methylprednisolon) are most commonly used. Treatment is best started at an intermediate dose (20-60 mg), which then needs to be gradually tapered off. When relapse occurs, the CS dose is commonly raised again to the starting level. In most cases quick remission is attained, even in the case of relapse after initial remission. The rationale behind the effectiveness of CS are their multiple points of action : they inhibit eosinophilic growth factors IL-3, IL-5 and GM-CSF, diminish production of chemokines and induce apoptosis (2,9).

Budesonide has also been used to treat EG. It has a high first-pass effect and therefore fewer systemic side effects. If the inflammation involves the duodenum, stomach or oesophagus, non-enteric coated tablets need to be used. If, however, the lesions are further down the gastro-intestinal tract, use of enteric coated tablets is advised.

Long term treatment with CS has several well-known side effects : immunosuppression, gastroduodenal ulcers, induction of glucose intolerance and dysregulation of diabetes, osteoporosis, cushingoid appearance, myopathy,

growth retardation, mineralocorticoid effect and hypertension. The side effects increase with dose and duration. Because of the high doses, the frequent relapses and possible long term effects, the adverse effects should always be taken into consideration when starting CS therapy. Especially in children or in patients with other relative contraindications, alternatives to CS therapy may be of value. When primary treatment with CS fails and in case of frequent relapses after or during tapering off steroids, association with other pharmacological treatments is indicated.

Diet

Many patients with EG have atopical complaints, or have a personal or family history of atopy (10). In case of proven food allergy, an elimination diet is the preferred treatment (11). A number of studies focus on this aspect : Chehade *et al.* (12) and Justinich *et al.* (13) report successful treatment of EG by elimination diets. RAST-tests and skin-prick tests can detect a sensitization to food allergens, but elimination of these suspected allergens does not always prove to be sufficient. When specific elimination diets fail, an elementary diet can be attempted (2).

Other treatments

Treating eosinophilic disorders by monoclonal anti-IL-5-antibodies (*mepolizumab*) seems a promising approach, because of the central role played by IL-5 in the pathophysiology of these disorders. Garrett *et al.* (14) and Stein *et al.* (15) have successfully tested mepolizumab as treatment for eosinophilic esophagitis, whereas it has also been used in asthma, hypereosinophilic syndrome and atopic dermatitis (16). Mepolizumab treatment is currently under investigation by the European Medicines Agency (EMA) for hypereosinophilic syndrome in children.

Omalizumab, a monoclonal antibody specific for free circulating IgE, was tested in 9 patients with eosinophilic gastrointestinal diseases (EGID's) (17,18). It proved to reduce the absolute number of plasma eosinophils and to improve symptoms. Omalizumab is commercially available as "Xolair" in Europe. It is relatively expensive and needs to be administrated subcutaneously.

Shirai *et al.* treated a 55 year old woman with EG successfully with *suplatast tosilate*, a selective TH2-cytokine-inhibitor (19). The exact working mechanism is not yet known (20-22). It blocks eosinophil chloride-channels, inhibits the transcription of IL-4 and the expression of the histamine-1 receptor. This molecule is only available in Japan, where it is mostly used for asthma.

Sodium cromoglycate is a well known agent which was frequently prescribed as treatment for asthma and is currently still indicated for exercise-induced asthma. The working mechanism is unknown so far, but it is commonly described as a mast cell stabilisator. It's use has been reported in 3 patients with EGID (23,24). Both authors describe an excellent clinical response, with disappearance of tissue eosinophilia in all 3 patients.

Immunosuppressive agents have also been prescribed for EGID's (25,26) : *azathioprine* proved to be efficient in 2 case reports. All patients were able to remain of CS, but 1 in 4 patients had serious nausea with azathioprine, which was then successfully replaced by *6-mercaptopurine*. Both agents can have serious side-effects like leucopenia and pancreatitis.

Ketotifen is an H1-antihistaminic agent which also proved to be efficient for EG (27,28) : in a study by Melamed *et al.*, all patients experienced a good clinical response and 5 of 7 patients had a complete disappearance of eosinophilic infiltrates on repeated endoscopic biopsies.

Another targeted, biological therapy could aim at the *CCR3-receptor for eotaxine*, because of it's central role in recruiting eosinophils (29,30). So far, there are no licensed molecules targeting CCR3. *Bertilimumab*, a monoclonal antibody against eotaxine-1, is currently under investigation (31).

Montelukast

Montelukast is a selective leukotriene receptor antagonist which binds twice as efficient as the natural ligands LTC4, D4 and E4 to the type 1 cysteinyl leukotriene receptors. By inhibition of the signaling of this receptor, it causes a diminished microvascular hyperpermeability, chemotaxis (mainly for eosinophils), mucus hypersecretion, neuronal stimulation and smooth muscle cell contraction (32).

We searched the Medline database with the following entry terms : "Montelukast", "Eosinophilic gastroenteritis" and "Eosinophilic oesophagitis", where possible we used "medical subject headings" (MeSH). Within the retrieved manuscripts the references were checked for additional relevant publications. In total we found 9 clinical studies in which the use of montelukast in EGID's was described (see table 4).

The largest study, by Friesen *et al.* (33), is a double blind randomised clinical trial with cross-over design. The relatively young study population consists of patients with dyspepsia and duodenal eosinophilia. In this study, Friesen *et al.* showed that montelukast was most efficient for symptom control in patients with a tissue eosinophilia higher then 20 per high power field (HPF). Response rate was 68%, in comparison with 32% responding to placebo ($p = 0,01$). An elevated plasma eosinophilic cationic protein (ECP) was also a good predictor for response (88% versus 55%, $p = 0,095$), but a normal ECP did not exclude response.

In a second study 4 years later, Friesen *et al.* (34) included 18 patients with a duodenal eosinophil peak number of more than 20 per HPF. Of these patients, 83% had a partial or complete response. After 3 weeks of treatment the patients underwent gastroduodenoscopy

Table 4. — **Use of montelukast in EGID's**

Author	Form	Condition	N =	Age (years)	Daily dose (mg)	Duration
Friesen et al. (33)	RCT	DED	37	6-18	10	2 w
Friesen et al. (34)	Clinical trial	DED	18	8-17	10	3 w
Daikh B et al. (35)	Case report	EG	1	25	20-30	5 m
Copeland B et al.(25)	Case report	EG	1	31	10	NA
Urek MC et al. (36)	Case report	EG	1	18	10	6 m
Quack I et al. (37)	Case report	EG	1	17	10	2 y
Schwartz et al. (38)	Case report	EG	1	27	10	20 m
Neustrom and Friesen (39)	Case report	EG	1	13	10	4 m
Vanderhoof et al. (40)	Case series	EG and EO	8	2-17	5-10	NA

N : number, RCT : randomised clinical trial, DED : duodenal eosinophilia and dyspepsia, EG : eosinophilic gastroenteritis, EO : eosinophilic oesophagitis, NA : not available, w : week, m : month, y : year.

with biopsy. Surprisingly, the patients responding to the treatment with montelukast, did not show a decrease in tissue eosinophilia density or activity.

Daikh *et al.* (35) describe a CS-dependent patient known with EG for 20 years, complicated by an oeso - phageal stricture with dysphagia. During a 5 months treatment with montelukast there was no clinical response.

In another case report Copeland *et al.* (25) also found no improvement with montelukast in monotherapy. After starting methylprednisolon and lansoprazole the patient quickly became asymptomatic. Imuran was successful for completely tapering off CS.

In 4 other case studies however, there was a good clinical response to treatment with montelukast. In 3 of the reported patients montelukast was added to a treatment with CS because of frequent relapses after tapering off CS (36-38). In the fourth case the patient had not yet been treated with CS (39). After 2 months of treatment with montelukast in monotherapy she still was asymptomatic, with a normal plasma eosinophilia.

In a brief article by Vanderhoof *et al.* (40), the use of montelukast in 8 children with EG and EO is described. There was significant improvement of symptomatology in all patients. There was no description of patient characteristics, diagnostic methodology, treatment duration or patient follow-up.

As shown in table 4, most papers on the use of montelukast in EG are case reports. There are 2 studies in which a larger number of patients have been randomised, both from Friesen *et al.* (33-34). These publications involve young children and adolescents, which the authors define as patients with dyspepsia and duodenal eosinophilia on endoscopic biopsy. According to the criteria from Talley *et al.* (4), the diagnosis of mucosal EG could be made in these cases. There are however a few considerations to keep in mind : [1] with regard to the low prevalence of EG, it is unlikely that typical EG was present in all 40 patients who were recruited in less then 7 months, in only one centre. [2] Friesen *et al.* used a duodenal eosinophilia of more then 10 eosinophils per HPF in their inclusion criteria. Talley *et al.* (4) did not mention any cut-offs as to define tissue hypereosinophilia. The cut-off value is currently still a matter of debate in literature, but several authors define it as 20 eosinophils per HPF (41-42). Although in the first study by Friesen *et al.*, their criterion was 10 eosinophils per HPF, yet 81% of the patients had values of over 20 per HPF. Moreover, the best response on montelukast was in patients with values over 20 per HPF. [3] Last but not least, because only endoscopic biopsies were taken, only mucosal type EG was included in these 2 studies. It cannot be excluded that findings could be different in mural or subserosal EG. Therefore, their results may not just be extrapolated to all EG patients.

From the studies mentioned in table 4, it is suggested that montelukast is an effective treatment modality in EG. It is however not always effective : Daikh (35) and Copeland (25) found no improvement using montelukast. Also in our case, the patient could not completely taper off steroids.

Friesen *et al.* (33-34) demonstrated that montelukast was able to induce a significant clinical response, but the eosinophilic infiltrate tended to persist. Other authors came to the same conclusion (25,36). A possible explanation could be that LTD_4 is only one step in the inflammatory cascade ; the eosinophilic infiltrate keeps being stimulated by other cyto- and chemokines. This could also explain why montelukast is not efficient in all patients. Higher doses could however result in better outcomes (43).

Montelukast has only few adverse effects, the most common being headache with a percentage comparable to placebo (44-46). In a recent report from the US Food and Drug Administration, a number of neuropsychiatric effects were described in association with the use of leukotriene-inhibitors (47). These events include cases of aggression, hallucinations, fear, depression and suicidal thoughts and behaviour. Also Wallerstedt *et al.* found different reports of neuropsychiatric events related to montelukast in a Swedish database (48). Following these reports, different studies could not find a relation between montelukast and neuropsychiatric events (49-53). It is unknown by which mechanisms montelukast should cause neuropsychiatric symptoms.

A rare complication associated with montelukast is the Churg-Strauss syndrome : a systemic vasculitis

which presents with asthma and polyposis nasi, eosinophilia and vasculitis of the lungs, kidneys, skin, neural system and other organs. Currently, over 100 cases of a montelukast-associated Churg-Strauss syndrome have been described (54-56), but no causal relationship has been found so far. A possible explanation might be the increased use of montelukast in patients with asthma and also in those in whom the asthma is the first symptom of a developing Churg-Strauss syndrome.

There are no formal contra-indications besides previous anaphylaxis to montelukast (57).

Conclusion

CS are the most efficient treatment for EG. Because of the many side effects associated with their use, CS dependency or frequent relapses after CS tapering, alternatives are needed. From the pathophysiology of EG, several targets can be identified for more directed, alternative treatments.

In the current literature there is some evidence for the use of montelukast, a leukotriene receptor antagonist. As demonstrated in our own case, montelukast can be efficient as a CS sparing agent in CS dependent EG. Different studies show it can also be used as a primary treatment.

Finally, we would like to point to the need of a uniform definition to diagnose EGID's. Also, multicentric studies regarding EG treatment would be useful to obtain more reliable data for evidence based practice guidelines.

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