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Research article

Long Term Results of Mesalazine Desensitization to Intolerant Patients with Inflammatory Bowel Disease

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Abstract

Background and Aims; Mesalazine intolerance induce severe symptoms. Desensitization has been known as useful method to overcome intolerance. Authors analysed long term results after desensitization to intolerant IBD patients Methods: To IBD patients intolerant to mesalazine, desensitization were performed. After desensitization, they were divided into success, failure, and no desensitization group. Relapse rate required biologics between intolerant and tolerant patients was compared. And interval from the onset to relapse between intolerant and tolerant patients was also compared. Results: Incidence of intolerance was 5.1% (68/1326). Fifty-four patients out of 68 were desensitized. Thirty-five patients (64.8%) succeeded and 19(35.2%) failed to desensitization. Relapse rate required biologics of intolerant patients was 22.1% (15/68), which was significantly higher than that of tolerant patients, 6.8% (85/1258) ($p<0.001$). Relapse rate of success, failure or no desensitization group was equally high. Interval from the onset to relapse of intolerant patients (2.7 ± 2.4 years) was significantly shorter than that of tolerant patients (5.3 ± 7.0 years) ($p<0.007$) Conclusion; Patients succeeded to desensitization could resume mesalazine without side effects. But relapse rate of intolerant patients was significantly higher than that of tolerant patients and was equally high in success, failure, or no desensitization patients. Interval from the onset to relapse of intolerant patients was significantly shorter than that of tolerant patients. Desensitization could not afford expected clinical results. Some unknown factor inducing intractability and relapse is suggested in patients with mesalazine intolerance.

Keywords: mesalazine intolerance, inflammatory bowel disease, desensitization, ulcerative colitis, crohn's disease, biologics

Introduction

Mesalazine has been basic anti-inflammatory agent for majority of the patients with inflammatory bowel disease (IBD). But a few patients are intolerant to mesalazine and severe symptoms, such as abdominal pain, diarrhea or fever occur within several days after beginning of the agent. To overcome intolerance, desensitization has been known as useful method. Authors attempted desensitization to the intolerant patients and followed up to evaluate the results. Relapse rate required biologics and time interval from the onset to relapse were compared between intolerant and tolerant group. And effects and problems of desensitization were reported in this manuscript.

Materials and methods

A number of IBD patients was 1513 from April 2008 to March 2018 at Matsushima Clinic. One hundred eighty-seven patients treated with masalazine suppository or enema, or no treatment were excluded. A total of 1326 IBD patients were given mesalazine orally and they were enrolled to this retrospective study. And 68 patients were diagnosed as mesalazine 5 intolerance from typical symptoms and laboratory tests. They were 47 ulcerative colitis (UC) and 21 Crohn's disease (CD), male: female ratio 35:33 with mean age of 41.0± 17.7 years old at the onset (Table 1).

A number of mesalazine tolerant patients was 1258 and they were 908 UC and 350 CD and male: female ratio 771:487 with mean age of 40.3 ± 16.2 years old at the onset. They were followed up until March 2019. To the patients with intolerance to mesalazine, desensitization was explained, and accepted patients were desensitized by method of Holdsworth [1,2]. They were divided into success, failure to desensitization and no desensitization group. Relapse rate required biologics was compared between intolerant and tolerant group. Either steroid resistant or dependent patients were determined as indication of biologic therapy. Time interval from the onset to relapse was compared between intolerant and tolerant group. Calculated number was expressed as mean ± lsd and statistical significance was defined as less than $p=0.05$ by student t-test.

Results

Incidence of mesalazine intolerance in IBD patients was

Table 1. Patients background

Number of total IBD patients	Treatment	Tolerance to mesalazine	Disease
1513	oral mesalazine 1326	intolerant to mesalazine 68 (41.0±17.7 y/o) ♂:♀=35 : 33	UC 47 CD 21
		tolerant to mesalazine 1258 (40.3±16.2 y/o) ♂:♀=771 : 487	UC 908 CD 350
	mesalazine enema, suppository or no treatment 187		

5.1% (68/1326) and 6 was 4.9% (471955) in UC and 5.7% (21/371) in CD respectively. Mean serum CRP level at the onset of intolerance was 5.2 ± 5.9 mg/d1(n=33) and DLST to mesalazine was positive in 58.3% (n=24).

Fifty four out of 68 patients accepted desensitization and the remaining 14 did not. Thirty-five patients (64.8% 35/54) succeeded to desensitization and could resume mesalazine thereafter. Nineteen patients (35.2%.19/54) developed the same symptoms during step up process of desensitization and failed and were treated with azathioprine (Table 2).

Table 2. A number of intolerant and tolerant patients to mesalazine and results of desensitization

	number (%)	desensitization (%)	results (%)
intolerant patients	68 (5.1)	Desensitization 54 (79.4)	success 35 (64.8)
		no desensitization 14 (20.6)	failure19 (35.5)
tolerant patients	1258		

The main symptoms of failure were diarrhoea (12 patients,), fever (3) and headache (4). Mean daily dose of mesalazine when desensitization was discontinued due to side effects was 309.3± 190.3 mg/day (16 cases). As the other side effects, one case of hyperamylasaemia, eruption on the upper body and pneumonitis was seen, respectively. Relapse rate of intolerant patients, 22.1% (15/68) was significantly higher than that of tolerant patients, 6.8% (85/1258) (p<0.001).

Relapse rate of success, failure group and no desensitization group was 20.0% (7/35), 26.3% (5/19) and 21.4% (3/14) respectively. Regardless of success, failure to desensitization or no desensitization, relapse rate was almost the equal (Table 7).

Desensitization could not lower relapse rate of IBD. Mean time interval from the onset of IBD to relapse of intolerant patients was 2.7 ± 2.4 years and was significantly shorter than that of tolerant patients (5.3 ± 7.0 years) (p<0.007).

Discussion

Intolerance to mesalazine has been seen in a few patients with IBD and mechanism of intolerance has not been known. Intolerance is a poorly defined term may refer to an unusual low threshold to the pharmacological side effect of a drug [3]. Intolerance is classified as one of non-allergic, non- immunological drug reaction and is not dose dependent complications. Rifampicin, anti-tuberculous agent is also known to induce intolerance and effectiveness of desensitization has been reported [4]. Our incidence of intolerance was 5.1% and Kitani reported incidence of 2.1% [5]. Higher incidence of intolerance (13.8%) was reported in paediatric patients [6]. Desensitization has been reported as useful method to overcome intolerance. Several reports of desensitization have been published and success rate ranged 45 to 100% [1,2,7,9]. But long-term results 8 of desensitization have not been reported. Therefore, authors analysed clinical follow up results of our desensitized patients. Clinical relapse of intolerant group required biologic therapy was significantly higher than that of tolerant group. Relapse rate was equally high in success, failure group and no desensitization group. Time interval from the onset of IBD to relapse of intolerant group was significantly shorter than that of tolerant group.

Desensitization was not useful from long follow up observation. Our results suggested the intolerant patients have to be treated carefully as high-risk group regardless of success or failure to desensitization. Nishio [10], reported clinical results of 50 patients with UC intolerant to mesalazine. They were not desensitized and 25.4% of them required biologic antibody and 16.9% of them required surgery during follow up. His results were similar to our results. At the onset, 33% of intolerant patients were recognized mucosal worsening endoscopically. Nakajima [11], reported colonoscopy findings of one intolerant patient with UC. Thirty-nine years old male noted rectal bleeding and colonoscopy on Sept 2015 revealed redness, granularity, and loss of vascular 9 pattern on the lower rectum. Mesalazine (2400 mg/day) was started and 7 days later, he noted fever, abdominal pain and diarrhea and colonoscopy revealed diffuse edema and loss of vascular pattern from the cecum to the rectum but no ulcers. Mesalazine was discontinued and symptoms were quickly disappeared and colonoscopy on Dec 2015 revealed complete recovery from inflammation. Miyoshi, et al. [12], reported 8 patients with UC exacerbated colitis after induction of 5-ASA that were improved by the withdrawal of 5-ASA. Seven of the 8 patients had a high fever and 3 of 5 patients undertook total colonoscopy showed right-side-dominant colitis. Similar 7 case reports were

Table 3. Incidence of relapse and time interval from the onset to relapse in intolerant and tolerant patients

	incidence of relapse	incidence of relapse in desensitized patients	time interval from the onset to relapse	time interval from the onset to relapse in desensitized patients
intolerant patients	25.0% (17/68)	success 22.9% (8/35) failure 21.1% (4/19) no desensitization 35.7% (5/14)	4.4±3.3 years	success 5.0 ± 3.2 years failure 5.3 ± 3.5 years no desensitization 2.8 ± 2.4 years
tolerant patients	6.8% (85/1258)		5.3 ±7 0 years	
	P<0.001		P>0.07	

published in which 10 patients presented aggravation of bloody diarrhoea after 5-ASA administration [13-19]. These findings were thought as local mesalazine effect to colonic mucosa of intolerant patient. Mesalazine induced inflammatory reaction on the affected colonic mucosa of intolerant patients as same as the systemic symptoms.

Hanauer [20], stated that mesalazine rarely can cause worsening of colitis. This may be masked when patients are receiving concurrent steroids and can 10 appear as “refractory colitis”. Generally, it is recommended that patients who are unable to taper steroids despite high dose of mesalazine be given a trial off mesalazine to rule out unanticipated hypersensitivity colitis. The worsening of colitis is distinguishable from loosening of stools or diarrhea related to increased ileal secretion induced by olsalazine. The latter is a dose- related phenomenon that usually improves as the colitis heals. Desensitization relieved intolerant symptoms in succeeded patients but could not afford the same clinical long-term results of tolerant patients. Intolerance was not simple clinical phenomenon solved by desensitization.

In intolerant patients, some unknown factor induced colonic inflammatory relapse earlier and more frequently. The fact we found in this clinical study was a only part of clinical aspect of intolerance and mechanism of intolerance is expected to be discovered to improve clinical results of IBD patients.

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