Clinical Case Report

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Case report

Pentoxifylline treatment in microscopic colitis

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Abstract

Rationale: Microscopic colitis is a common cause of diarrhea. Pentoxifylline, a xanthine derivative with anti-tumor necrosis factor-alpha properties, is prescribed for intermittent claudication and other disorders. Our goal was to evaluate the outcomes of patients with microscopic colitis treated with pentoxifylline.

Patient concerns: Nine patients with microscopic colitis (8 collagenous colitis and 1 lymphocytic colitis) seen at Mayo Clinic, Rochester, between January 1, 1997 and November 30, 2016, were included. The median age was 56.9 years (range 51.6–60.2), 8 were female (89%), and the median disease duration was 64.8 months (range 60–109). The indications for treatment were budesonide refractoriness in 7 patients, budesonide dependence in 1 patient, and budesonide intolerance in 1 patient.

Diagnoses: A histological diagnosis of microscopic colitis was confirmed in all patients.

Interventions: Pentoxifylline 400 mg three times a day was used for a median of 3 months (range 2.5–8.3).

Outcomes: Complete response occurred in 1 patient (11%) and partial response in 3 patients (33%). The patient who achieved complete response was treated with pentoxifylline due to budesonide intolerance, and completed 43 months of successful maintenance therapy. There were no adverse effects reported.

Lessons: The majority of budesonide-experienced patients with active microscopic colitis did not respond to pentoxifylline. However, it was well-tolerated, with 1 patient achieving long-term remission and one-third of the cohort having a partial response. Larger controlled studies are required to evaluate the efficacy of pentoxifylline and predictors of response in microscopic colitis. In particular, patients who are not budesonide-refractory may be more likely to respond.

Abbreviations: CC = collagenous colitis, LC = lymphocytic colitis, MC = microscopic colitis, TNF-α = tumor necrosis factor-alpha.

Keywords: collagenous colitis, lymphocytic colitis, microscopic colitis, pentoxifylline

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1. Introduction

Microscopic colitis (MC) is an inflammatory disease of the colon, and a common cause of chronic watery diarrhea, especially in the elderly.[1] There are 2 main subtypes of MC, namely lymphocytic colitis (LC) and collagenous colitis (CC). Initial management involves gathering a thorough dietary history and careful medication review to eliminate exacerbating factors.[1] The American Gastroenterological Association recommends first-line pharmacologic treatment with budesonide.[2] Alternative therapies such as antidiarrheal agents, bismuth subsalicylate, corticosteroids, thiopurines, methotrexate, and antitumor necrosis factor-alpha (TNF-α) therapy[3–5] have been used with varying rates of success.

Pentoxifylline is a xanthine derivative that reduces blood viscosity, improves erythrocyte flexibility, and decreases platelet aggregation.[6] Additionally, it inhibits mast cell transcription of the TNF-α gene.[7] It is US Food and Drug Administration-approved for the treatment of intermittent claudication.[8] While pentoxifylline has previously been used for the treatment of colitis in animal models,[9] its use for inflammatory conditions of the colon in humans has not been previously described. In this case series, we sought to evaluate the outcomes of patients with active MC treated with pentoxifylline.

2. Materials and methods

Patients with chronic diarrhea and a histologic diagnosis of MC between January 1, 1997 and November 30, 2016 at Mayo Clinic, Rochester, were identified through a pathology database.

Table 1

Demographic and clinical characteristics of microscopic colitis study cohort treated with pentoxifylline* (N = 9).

Patient	Age	Sex	Type	Disease duration	Smoking status	Comorbidities	No. stools/d	Prior treatment†	Treatment duration	Response
1	54	F	CC	120	Never	None	15	Pred, MTX, BAB, 5-ASA	3	None
2	51	F	CC	60	Current	None	13	Pred, AZA, BAB	3†	Partial
3	58	F	LC	36	Never	None	10	5-ASA, BAB	2.5	Partial
4	42	F	CC	72	Former	Celiac	5	Pred, 5-ASA, BAB	1	None
5	41	F	CC	60	Former	None	8	5-ASA, AZA, BAB	4	Partial
6	60	M	CC	57	Never	None	6	5-ASA, BAB	0.7	None
7	63	F	CC	132	Former	None	5	No additional medications	15	None
8	56	F	CC	109	Never	Celiac	3	5-ASA	43	Complete
9	65	F	CC	64.8	Never	Celiac	3	5-ASA	8.3‡	None

5-ASA = 5-aminosalicylic acid, AZA = azathioprine, BAS = bile acid binder, CC = collagenous colitis, celiac = celiac disease, F = female, LC = lymphocytic colitis, M = male, MTX = methotrexate, Pred = prednisone.

* All doses 400 mg 3 times daily.

† All patients treated with budesonide previously.

‡ On concomitant budesonide.

The histologic features of LC were defined as increased intraepithelial lymphocytes (>20 lymphocytes per 100 epithelial cells) and a mixed inflammatory infiltrate in the lamina propria. The histologic features of CC included the above criteria, plus an abnormally thick subepithelial collagen band (>10 μm). Patients with active MC treated with pentoxifylline were identified through an electronic search of the medical record. All patients had documentation in their chart of discussion of the off-label use pentoxifylline. Budesonide-refractory patients were defined as having inadequate control of diarrhea after an appropriate course of therapy, whereas budesonide dependence was defined as recurrence of diarrhea after discontinuation of budesonide. Demographics, clinical data, and outcomes were collected.

Complete response to treatment was defined as <3 stools daily and <1 watery stool daily on average, partial response as improvement in stool frequency ≥50%,[4] and no response was defined as improvement <50%.[10] Patients were followed either until the end of treatment or until the time of last follow-up on treatment. The statistics were descriptive with continuous data presented as mean ± standard deviation (S.D.) or median (range), as appropriate, and categorical data summarized as proportions and percentages. The Stata software (version 13.1, StataCorp, College Station, TX) was used for statistical analysis. The Institutional Review Board approved the study.

3. Results

3.1. Patient characteristics

The study cohort consisted of 9 patients (8 females, 88%); 8 patients had CC, whereas 1 had LC (Table 1). All had been previously treated with budesonide, antidiarrheals, and bismuth subsalicylate. Additionally, 6 patients had prior treatment with bile-acid binders, 3 patients had prior treatment with prednisone, and 6 patients had prior treatment with 5-aminosalicylic acid agents. The indications for treatment included budesonide-refractory symptoms in 7 patients, budesonide dependence in 1 patient, and budesonide intolerance in 1 patient. The median age at treatment initiation was 56.9 years (range 51.6–60.2), with median disease duration of 64.8 months (range 60–109). The mean number of bowel movements daily (±SD) was 9.5 ± 4.3.

3.2. Treatment response

Pentoxifylline was used for a median of 4 months (range 1.5–15) at a dose of 400 mg 3 times daily. Complete response occurred in 1 patient (11%) and partial response in 3 (33%), whereas 5 (55%) did not respond. Two patients (76%) were on a concomitant budesonide taper, whereas none of the patients were on a concomitant immune modulator. The 1 patient who achieved complete remission was a 57-year-old woman who had CC for 9 years and averaged 3 loose bowel movements before treatment initiation. She was budesonide-intolerant, was no longer on budesonide, and completed 43 months of successful maintenance therapy, up to the date of last follow-up, without relapse. There were no recorded adverse effects in the study cohort.

4. Discussion

To our knowledge, this is the first study describing the use of pentoxifylline in a cohort of patients with MC. The majority did not respond. However, one-third of the cohort had a partial response, and 1 patient achieved complete response and experienced long-term remission. Pentoxifylline was well-tolerated with no adverse effects reported.

The clinical response seen with pentoxifylline is likely secondary to its anti-TNF-α properties. An adjunctive mechanism of action worth considering is the inhibition of inflammatory cells endothelial adhesion, which has been shown in experimental animal models [11] Anti-TNF therapy with infliximab and adalimumab in MC has been described. In a study of 4 patients with severe MC refractory to standard treatment, there was a 60% to 90% decrease in bowel movements after 1 dose of infliximab.[12] Moreover, long-term remission was achieved in 3 of 4 patients.[12] In another study, 10 patients with MC received anti-TNF therapy, with 4 having complete response and 4 having partial response.[5] Other smaller case series have shown promising results.[13,14] The anti-TNF properties of pentoxifylline have been utilized to treat a broad spectrum of diseases apart from claudication, ranging from ocular cicatricial pemphigoid[15] to rheumatoid arthritis.[16,17] However, its use in MC has not been previously described.

This cases series has some limitations, in particular, its retrospective nature, the small sample size, and relatively treatment-refractory nature of the cohort, which limit the generalizability of the study results to the general population of patients with MC. Nonetheless, it highlights a potentially novel use of an established medication with a favorable safety profile.

5. Conclusions

In conclusion, while pentoxifylline did not result in a clinical response in the majority of patients, it showed some efficacy in a small cohort of patients and was well-tolerated. Pentoxifylline may have some utility in the treatment of MC, particularly in patients with a concomitant indication for therapy. Furthermore, it may be more effective in patients with MC who are not budesonide-refractory. Larger controlled studies are necessary to further evaluate the efficacy of pentoxifylline in MC and identify predictors of treatment response.

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