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CASE REPORT

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Combination therapy using fexofenadine, disodium cromoglycate, and a hypoallergenic amino acid-based formula induced remission in a patient with steroid-dependent, chronically active ulcerative colitis

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Abstract Corticosteroids and 5-aminosalicylic acid are the primary standard therapy for inflammatory bowel disease. Recent immunologic data implicate an involvement of mast cell activation followed by increased histamine secretion and elevated tissue concentrations of histamine in the pathogenesis of ulcerative colitis. In the present case, the clinical course of a 35-year-old man with steroid-dependent chronic active ulcerative colitis, who did not respond to high-dose steroids, antibiotics, or azathioprine during 3 years, is reported. Clinical disease activity and established serological markers were recorded during 6 weeks of unsuccessful therapy and during the next 6 weeks, as a new nonsedative antihistaminergic drug, a mast cell stabilizer, and an hypoallergenic diet were implemented in addition to conventional therapy. Induction of remission was achieved within 2 weeks after treatment with fexofenadine, disodium cromoglycate, and an amino acid-based formula. Clinical disease activity, stool frequency, leukocytes, c-reactive protein, and orosomucoid levels in serum decreased rapidly. Daily steroid administration could be gradually reduced along with 6 weeks of this treatment. This report suggests that histamine and mast cell activity may be important pathophysiological factors responsible for persistent clinical and mucosal inflammatory activity in ulcerative colitis despite the use of steroids. In ulcerative colitis, patients unresponsive to conventional treatment, therapeutic considerations should also include an antiallergic approach when further signs of atopy or intestinal hypersensitivity are present.

Keywords Ulcerative colitis · Steroid dependency · Mast cells · Antihistamines

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon and rectum, mostly leading to watery or hemorrhagic diarrhea, anemia, fever, weight-loss, and occasionally to toxic megacolon. In inflammatory lesions of UC, several highly activated immune cell types have been described, including CD4-positive TH2 cells, CD14-positive macrophages, as well as degranulating neutrophils, mast cells, and eosinophils [1–3]. Current immunologic findings favor an exaggerated TH2 immune cell response in UC producing high levels of immunoregulatory cytokines such as interleukin 1, 2, 5, 13, and TNFalpha in gut mucosa [3, 4].

In colonic mucosa, not only simple arachidonic acid metabolites (prostaglandins, leucotrienes, thromboxane) and biogenic amines like histamine have been detected as inflammatory and tissue damaging compounds in UC, but also several other profound proinflammatory agents like complement factors C3a and C5a, neuropeptides like substance P, nitric oxide, eosinophilic cationic protein (ECP), myeloperoxidase (MPO), and interleukin 8 or reactive oxygen metabolites [2, 3, 5]. Their relative contribution, however, to the increased inflammatory and

clinical disease activity remains unclear. One major problem around all mediator investigations is to adequately estimate the pathogenic role of a sole mediator in the complex disease field of UC. Therefore, therapies using specific antagonists for each mediator are required to clarify their pathogenic significance. Leucotrienes, for example, have long been assumed to be important disease inciting mediators in UC, but administration of lipoxygenase inhibitors or leucotriene receptor antagonists has revealed disappointing results in UC patients [5, 6]. As recently suggested from studies yielding negative results using leucotriene- or platelet activating factor-inhibitors, one or several other (primary) mediators may be responsible for disease induction or maintenance in UC [5–7].

Therapeutic antagonism of a single inflammatory mediator in UC has thus been supposed to be ineffective to achieve clinical remission [3, 5]. However, the present case of a 35-year-old man with steroid-dependent active UC provides clinical data that some patients with UC may have significant benefit from a therapy focussing on mast cell stabilization and histamine antagonism.

Case report

Patient under discussion

A 35-year-old physicist (H.J.), was diagnosed to have UC in 1997 after developing anemia and slimy to bloody diarrhea. Initial diagnosis was made by history, physical examination, laboratory as well as endoscopy. Histology showed primarily continuous inflammation from the rectum to the ascending colon with dense inflammatory infiltrates, plasmocytosis, formation of crypt abscesses, multiple erosions, and ulcerations.

The patient's history also revealed the existence of a panic disorder with frequent episodes of excessive anxiety attacks and concomitant vegetative cardiopulmonary reactions (cold extremities, pallescence, tachycardia, hypertension, dyspnea, perspiration, and dizziness) along with manifestation of UC. The panic disorder forced the patient to interrupt his personal career as a physicist and different medications with selective serotonine reuptake inhibitors (citalopram, mirtazepam), benzodiazepines (alprazoloam, bromazepam), antidepressants (doxepine), and a selective beta-receptor blocking drug (metoprolol) were tried. Since adolescence, the patient experienced several allergic reactions in the oral cavity, eyes, and nose after exposure to several tree pollens, hazelnut, and various fruits (apricot, banana), but a complete allergen avoidance was not performed.

Before admission in April 1999, the patient had received three unsuccessful acute phase therapies with prednisolone (each course starting with 60 mg prednisolone daily), which failed to achieve long-term remission, as the patient was not able to taper steroids after 12 to 14 weeks below 10 to 7.5 mg per day. Therefore, in December 1998, an immunosuppressive therapy with azathioprine was introduced. Due to intolerance, azathioprine had to be withdrawn (nausea, vomiting, and abdominal pain). Subsequently, treatment with ciprofloxacine (2×500 mg/die) and metronidazole (3×400 mg/die) was started, but turned out to be ineffective to achieve clinical remission. 5-Aminosalicylic acid (mesalamine) was given in high doses of 4 g daily throughout the entire period after diagnosis of UC had been established.

In April 1999, actual complaints of the patient (183 cm, 56 kg) included persistent hemorrhagic stools, moderate abdominal postprandial pain and tenderness, anemia with a hemoglobin level of 10.8 g/dl, and weight loss of 2 kg within the last 4 weeks. Colitis activity index according to Rachmilewitz (CAI [8]) revealed nine points. At the time of admission, the patient's treatment included 40 mg prednisolone daily and 4 g of 5-aminosalicylic acid for more than 4 weeks (Fig. 1).

Physical examination showed hypertension (172/105 mmHg) and a heart rate of 97 beats/min, slight abdominal pressure pain on provocation in the left and right lower abdomen, normal intestinal peristalsis, and no edema. The patient presented with a cushingoid, pale aspect (without exsiccosis), but with moderate steroid acne. Rectal digital examination remained inapparent, but the stool had traces of blood.

Despite the above listed therapeutic regimen, laboratory findings again revealed chronic active disease with an elevated white blood cell count (12,500 leukocytes/μl;

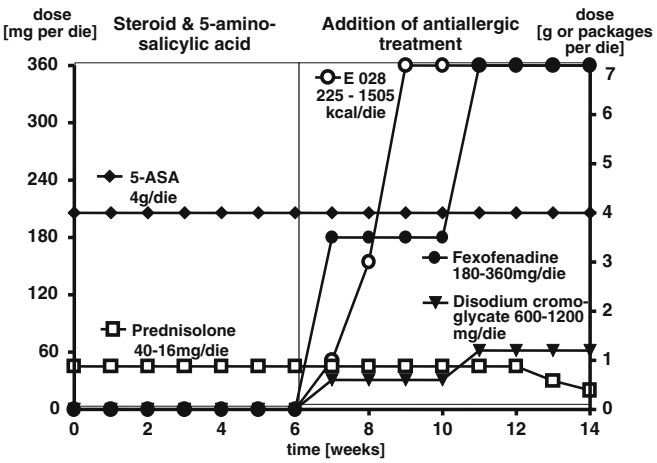

Fig. 1 Time course of drug application in steroid-dependent chronic active ulcerative colitis. Despite a daily application of 40 mg prednisolone and 4 g 5-aminosalicylic acid (5-ASA) no clinical response was obtained in the 35-year-old patient with chronic active ulcerative colitis. After having ruled out infectious complications or other diseases responsible for exacerbation of colitis, an antiallergic trial with fexofenadine, disodium cromoglycate, and an amino acid-based formula was started. Because application of this regimen showed rapid clinical effectiveness and revealed no side effects, a further increase of each therapeutic principle was performed as depicted in Figure 1

13% stab cells), c-reactive protein levels of 77 mg per litre (normal <1 mg/l), an orosomucoid level of 1,910 mg per litre (normal <1,200 mg/l) and a serum iron level of 44 μg/dl (normal 60–160 μg/dl). Infectious colitis was excluded by three negative stool cultures for salmonella, shigella, yersinia, campylobacter, lambliasis, ova, parasites, and clostridium difficile toxin A. Immunologic parameters revealed normal immunoglobulin levels for IgG, IgA, IgM, but elevated serum IgE concentrations (170 U/ml, normal <100 U/l). Food-specific IgE was not detected because of long-term steroid treatment. Anti-DNS antibodies, antinuclear antibodies, and anticardiolipin antibodies were negative, whereas anti-neutrophilic cytoplasmic antibodies were slightly elevated (3.2 U/ml, normal <2 U/ml).

Transabdominal ultrasonography was suggestive of steatosis of the liver. Upper gastrointestinal endoscopy showed a few hematin spots in the stomach (histologically normal stomach mucosa devoid of helicobacter pylori). Histologic evidence for Crohn's disease or other diseases of the small bowel could not be detected. Endoscopy of the lower gastrointestinal tract showed continuous chronic active pancolitis with friable mucosa, edema, erythema, and numerous superficial ulcerations and some pseudopolyps. Histology, performed by routine hematoxylin–eosin stain, revealed chronic active disease in all segments of the colon with a pronounced inflammatory cell infiltrate, many crypt abscesses, subtotal, but marked distortion of the mucosa, partially with necroses, and several ulcers. Samples from the terminal ileum were free of inflammation, but showed slightly elevated numbers of eosinophils. Eosinophil counts in the colon, as established by semiquantitative analysis, were moderately elevated.

Measurement of bone mineral density by dual X-ray absorptiometry using a total body scanner (DPX-L, Lunar, Cologne, Germany) at the lumbar spine (L2–L4) and femoral neck showed markedly reduced bone mass (88% of peak bone mass) with T- and Z-score levels of −1.2 and −0.8 or −1.9 and −1.5, respectively. X-ray of the lumbar spine found fractures of the vertebral body L1–L3 consistent with severe osteoporosis.

Therapeutic considerations and antiallergic treatment

Because of several marked steroid side effects, the patient was subsequently counseled for therapy with cyclosporine A. When discussing with the patient known side effects of cyclosporine A (hypertension, increase of serum creatinine or renal failure, paresthesia, electrolyte disturbances, etc.), the patient refused a therapy with this immunsuppressant because he feared the occurrence of several symptoms like hypertensive episodes, palpitations, or paresthesia from his panic disorder. An intensification of the yet ineffective prednisolone therapy was also not justified in view of the severe osteoporosis in the 35-year-old man. Therefore, other treatment options had to be considered.

Because the anxious patient could only tolerate a few foodstuffs (potato, rice, lamb), an amino acid-based formula (Elemental 028, Pfrimmer-Nutricia, Erlangen, Germany) was chosen as an adjunctive dietary supplement to maintain sufficient calory intake. This hypoallergenic formula was initially diluted with tea (1:1 v/v) and very slowly applied by a nasogastric tube. The dose of the amino acid preparation was gradually increased from one package per day (125 ml, 215 kcal) up to seven packages daily after 2 weeks, thus accounting for approximately 1,500 kcal daily. As the general condition showed significant improvement, the nasogastric tube could be removed and the amino acid-based formula was continued orally along with well-tolerated foods.

In addition, taking his elevated serum IgE level, several adverse reactions to foods and the slight eosinophilia in colonic mucosa into account, the decision was made to start a treatment with an antihistamine and disodium cromoglycate [9–17] as a potential therapeutic trial. Exacerbations of UC have been associated with foodstuffs previously [17–21]. There were no other established therapeutic options with a comparable spectrum of few or only harmless side effects [22–24].

Figure 1 shows the course of this therapy using 180–360 mg fexofenadine daily, 600–1,200 mg disodium cromoglycate daily, and 125–875 ml of an amino acid formula (215–1,505 kcal/day) in addition to the conventional UC therapy with steroids and mesalamine. After this treatment approach, the patient's condition improved rapidly and no side effects occurred within the first 2 weeks, and a dosage increase was well tolerated.

Clinical course after treatment with fexofenadine, disodium cromoglycate, and amino acids in addition to conventional therapy

Clinical activity

After addition of fexofenadine, disodium cromoglycate, and the amino acid based formula, stool frequency decreased rapidly within 2 weeks to four loose stools per day. Stool frequency and consistency normalized after 4 weeks. Clinical disease activity decreased from eight points to four points within 4 weeks and reached three points within 6 weeks. The body weight of the patient rose from 56 to 58 kg within 6 weeks.

Laboratory results

As shown in Fig. 2, leukocytes, serum orosomucoid, and c-reactive protein showed a marked fall within 6 weeks during the intensified antiallergic therapy. Hemoglobin and

serum iron levels increased slightly to 11.8 g/dl and 60 μg/dl, respectively, whereas immunologic parameters did not change.

Steroid intake

Although the patient showed persistent disease activity during therapy with 40 mg prednisolone daily before the antiallergic therapy (Fig. 1), steroid dosage could be slowly reduced after 6 weeks treatment with fexofenadine, disodium cromoglycate, and an amino acid-based formula. Six weeks after induction of remission, the patient's daily steroid dose was reduced to 30 mg—and at week 8 to 16 mg daily. The patient remained stable and the steroid dose could be reduced in 4 mg increments every 7 to 10 days. In July 1999, the patient was off prednisolone, whereas medication with mesalamine, fexofenadine, and disodium cromoglycate was continued.

Discussion

This case report describes the clinical course of a 35-year-old man with UC who did not respond to conventional acute phase therapy consisting of corticosteroids and mesalamine or antibiotics as adjunctive therapeutics [22–25]. Unfortunately, immunosuppressive therapy with azathioprine was not tolerated and cyclosporine A therapy was rejected by the patient. When the patient presented again with seven bloody stools per day and moderate to severe disease activity in spite of a medication of 40 mg prednisolone and 4 g of mesalamine daily. An antiallergic approach was introduced because of several reported adverse reactions to foods, elevated serum IgE, and increased numbers of eosinophils in the gut mucosa. Although there are only few data in the literature about the efficacy of mast cell inhibition in UC [9–17], treatment of this patient with fexofenadine as an antihistamine [27–29], disodium cromoglycate as a mast cell stabilizer, and amino acids as food supplements appeared to be justified as a therapeutic trial before the use of potentially harmful, not yet sufficiently established immunosuppressants like tacrolimus or methotrexate were considered [30–32]. With respect to potential side effects, fexofenadine and disodium cromoglycate seemed superior as compared with these two strong immunosuppressants. On the other hand, there is only limited experience addressing the efficacy of disodium cromoglycate in UC, providing rather variable remission rates, ranging from 30–93% in patients with UC or proctocolitis [9–17].

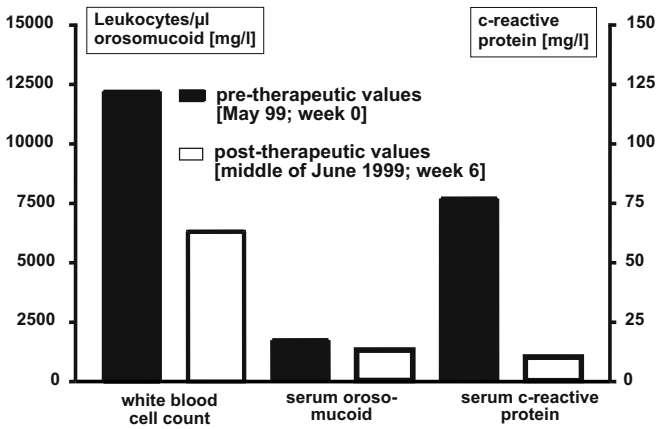

Fig. 2 Laboratory findings before and 6 weeks after addition of fexofenadine, disodium cromoglycate, and an amino acid-based diet to the conventional standard therapy in steroid-dependent chronic active ulcerative colitis. White blood cell count, serum orosomucoid, and c-reactive protein levels were obtained during the unsuccessful therapy with 40 mg prednisolone/die and 4 g 5-aminosalicylic acid/die (therapeutic dosages before addition of the antiallergic principles) and after 6 weeks of application of fexofenadine, disodium cromoglycate, and an amino acid based formula (post-therapeutic values)

Disodium cromoglycate has been shown to inhibit mast cell degranulation, to reduce formation of immune complexes, and to improve gut mucosal barrier in several animal models of colitis and patients with food allergies [15, 16, 33, 34]. However, in UC, the extent of mast cell involvement and eosinophil recruitment is not yet fully understood. But the use of ketotifen has recently been reported in a small cohort of pediatric patients with UC [35], showing only limited therapeutic advantage, particularly in those patients with prominent mucosal eosinophilic infiltrates in the gut [26, 35].

Human mucosal mast cells, which are supposed to be T-cell dependent, may produce a wide array of proinflammatory and immunoregulatory mediators as well as cytokines like histamine, prostaglandins, proteases, interleukin 3, 4, 6, 8 including TNF alpha in response to nonspecific (innate immunity), as well as to specific stimuli (acquired immunity) [36]. In fact, several of these mast cell activating stimuli have been detected both in affected and unaffected UC mucosa primarily in basic scientific investigations (Table 1), while they seem to be extremely rarely detectable in individual patients as causative agents responsible for induction or maintenance of UC [3, 5, 18, 19, 28, 29, 36–38]. Although the clinical relevance of these potentially inciting stimuli (e.g., nutritive or luminal antigens, neuropeptides, or autoantigens etc.) has to be further elucidated in large patient populations, there is accumulating evidence that degranulation of mast cells in healthy tissues may provide an initial mediator pool of proinflammatory substances (histamine, tryptase, TNF alpha, etc.). Thereby, the recruitment and activation of other inflammatory cell types is induced, resulting in generation of a secondary mediator pool (cytokines like interleukin 8; mast cell—leukocyte cascade [39–44]). Because mast cells and T cells have been shown to share common homing and adhesion receptors in gastrointestinal tissues [36], it appears likely that mast cells do not only modify activities

of pure inflammatory cell types (e.g., eosinophil granulocytes), but also those within the mucosal immunoregulatory compartment (e.g., T cells). Both cell types—mast cells and T cells—bear the potential for TH2 cytokine release (interleukin 3, 4, 5, 13), which has been observed in UC more frequently than in normal colorectal mucosa or Crohn's disease [1, 3–5, 45]. Apart from their important immunoregulatory effects, all these TH2 cytokines have more or less trophic effects on mast cells, resulting in induction of mast cell proliferation, activation, and mediator discharge [36, 41–45]. Given the complex interactions within the tissue microenvironment on mast cell biology and homing receptors, intestinal maturing mast cells have been found to express alpha$_E$ integrin, which appears to be responsible for retaining mast cells in the mucosal compartment [36]. Because UC has been immunologically characterized as an exaggerated TH2 cell response [1, 4, 43–45], the development of an increased mucosal mast cell pool (mast cell hyperplasia) may be a natural consequence. Whether a chronically activated mucosal mast cell pool may induce a similar disease (type) like UC remains yet elusive. But some data from the literature including this patient support this hypothesis: First, there are similarities of the clinical, endoscopical and histological presentation of allergic enterocolitis with UC in pediatric patients [18–21, 40–43, 45]. Second, extremely elevated tissue histamine levels are equally found in UC and food allergy [19, 28]. Third, the prompt response of the reported patient with mucosal eosinophilia, elevated serum IgE, and allergic rhino-conjunctivitis to fexofenadine and disodium cromoglycate inevitably suggests involvement of histamine and mast cells in some cases of UC.

The use and effectiveness of fexofenadine, a new nonsedative H1-receptor antagonist, beside disodium cromoglycate has not been reported in inflammatory bowel disease so far, but was intended because of its antiinflammatory effects apart from H1-receptor antagonism [27–29, 46]. This newer group of H1-antihistamines has been shown to inhibit mast cell degranulation (arachidonic acid-, histamine-, and protease secretion), to inhibit eosinophil activity and to reduce ICAM-1 adhesion molecule expression [27, 46]. Because all these inflammatory mechanisms have been proposed to contribute to mucosal disease activity in UC for several years, fexofenadine was chosen as therapeutic agent. This H1-antihistaminergic drug was used in a higher dose (360 mg per day) than usually chosen for allergic rhino-conjunctivitis [46] considering the greater mucosal surface of the colon, which may carry far more H1-receptors than the nose or eye. Because an uncommonly high dose of the H1-blocker was anticipated for gastrointestinal disease, fexofenadine has been chosen because it is well tolerated and does not exhibit cardiac toxicity [27, 46]. This therapeutic consideration appeared very important in this particular patient who had to use metoprolol because of his recurrent sympaticovasal attacks (panic disorder).

Table 1 Potential stimuli or activators of mast cells in ulcerative colitis [2–5, 9–21, 28, 29, 34, 37, 41–44]

Allergens	(e.g. lactalbumin, ovalbumin)
Auto- and/or anti-IgE antibodies	(e.g. tropomyosin)
Constituents of connective tissue	(e.g. CTAB)
Bacteria and their products	(e.g. LPS, FMLP)
Chemotactic mediators from granulocytes or monocytes	(e.g. NAP-2, MCP-1, RANTES)
Complement factors	(e.g. C3a, C5a)
Cationic proteins from eosinophil granulocytes	(e.g. ECP, EPO, MBP)
Enterotoxine	(e.g. Cl. difficile toxine A)
Cell proteins from death intestinal epithelium	
Neuropeptides	(e.g. substance P)
Non-immunologic mast cell activators	(e.g. bile acids)
Reactive oxygen metabolites	(e.g. O_2^-, H_2O_2)

Mast cells represent an important cell type in the gastrointestinal tract connecting mechanisms of innate and acquired immunity to maintain intestinal immune function. Mucosal mast cells may be activated by non-immunological and immunological stimuli. Both groups of stimuli may therefore be considered as mast cell activating principles in chronic active ulcerative colitis

Histamine is well known to exert a broad range of proinflammatory and immunoregulatory effects in the body (e.g., chemotactic activity, induction of ICAM-1 expression, suppression of mononuclear cell function, etc. [28, 29, 41–43]). Blockage of intestinal H1-receptors, therefore, appeared to add further antiinflammatory effects to the conventional, yet ineffective standard therapy. In fact, although largely unknown, similar therapeutic considerations to add disodium cromoglycate to UC patients have already been published in few previous reports [9–12, 14, 15, 18–20]. It is interesting to note that these studies clearly show the same therapeutic approach as performed in this patient, namely, the addition of disodium cromoglycate to patients unresponsive to steroids or sulfasalazine to achieve remission. These findings suggest that mast cell inhibition or histamine antagonism may exert additional therapeutic benefit in steroid-treated patients with UC.

In view of an increased incidence of atopy in UC [20–37, 47], elevated rates of histamine secretion in IBD and extremely enhanced tissue histamine levels in UC [28, 29], clinical interest in histamine antagonism raised tremendously. Several other mediator antagonising studies using leucotriene antagonists, lipoxygenase inhibitors, or platelet-activating factor antagonists failed to show a clear benefit in acute UC [5–7]. As a result, these studies prompted us to use the new nonsedative, absorbable antihistamine fexofenadine in conjunction with the old, but largely unabsorbable mast cell stabilizer, disodium cromoglycate [9, 16].

Administration of 1,000–1,500 kcal daily as an amino acid-based formula diet should guarantee adequate nutritional dietary intake in this uncertain patient who faced several types of food intolerance or allergy. Although food allergy is often encountered by patients with inflammatory bowel disease [20, 21, 42, 47], physicians attributed these fears of adverse food reactions primarily to the panic disorder of the anxious patient. The idea to use a hypoallergenic formula was raised by the observation that the patient could well tolerate potato, rice, and lamb (described as hypoallergenic diet [48, 49]) without occurrence of any physical symptoms, while addition of other foodstuffs like flour, pork, or nuts induced abdominal symptoms like pain, increased bowel movements, and bloating despite the use of steroids. The use and efficacy of enteral nutritional therapy has been reported primarily in Crohn's disease [22, 24, 49, 50]. But in conjunction with the above listed antiallergic drugs, this patient with UC showed a favorable clinical and serological response and a gain in body weight during the modified diet. Hypothesizing an allergic mechanism in colonic disease of this patient with UC [18, 20, 21], addition of the hypoallergenic formula could have resulted in stopping the continuous mast cell stimulation as a response to nutritional antigens. Unfortunately, due to the severity of the disease and the long-term use of steroids, a standardised protocol for oral food challenge tests to identify causative food antigens could not be performed in this patient. But such a protocol has recently identified some food allergens as exacerbating agents in a small group of patients initially diagnosed as UC [37].

Taking the observations made in the present patient into account, antiallergic treatment approaches in patients with UC unresponsive to conventional medical therapy or showing signs of atopy should be considered. Larger studies are required to identify subgroups of patients who are likely to respond to this new treatment approach.

References

1. Rugtveit J, Nilsen EM, Bakka A et al (1997) Cytokine profiles differ in newly recruited and resident subsets of mucosal macrophages from inflammatory bowel disease. Gastroenterology 112:1493–1505
2. Raab Y, Sundberg Ch, Hällgren R et al (1995) Mucosal synthesis and release of prostaglandin E2 from activated eosinophils and macrophages in ulcerative colitis. Am J Gastroenterol 90:614–620
3. Greenwald BD, James St P (1997) Immunology of inflammatory bowel disease. Curr Opin Gastroenterol 13:293–301
4. Montelone G, Biancone L, Marasco R et al (1997) Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. Gastroenterology 112:1169–1178
5. Cominelli F, Kam L (1993) Inflammatory mediators of inflammatory bowel disease. Curr Opin Gastroenterol 9:534–539
6. Roberts WG, Simon ThJ, Berlin RG et al (1997) Leukotrienes in ulcerative colitis: results of a multicenter trial of a leukotriene biosynthesis inhibitor, MK 591. Gastroenterology 112:725–732
7. Stack WA, Jenkins D, Vivet P et al (1998) for the Platelet activating factor Antagonist Study Group in Ulcerative colitis: lack of effectiveness of the platelet-activating factor antagonist SR 27417A in patients with active ulcerative colitis: a randomized controlled trial. Gastroenterology 115:1340–1345
8. Tromm A, Hüppe D, Eckenburg K et al (1993) Laboratory tests and activity indices in acute ulcerative colitis with respect to the extent of disease. Eur J Gastroenterol Hepatol 5:21–25
9. Heatley RV, Calcraft BJ, Rhodes J et al (1975) Disodium cromoglycate in the treatment of chronic proctitis. Gut 16:559–563
10. Mani V (1976) Treatment of ulcerative colitis with oral disodium cromoglycate. A double blind controlled trial. Lancet 1:439
11. Malolepszy J (1977) Treatment of ulcerative colitis with disodium cromoglycate. Acta Allergol 32:82
12. Gould SR, Buckell NA, Day DW et al (1978) Controlled trial of disodium cromoglycate in chronic persistent colitis. Gut 19:1140–1143
13. Pugh SM (1979) Atopic disease in ulcerative colitis and Crohn's disease. Clin Allergy 9:221
14. Babb RR (1980) Cromolyn sodium in the treatment of ulcerative colitis. J Clin Gastroenterol 2:229
15. Rosenkrans PCM, Meijer CLJM, Van der Wal AM et al (1980) Allergic proctitis, a clinical and immunopathological entity. Gut 21:1017–1023
16. Whorwell PJ, Whorwell GN, Bamforth J et al (1981) A double-blind controlled trial of the effect of sodium cromoglycate in preventing relapse in ulcerative colitis. Postgrad Med J 57:436–438
17. Odze RD, Wershil BK, Leichtner AM et al (1995) Allergic colitis in infants. J Pediatr 126:163–170
18. Truelove SC (1961) Ulcerative colitis provoked by milk. Br Med J I:154–155
19. Senju M (1988) Reaginic hypersensitivity in ulcerative colitis. Jpn J Gastroenterol 85:2168–2177 (in Jpn)
20. Jewell DB, Truelove SC (1972) Reaginic hypersensitivity in ulcerative colitis. Gut 13:903–906
21. Catlett JB (1988) Ulcerative colitis in an allergic person: case report. Va Med 115:434–435
22. Hanauer SB (1993) Medical therapy of ulcerative colitis. Lancet 342:412–417
23. Hawthorne AB, Hawkey CJ (1989) Immunsuppressive drugs in inflammatory bowel disease: a review of their mechanisms of efficacy and place in therapy. Drugs 38:267–288
24. Hanauer St B (1996) Inflammatory bowel disease. N Engl J Med 334: 841–848

25. Turunen UM, Farkkila MA, Hakala K et al (1998) Long-term treatment of ulcerative colitis with ciprofloxacin: a prospective, double-blind, placebo-controlled study. Gastroenterology 115:1072–1078
26. Ooi ChJ, Sands BE (1999) Treatment of ulcerative colitis. Curr Opin Gastroenterol 15:298–301
27. Abdelaziz MM, Devalia JL, Khair OA et al (1998) Effect of fexofenadine on eosinophil-induced changes in epithelial permeability and cytokine release from nasal epithelial cells of patients with seasonal allergic rhinitis. J Allergy Clin Immunol 101:410–420
28. Raithel M, Matek M, Baenkler HW et al (1995) Mucosal histamine content and histamine secretion in Crohn's disease, ulcerative colitis and allergic enteropathy. Int Arch Allergy Immunol 108:127–133
29. Raithel M, Schneider Th, Hahn EG (1999) Effect of substance P on histamine secretion from gut mucosa in inflammatory bowel disease. Scand J Gastroenterol 34:496–503
30. Fellermann K, Ludwig D, Stahl M et al (1998) Steroid-unresponsive acute attacks of inflammatory bowel disease: immunomodulation by tacrolimus (FK 506). Am J Gastroenterol 93(10): 1860–1866
31. Kozarek RA, Patterson DJ, Gelfand MD et al (1989) Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. Ann Intern Med 110:353–356
32. Oren R, Arber N, Odes S et al (1996) Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. Gastroenterology 110:1416–1421
33. Ortolani C, Pastorello E, Zanussi C (1983) Prophylaxis of adverse reactrions to foods: a double-blind study of oral sodium cromoglycate for the prophylaxis of adverse reactions to foods and additives. Ann Allergy 50:105–109
34. Andre´ F, Andre´ C, Colin L et al (1995) IgE in stool as indicator of food sensitization. Allergy 50:328–333
35. Jones NL, Roifman CM, Griffiths AM et al (1998) Ketotifen therapy for acute ulcerative colitis in children: a pilot study. Dig Dis Sci 43(3):609–615
36. Smith TJ, Weis JH (1996) Mucosal T cells and mast cells share common adhesion receptors. Immunol Today 17:560–564
37. Raithel M, Weidenhiller M, Winterkamp S et al (1999) Is inflammatory bowel disease (IBD) always an idiopathic condition ? Identification of IBD patients with hypersensitivity to specific antigens. Gastroenterology 116 (No. 4):G 3475
38. Fiocchi C (1990) Immune events associated with inflammatory bowel disease. Scand J Gastroenterol 25(Suppl 172):4–12
39. Iizuka M (1990) IgG subclass-containing cells in the human large bowel of normal controls, non-IBD colitis, and ulcerative colitis. Gastroenterol Jpn 25:24–31
40. Balazs M, Illyes G, Vadasz G (1989) Mast cells in ulcerative colitis. Quantitative and ultrastructural studies. Virchows Arch B Pathol 57:353–360
41. Marshall JS, Bienenstock J (1990) Mast cells. Springer Semin Immunopathol 12:191–202
42. Crowe SE, Luthra GK, Perdue MH (1997) Mast cell mediated ion transport in intestine from patients with and without inflammatory bowel disease. Gut 41:785–792
43. Stenton GR, Vliagoftis H, Befus D (1998) Role of intestinal mast cells in modulating gastrointestinal pathopyhsiology. Ann Allergy Asthma Immunol 81:1–15
44. Galli St J, Maurer M, Lantz ChS (1999) Mast cells as sentinels of innate immunity. Curr Opin Immunol 11:53–59
45. Collins SM (1996) Similarities and dissimilarities between asthma and inflammatory bowel disease. Aliment Pharmacol Ther 10(Suppl. 2):25–31
46. Simons FER (1997) Antihistamines. In: Kaplan AP (ed) Allergy, 2nd edn. WB Saunders, Philadelphia, pp 679–692
47. Glassmann MS, Newmann LJ, Berezin S et al (1990) Cow's milk sensitivity during infancy in patients with inflammatory bowel disease. Am J Gastroenterol 85:838–840
48. Aiuti F, Paganelli R (1983) Food allergy and gastrointestinal diseases. Ann Allergy 51:275–280
49. Sampson HA (1997) Food allergy. JAMA 278:1888–1894
50. Mishkin S (1997) Dairy sensitivity, lactose malabsorption, and elimination diets in inflammatory bowel disease. Am J Clin Nutr 65:564–567