

ORIGINAL ARTICLE

Ulcerative colitis patients with an inflammatory response upon mesalazine cannot be desensitized: a randomized study

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Abstract

Background and aims. Mesalazine is a key drug in the treatment of ulcerative colitis (UC). Intolerance to mesalazine has been described, including fever and gastrointestinal symptoms. Several case reports reported successful desensitization of patients with mesalazine intolerance. The aim was to assess the number of UC patients who are persistently intolerant to mesalazine after single-blinded rechallenge and to test the effectiveness of a rapid desensitization protocol in UC patients demonstrated mesalazine intolerance. **Methods.** This is a prospective, single-blind randomized study in UC patients who discontinued mesalazine because of intolerance. Patients with severe reactions were excluded. Eligible patients underwent a skin patch test with mesalazine followed by a single-blinded randomized crossover rechallenge with 500 mg mesalazine or placebo. Patients with symptoms upon rechallenge were admitted to the hospital for 3 days oral desensitization. **Results.** Nine of the 37 identified UC patients who discontinued mesalazine because of intolerance were included. All nine patients had negative patch tests, seven patients had symptoms (fever, nausea, vomiting and diarrhea) within 2 h upon rechallenge. Four of these seven patients participated in the desensitization protocol and in none a successful desensitization could be performed. All four had an inflammatory intolerance reaction with rise in C-reactive protein. There were no elevations in serum tryptase or urinary-methylhistamine levels observed and no signs of immediate type allergic reactions, like urticaria, bronchial obstruction or anaphylaxis. **Conclusion.** We recommend not to rechallenge UC patients with an inflammatory response upon mesalazine and these patients will not benefit from a rapid desensitization protocol.

Key Words: immunology, inflammatory bowel disease, mesalazine, ulcerative colitis

Background and aims

Mesalazine (5-amino salicylic acid [5-ASA])-containing agents are very important in the treatment of ulcerative colitis (UC). They are highly effective for both inducing and maintaining remission in UC at doses ≥ 2 g [1]. In Crohn's disease (CD), the role of 5-ASA remains uncertain in inducing and maintenance remission [2]. CD patients who are in remission after surgery could have some benefit from 5-ASA to maintain remission [3].

Mesalazine is a relatively safe drug and has fewer side effects than comparable drugs as sulfasalazine or olsalazine [4]. Although the frequency of adverse events in clinical trials in UC and CD patients were similar between 5-ASA and placebo, about 6.5% of patients using 5-ASA develop adverse effects [5]. The most common adverse effects are nausea, vomiting, headache, abdominal pain, rash and diarrhea. Rare adverse effects are hepatotoxicity, pancreatitis, pneumonitis and interstitial nephritis [6–9]. Adverse effects can be classified into predictable (type A)

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and unpredictable (type B) reactions. Type B reactions are responsible for 10–15% of all drug side effects. They consist of allergic reactions, idiosyncratic and intolerance/hypersensitivity reactions. For many drug hypersensitivity/ allergic reactions, the exact immunologic mechanism is difficult to identify. Symptoms in nonallergic hypersensitivity can be identical to an allergic reaction and arise normally after the first administration of the drug. It is not known whether adverse effects upon 5-ASA are type A or B reactions. In some forms of type B reactions, especially in case of immunologic/allergic reactions, mast cell-associated (type-1) desensitization can be achieved. Desensitization is the procedure to induce tolerance to drugs responsible for hypersensitivity reactions using a slowly incremental dose of the drug. Effective desensitization is described for cytostatics, antibiotics and also for sulfasalazine [10,11]. A few case reports reported successful desensitization for patients intolerant for 5-ASA. In these cases, patients had a variety of side effects, e.g. urticaria, fever, exanthema, diarrhea and nausea, sometimes combined with eosinophilia [12–17]. The mechanism of desensitization is not clearly understood. The cell targets for rapid desensitization are thought to be mast cells and possibly basophiles [18].

The aim of this study is to assess the number of UC patients who are persistently intolerant to 5-ASA after single-blind rechallenge, to describe the symptoms appearing and to test the effectiveness of a rapid desensitization protocol in patients with UC with demonstrated 5-ASA intolerance.

Methods

Patient population

Patients with UC and suspected 5-ASA intolerance were identified and recruited by one research investigator at the University Medical Center Groningen (UMCG) and the Martini hospital in Groningen for this dual center, partially single-blind and randomized crossover study. Eligibility criteria were as follows: 18 years of age or older, UC, objective adverse side effects upon 5-ASA (e.g. fever, acute mild pancreatitis, urticaria, elevated C-reactive protein [CRP] > 30 mg/l), subjective adverse side effects upon 5-ASA (e.g. [increase] of diarrhea, nausea and vomiting) and signed written informed consent approved by local ethics review board. Reasons for exclusion were interstitial nephritis, bullous skin lesions, bronchospasm, anaphylactic shock, severe acute pancreatitis, severe comorbidity (e.g. cardiopulmonary, malignancy), or renal dysfunction, patients using corticosteroids,

pregnant/breastfeeding patients and mentally incompetent patients. The study was registered at the Central Committee on Research Involving Human Subjects (CCMO) at CCMO.nl; reference number NL31411.042.10.

Primary and secondary outcomes

Primary outcome was successful desensitization of patients with intolerance upon blinded rechallenge with 5-ASA. As a secondary outcome, we recorded signs and symptoms appearing upon blinded rechallenge with 5-ASA.

First outpatient clinic visit

Eligible patients were seen at the outpatient clinic of the UMCG. The severity of UC, exacerbation rate, medical history, medication, intolerance pattern to 5-ASA, disease activity and the consequences of the intolerance reaction, i.e. use of steroids, use of immunomodulatory agents, use of biologicals or surgery, were recorded. Physical examination was performed and weight, length, blood pressure and temperature were measured.

Patch tests

Prior to rechallenge a patch test with 5-ASA dissolved in white soft paraffin in 0.1%, 1% and 10% was performed. Patches were applied under occlusion on to the skin of the upper back of the patient. Patients were instructed not to shower during the patch test. After 72 h, skin reaction upon the mesalazine patch test was examined by an independent expert.

Blood tests

At baseline, after each rechallenge and twice a day (10:00 am and 4:00 pm) during desensitization a blood test was performed. The following parameters were determined: blood count, white blood cell differentiation, CRP, sodium, potassium, urea, creatinine, aspartate transaminase, alanine transaminase, alkaline phosphatase, γ -glutamyltransferase, tryptase and complement factor 3 and 4. Urinalysis to methylhistamine was performed in patients who developed symptoms upon administration of 5-ASA or placebo.

Rechallenge

Patients with a positive 5-ASA patch test would directly enter the desensitization protocol. Those with a negative patch test entered the single-blind

randomized crossover rechallenge with 5-ASA or placebo, at the outpatient clinic, and were administered a daily dosage of 3 times 500 mg of 5-ASA or placebo for a week. The 5-ASA and placebo powder were both pink colored with azorubin to reduce the inherent color difference between the two compounds. As the investigator was aware of the remaining color difference between 5-ASA and placebo, only the patient was blinded for the study drug. Both products were manufactured under the supervision of the hospital pharmacist according to European good manufacturing practice regulations. After a 3-week washout, the patient received the drug or placebo for a second rechallenge week. In case of symptoms, patients stopped the medication and blood and urine tests were performed.

The randomization for this single-blind crossover part of the study was accomplished with the use of two by two blocks.

Desensitization

Patients who developed symptoms upon 5-ASA underwent the desensitization procedure. Patients were admitted for a 3-day 16 steps (depicted in dosing Table I) desensitization protocol. For administration of 5-ASA at low dose (<500 mg), 5-ASA was dissolved in sugar syrup. Dosages of >500 mg 5-ASA were administered as a powder. Blood pressure, heart rate, temperature and oxygen saturation were assessed at baseline ($t = 0$), every half an hour and in case of symptoms. Epinephrine, clemastine (tavegil) and prednisolone were stand-by in case of type-1 allergic reactions such as anaphylaxis or severe angioedema. In case of bronchial obstruction, patients could be nebulized with salbutamol/ipratropiumbromide immediately. In cases of severe adverse effects, the desensitization was instantaneously discontinued. A summary of the study protocol is shown in Figure 1.

Data analysis

Baseline descriptive statistics are presented as mean $\pm$ standard deviation or median (range) for continuous variables and counts with percentages for categorical variables.

All co-authors had access to the study data and reviewed and approved the final manuscript.

Results

Patients

Thirty-seven UC patients with apparent prior 5-ASA intolerance who met the inclusion criteria were identified. Of these patients, nine (24%) were willing to participate in the single-blinded study. Twenty-eight patients (76%) did not participate in the study because of several reasons; anxiety to a recurrence of symptoms ($n = 13$), patients in remission not willing to use 5-ASA ($n = 10$) and further reasons like the intensity of the study ($n = 5$). Characteristics of the nine enrolled patients are presented in Table II.

Patch test/ rechallenge

All nine patients had a negative patch test. After the patch test one patient was not willing to proceed with the rechallenge. None of the remaining eight patients developed symptoms upon administration of placebo. However, six of the eight patients developed symptoms within 2 h after rechallenge with 5-ASA. A similar pattern of symptoms was observed among all patients at rechallenge as they experienced before. These symptoms were abdominal pain, diarrhea, vomiting and fever with a high CRP and leukocytosis. One of these six patients had a severe adverse reaction with vomiting, diarrhea and signs of dehydration. This patient had to be admitted to the hospital for two nights for rehydration. Immediate type allergic reactions, like urticaria, bronchial obstruction or

Table I. Desensitization protocol (Varela et al. [16]).

Time	Day 1	Time	Day 2	Time	Day 3
	10mg/ml		100 mg/ml		
10:00	1 mg = 0.1 ml	9:00	200 mg = 2 ml	10:00	2 g
10:20	2 mg = 0.2 ml	9:30	300 mg = 3 ml	12:00	Therapeutic doses = 4 g
10:40	4 mg = 0.4 ml	10:00	500 mg		
11:00	8 mg = 0.8 ml	11:00	1000 mg		
11:20	15 mg = 1.5 ml				
11:40	30 mg = 3.0 ml				
12:00	60 mg = 6.0 ml				
	100 mg/ml				
12:20	100 mg = 1.0 ml				
12:40	150 mg = 1.5 ml				
13:00	200 mg = 2.0 ml				

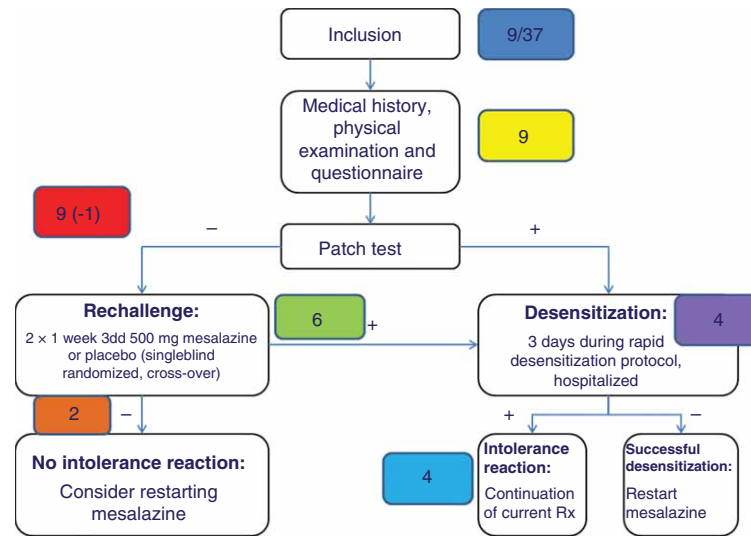


Figure 1. Study design.

anaphylaxis were not observed. Laboratory parameters showed rise in CRP (Figure 2) without rise in serum tryptase and urinary methylhistamine. Two

patients did not develop symptoms during the single-blinded crossover study. Prior to this study, these two patients had experienced headache and abdominal cramps without fever, diarrhea or laboratory abnormalities.

Table II. Patient characteristics.

Characteristics	Number (n = 9)
Gender	
Male	6 (67%)
Female	3 (33%)
Age, mean (SD) – years	45.9 (± 16.4)
Localization ulcerative colitis – no. (%)	
Pancolitis	5 (55%)
Left-sided	2 (23%)
Procto-sigmoiditis	1 (11%)
Pouchitis	1 (11%)
Duration of disease, mean (range) – years	6.3 (0.5–21)
Disease activity – no. (%)	
Mild	5 (55%)
Moderate	4 (45%)
Severe	0 (0%)
Concomitant medication – no. (%)	
Steroids	1 (11%)
Thiopurines	1 (11%)
Anti-TNF- α - drugs	1 (11%)
Antibiotics	1 (11%)
Other	4 (44%)
None	2 (22%)
Reported reaction to mesalazine – no. (%)	
Fever	6 (67%)
Nausea/vomiting	5 (55%)
Diarrhea	5 (55%)
Pancreatitis	1 (11%)
Other	3 (33%)
Other intolerances – no. (%)	
Hay fever	3 (33%)
Dust mites allergy	0 (0%)
Food allergy	0 (0%)
Other allergy to medication	3 (33%)
None	3 (33%)

Desensitization

Four of the six patients with proven symptoms upon rechallenge with 5-ASA were willing to undergo the desensitization procedure. These four patients developed symptoms within 3 h after start of the protocol. Symptoms occurred already at a cumulative maximum dose of 220 mg 5-ASA (mean cumulative dose of 200 mg). The symptoms were similar to the symptoms they experienced in the past and also during the rechallenge. Once again there were no clinical signs of immediate type allergic reactions during desensitization. Laboratory parameters showed increased CRP levels and leukocytosis without clinical relevant increase in levels of tryptase or urinary methylhistamine (Figures 3 and 4). In case of intolerance symptoms, patients were administered primperan, paracetamol and intravenous fluid. All symptoms disappeared within 24 h after discontinuation of 5-ASA.

Discussion

The present study showed that patients with UC and intolerance to mesalazine can be safely rechallenged and that 25% will tolerate the drug. However, we showed that patients with an inflammatory response upon mesalazine cannot be rechallenged and cannot be desensitized.

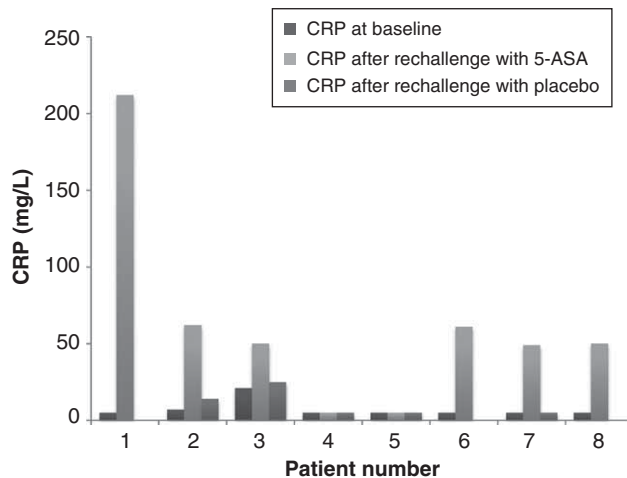


Figure 2. CRP levels of eight patients during rechallenge at day 1 and day 8 or the day patients develop adverse effects. CRP = C-reactive protein.

5-ASA is a very effective and safe drug in the treatment of UC. Unfortunately, about 6.5% of patients using 5-ASA develop adverse reactions [5]. These patients might benefit from 5-ASA rechallenge or with another formulation of 5-ASA. In our study two of eight patients (25%) who had subjective symptoms such as headache and nausea tolerated the drug in a blinded rechallenge. Ideally, a rechallenge should be performed in a blinded fashion. However, as shown in this study this proves to be hard to realize in clinical practice as 28 out of 37 patients (76%) did not comply with such a protocol. Nevertheless, the remaining patients were included in a strict protocol

and strict desensitization protocol, which resulted in solid reproducible clinical evidence.

A rechallenge with another formulation of 5-ASA is probably a more feasible strategy in clinical practice. Furthermore, we show that patients with objective signs (e.g. fever, rise in CRP, leukocytosis) and symptoms (e.g. diarrhea, vomiting) will experience the same reaction within 2 h after intake of even 200 mg of mesalazine. This study identified patients with an inflammatory response upon mesalazine that has not yet been reported. The mechanism behind this inflammatory response is unclear. Since all patients had negative patch tests and showed no increased serum tryptase or urinary methylhistamine, the reaction to 5-ASA is probably not related to mast cell activation. A delayed type allergic reaction cannot be fully excluded but is less likely because of the early onset of symptoms and the negative patch tests (in delayed type IV allergic reactions [T-cell-related], the patch test would be positive after 48–72 h). The observed inflammatory reaction could be due to a pharmacological idiosyncratic reaction. Scheurlen et al. showed that olsalazine and mesalazine could induce diarrhea by reducing small intestinal salt and water absorption [19].

Therefore, an increase in diarrhea upon mesalazine could be a distinct mechanism from the inflammatory response we observed in our study.

All patients with this rapid inflammatory response upon mesalazine administration could not be desensitized with a 3-day desensitization protocol. This is in contrast with the case report by Varela et al. who

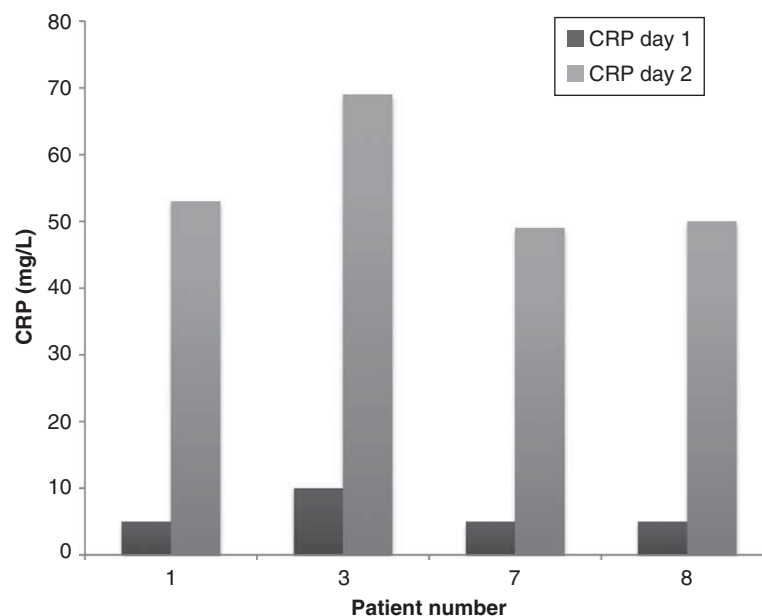


Figure 3. CRP levels during desensitization at baseline and day 2. All four of our patients had symptoms and showed an increased CRP. CRP = C-reactive protein.

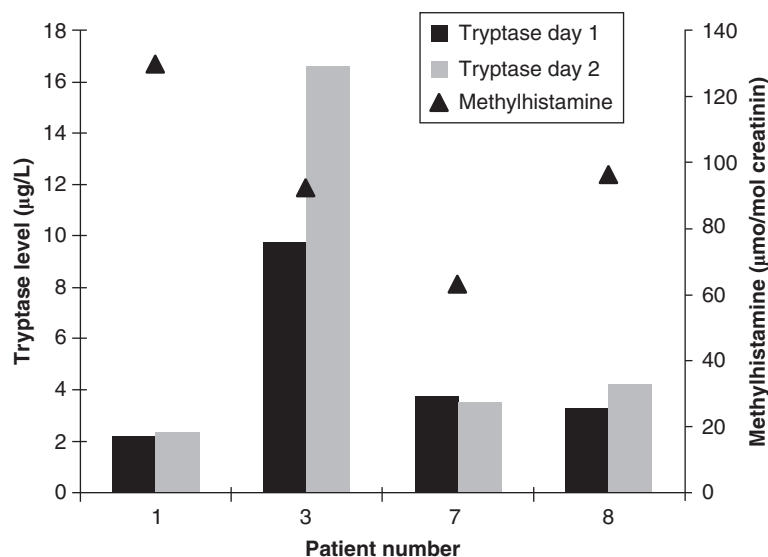


Figure 4. Tryptase level during desensitization at baseline and day 2. All four patients had symptoms. One patient had a high tryptase level already at baseline. Highest urine methylhistamine level in four patients during desensitization. A level below 150 µmol/mol creatinin showed there is no mast cell activation.

demonstrated that it is possible to desensitize a patient with 5-ASA intolerance (with symptoms of generalized urticaria, facial angioedema, shortness of breath and vomiting) with a 3-day desensitization protocol [16]. Tolerance induction by exposure to an increasing dose of drug has been proposed as a safe way to suppress the allergic responses. So why were we not able to desensitize these patients? There are several explanations why our desensitization protocol could have failed. First, we found no evidence for mast cell activation or an immune-mediated reaction. Two other studies showed that it was possible to desensitize patients with mesalazine-induced urticaria or rash accompanied by facial angioedema with a 20 and 3 days desensitization protocol, respectively [13,16]. This kind of reaction could be a type 1, IgE-mediated reaction that thus was not observed in the present study. Second, a 3-day desensitization protocol may be too short. However, with the development of an inflammatory response within 2 h after on average mesalazine dose of 200 mg, it is unlikely that a longer desensitization protocol would be effective. Additionally, it is possible that the dosages of mesalazine were increased too fast. A few case reports reported successful desensitization with a slower protocol as in a report by Gonzalo et al. who used a 32-day desensitization protocol patients with mesalazine-induced fever could be desensitized; however, it is not clear whether or not there was an immune response (symptoms of this patient were fever, tiredness, headache, thoracic pain, myalgias and arthralgias 5 days after starting mesalazine) in these patients [14]. Another case report that described

a 100-day desensitization protocol, one patient with fever and myalgia after mesalazine reported that this was successful [17].

In conclusion, this is the first study that describes a blinded, randomized crossover rechallenge and desensitization for mesalazine intolerance in UC patients. This is of pivotal importance as patients who report adverse reactions need careful evaluation as it may lead to discontinuation of an important drug for the treatment of UC. We recommend to rechallenge patients with reported mesalazine intolerance preferable in a blinded fashion. However, we recommend not to rechallenge UC patients with fever, increased CRP, vomiting and diarrhea upon mesalazine administration and these patients cannot be desensitized with a 3-day desensitization protocol.

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