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CASE SERIES

Lack of effect of methotrexate in budesonide-refractory collagenous colitis

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Background: In most cases, collagenous colitis can be treated effectively with budesonide. However, some patients develop side effects or have chronic symptoms refractory to budesonide. This paper reports an open case series of patients intolerant or refractory to budesonide who were treated with methotrexate (MTX).

Methods and patients: Nine patients (seven women) with a median (range) age of 62 (44–77) years were studied. Bowel movements were registered during 1 week prior to baseline and after 6 and 12 weeks' treatment, enabling calculation of the mean bowel movements/day. All patients underwent colonoscopy with biopsies before inclusion to confirm diagnosis. Open treatment with MTX was given 15 mg subcutaneously weekly for 6 weeks and was increased to 25 mg for a further 6 weeks if symptoms were unresponsive to the first 6 weeks' treatment. The endpoint was clinical remission, which was defined as a mean <3 stools/day and mean <1 watery stool/day/week at Week 12. The Short Health Scale was used at baseline and Week 12 to assess health-related quality of life.

Results: Five patients fulfilled the treatment according to the protocol and four patients discontinued the study after 3–6 weeks because of adverse events. No patient achieved clinical remission at Week 12. The mean stool frequency/day at baseline was 6.0 stools/day, thereof 5.4 watery stools/day and after 12 weeks treatment 6.4 stools/day, thereof 5.7 watery/day. No patient appreciated an improvement of health-related quality of life.

Conclusion: Short-term treatment with MTX had no clinical effect in collagenous colitis patients intolerant or refractory to budesonide. Alternative therapies should be investigated in these patients.

Keywords: microscopic colitis, health-related quality of life, Short Health Scale, MTX, stools, diarrhea

Background

"Collagenous colitis" (CC) is a chronic inflammatory bowel disease presenting mainly with non-bloody, watery diarrhea and few or no endoscopic abnormalities. The diagnosis is based on clinical presentation and histopathological findings – typically inflammation of the lamina propria with an increase in intraepithelial lymphocytes – and epithelial damage together with a characteristic thickening of the subepithelial collagen layer.[1] CC is common, with an incidence rate of 5–6 per 100,000 inhabitants.[2,3] Budesonide is the best-documented treatment in CC.[4–6] In a Cochrane meta-analysis, budesonide was described to be effective and well tolerated for inducing remission (pooled odds ratio 12.32 [95% confidence interval {CI} 5.53–27.46]) and maintaining remission (pooled odds ratio 8.40 [95% CI 2.73–25.81]) with a number needed to

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treat of two.[7] In contrast, after withdrawal of short-term budesonide treatment, relapse rates were high and reached 61%–80% and the median time until recurrence of symptoms was 2 weeks (range 1–104 weeks).[8] The risk for relapse also remains high after 6 months' maintenance treatment with 6 mg budesonide,[9] and these studies support that maintenance therapy is necessary in selected patients.

The evidence for use of immunomodulators in CC is almost nonexistent. Treatment with azathioprine or 6-mercaptopurine has been tested in a small group of patients (N = 9) with steroid-dependent or refractory CC. A response rate of 89% and a steroid-sparing effect were found.[10] In a retrospective report, beneficial effects of oral low-dose methotrexate (MTX; 5–25 mg/week) were observed in 16 of 19 treated patients.[11]

In this paper, which reports an open case series, we describe nine patients intolerant or not responding to budesonide who were treated with MTX 15–25 mg/week subcutaneously (sc) for 12 weeks. The primary endpoint was clinical remission at 12 weeks, defined according to Hjortswang et al.[12]

Methods and patients

From June 2010 to May 2011, nine patients (seven women) with CC were treated with MTX. The median (range) age of the patients was 62 (44–77) years. Five patients were classified as being intolerant to budesonide due to unacceptable side effects, especially weight gain and moon face. The other four patients were nonresponders and had active disease and persistent diarrhea despite 6 mg budesonide maintenance treatment. Patient characteristics are given in Table 1.

All patients kept a stool diary for 1 week prior to baseline and after 6 (or exclusion) and 12 weeks' treatment, monitoring the daily number of bowel movements and the consistency of these (arbitrary: 1 = formed, 2 = loose, 3 = watery). Total colonoscopy with biopsies was performed prior to inclusion to confirm diagnosis. Infectious causes, celiac disease, or drug-induced CC were ruled out. All patients had tested cholestyramine previously without effect. Two patients had concomitant bile acid malabsorption (measured by SeHCAT [23-seleno-25-homo-tauro-cholic acid]; cutoff value <10%) but had not responded to high doses of cholestyramine (up to 30 g/day). MTX 15 mg sc was given once weekly and increased to 25 mg sc if the patient was not in clinical remission after Week 6. Folic acid supplementation was given. Blood samples were taken according to routine safety procedures.

Clinical remission was defined as mean <3 stools/day and mean <1 watery stool/day according to the disease activity criteria of Hjortswang et al.[12] To assess quality of life the Short Health Scale (SHS)[13] was used at baseline, Week 6, and Week 12 or at exclusion. All patients gave their written informed consent before start of treatment.

Results

In three patients, the budesonide dose (6 mg) at screening was tapered and discontinued after 4 weeks' treatment with MTX. All other patients had stopped their budesonide maintenance treatment prior to baseline due to intolerance or nonresponse. Otherwise, no concomitant antidiarrheal treatment was given to any patient during the treatment period.

Four patients discontinued MTX due to adverse events and five patients fulfilled the 12 weeks' therapy according to the protocol (Table 2). No patient improved during MTX treatment and no patient was in clinical remission at Week 12. At baseline, the mean stool number for all patients was

Table 1 Patient characteristics

Patient	Sex	Age (years)	Date of diagnosis	Comorbidity	Previous treatment for CC
1	F	47	06/2006	Anxiety, depression, pustulosis palmoplantaris, bile acid malabsorption	lop, chol, bud
2	F	44	03/2010	Raynaud's phenomenon, asthma	lop, chol, bud
3	M	74	02/2006	Whipple operation in 2009 due to benign pancreatic tumor, bile acid malabsorption	lop, chol, bud, mes, pred
4	F	49	03/2001	None	lop, chol, bud, aza
5	M	77	06/2009	Prostatic cancer treated with radiotherapy in 2005	lop, chol, bud, pred
6	F	54	10/2006	None	lop, chol, bud
7	F	62	05/2003	Hypothyreosis, cholecystectomy	lop, chol, mes, pred, bud, ab
8	F	72	04/2006	Breast cancer, asthma, hyperthyreosis	lop, chol, mes, bud, ab
9	F	65	11/1997	Hypertension Billroth II operation due to bleeding gastric ulcer in 2006	lop, chol, mes, sulf, ab, bud

Abbreviations: ab, antibiotics; aza, azathioprine; bud, budesonide; CC, collagenous colitis; chol, cholestyramine; lop, loperamide; mes, mesalazine; pred, prednisolone; sulf, sulfasalazine.

Table 2 Results of methotrexate (MTX) treatment

Patient	Duration of MTX treatment (weeks)	Mean number of stools/watery stools per day at baseline	Mean number of stools/watery stools per day after 6 weeks or at withdrawal	Mean number of stools/watery stools per day after 12 weeks	Effect of MTX
1	3	6.5/3.0	6.0/4.0		Discontinued due to AE (nausea, mood swings)
2	12	8.0/8.0	9.0/9.0	6.5/6.5	No clinical effect
3	12	7.0/7.0	4.0/4.0	9.0/7.0	No clinical effect
4	12	3.5/1.0	6.5/6.5	7.0/7.0	No clinical effect
5	6	4.5/4.5	3.5/3.5		Discontinued due to AE (nausea, conjunctivitis, fatigue)
6	12	3.5/1.5	1.0/0.0	3.5/2.0	No clinical effect
7	4	8.0/4.0	6.0/3.0		Discontinued due to AE (more diarrhea, nausea, chills)
8	3	5/1	4.5/1.5		Discontinued due to AE (allergic reaction = intense erythema and edema in the eyes and face)
9	12	8/8	7.5/7.5	6/6	No clinical effect

Abbreviation: AE, adverse effect.

6.0 stools/day, thereof 5.4 watery stools/day versus mean 6.4 stools/day, thereof 5.7 watery/day after 12 weeks. No patient experienced an improvement in health-related quality of life (data not shown).

Discussion

To our knowledge, this is the first evaluation of the efficacy of MTX sc in CC patients intolerant or not responding to budesonide. None of our patients obtained a beneficial clinical effect of MTX, despite a dose of up to 25 mg per week. Four of nine developed adverse events on 15 mg MTX. Although these were mild in all cases, they led to discontinuation of the treatment.

In general, patients with active CC respond well to induction treatment with budesonide.[7] However, up to 80% of the patients relapse after budesonide cessation, highlighting that the natural course of the disease is not altered.[8] In these cases, maintenance treatment is advisable and two studies have shown efficacy for 6 mg budesonide over a 6-month period.[9,14] However, a daily dose of 6 mg might be too high for long-term treatment, causing steroid side effects in elderly patients. To determine whether a lower budesonide dose is equally efficacious, an ongoing maintenance trial with 4.5 mg is currently underway.[15] Budesonide has high efficacy in most CC cases, but some patients may develop side effects or stop responding to treatment.

In a retrospective study, Riddell et al described 19 patients who were treated with oral MTX (median dose 7.5–10 mg/week) for varying durations. Fourteen patients had a "good" and two patients had a "partial" response, and the clinical response was seen early, generally within 2–3 weeks. The definition of "response," however, was not elucidated. Six of the 14 patients who had a "good" response had earlier received prednisolone, and only one patient had been treated with budesonide.[11] The discrepancy with the results of our study is likely due to selection, as our patients were unresponsive to numerous treatment options including budesonide (Table 2) and were classified as having chronic, active disease. All our patients had previously received treatment with cholestyramine without obtaining clinical effect. The two patients with bile acid malabsorption were given doses of up to 30 g without clinical improvement, making it unlikely that bile acids were the sole cause of their watery stools. The two patients with thyroid disease were euthyroid. Furthermore, our criteria of remission were not comparable to the endpoints in Riddell's report.

Considering the variable bioavailability of MTX, we chose to administer MTX sc to control for variations in drug absorption. Our initial dose of 15 mg was higher than in Riddell et al's report, which might have provoked side effects. All adverse events were benign and reversible. In Riddell's study, only three patients discontinued MTX. Considering the rapid clinical response seen within 2–3 weeks in their study, we assessed our treatment period of 12 weeks sufficient to achieve clinical response.

Another interesting observation is that only one patient in our study had never smoked, four were active smokers, and four had ceased smoking. Smoking seems to be a risk factor

for CC, as smokers develop their disease earlier in life and smoking possibly aggravates activity.[16]

In daily practice, patients with budesonide-refractory CC should undergo an extensive investigation to exclude other concomitant causes of diarrhea besides irritable bowel syndrome – diarrhea (IBS-D), especially celiac disease and bile acid malabsorption, which may be associated with microscopic colitis. According to our clinical experience, these patients have a poor quality of life, are socially handicapped, and need extensive medical attention. Although the number of cases herein is small, the results are clearly negative and do not support MTX as second-line treatment in CC.

Conclusion

MTX (15–25 mg/week sc) seems ineffective in patients with CC who have lost response or become intolerant to budesonide and alternative therapy should be investigated.

Disclosure

The authors declare no conflicts of interest in this work.

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