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Outcomes of Patients with Microscopic Colitis Treated with Corticosteroids: A population-based study

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Abstract

Objectives—To evaluate the outcomes of corticosteroid-treated microscopic colitis in a population-based cohort, and to compare these outcomes in patients treated with prednisone or budesonide

Methods—A historical cohort study of Olmsted County, Minnesota residents diagnosed with collagenous colitis or lymphocytic colitis from 1986 to 2010 was performed using the resources of the Rochester Epidemiology Project.

Results—Of 315 patients, 80 (25.4%) were treated with corticosteroids. The median age was 66.5 years (range: 16 – 95) and 78.7% were female. Forty patients (50%) had lymphocytic colitis and 40 (50%) had collagenous colitis. Six patients were lost to follow-up. The remaining 74 had a median follow-up of 4 years (range: 0.2 – 14); 56 (75.6%) had complete response and 15 (20.3%) had partial response. Fifty patients out of 71 who responded (70.4%) had a recurrence after corticosteroid discontinuation. After 397 person years of follow-up in the 73 patients with long-term data, 47 (64.4%) required maintenance with corticosteroids.

Prednisone was used in 17 patients (21.2%) and budesonide in 63 (78.8%). Patients treated with budesonide had a higher rate of complete response than those treated with prednisone (82.5% vs 52.9%; odds ratio, 4.18; 95% CI, 1.3 – 13.5) and were less likely to recur (hazard ratio, 0.38; 95% CI, 0.18 – 0.85; p=0.02).

Conclusion—Patients with microscopic colitis often respond to corticosteroid therapy, but with a high relapse rate. Budesonide had a higher response rate and a lower risk of recurrence than prednisone.

Keywords

microscopic colitis; corticosteroid; outcomes; response; recurrence

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Introduction

Microscopic colitis (MC) is a common cause of chronic watery diarrhea and gastrointestinal symptoms (1). Diarrhea can range from mild and intermittent to severe and persistent, with an impact on quality of life, especially if there is significant fecal incontinence (1). In patients with severe symptoms, treatment with corticosteroids is often used (1). In randomized clinical trials, the response rate to corticosteroid therapy is high, but a significant number of patients experience recurrence after corticosteroid withdrawal (2–7). No studies have directly compared the effectiveness of prednisone to budesonide (8). A recent meta-analysis included 6 induction trials with 9 subjects treated with prednisolone, 82 treated with budesonide, and 77 treated with placebo (8). Response was reported in 80% in the budesonide group versus 26% in the placebo group. In the small study of subjects treated with prednisolone, no statistically significant difference in response was seen compared to those treated with placebo (8).

These studies are limited because they mostly involve patients with collagenous colitis (CC) (8). Furthermore, the results of clinical trials are not always representative of clinical experience, in part because of potential referral bias and exclusion criteria, and no studies have directly compared outcomes in patients treated with budesonide to those treated with prednisone. Thus, this population-based study aimed to investigate the clinical characteristics and outcomes in a cohort of patients with both CC and lymphocytic colitis (LC) who were treated with corticosteroids. We also aimed to compare outcomes in patients treated with prednisone to those treated with budesonide.

Methods

A retrospective chart review of Olmsted County, Minnesota residents diagnosed with CC or LC from January 1, 1985 to December 31, 2010 was performed using the Rochester Epidemiology Project (REP). This centralized diagnostic index maintains records from all outpatient visits, emergency room visits, hospitalizations, nursing home visits, surgical procedures, autopsy examinations, and death certificates for all residents since 1908 (9). All medical records, from all sources of care available to Olmsted County residents, are linked and accessible through the REP, including drug prescriptions (9). The REP therefore allows investigators to follow subjects through their outpatient and hospitalization contacts across all local medical facilities, regardless of where the care was delivered and of insurance status (9).

We identified potential cases of microscopic colitis using ICD-9 codes 558.9, 561, and 563.9, and a code that is specific to our institution for “non-infectious colitis”. An additional search was performed using the Mayo Clinic Pathology database. Using this strategy, which was used previously to identify cases in an epidemiological study of microscopic colitis in Olmsted County (10), records for potential subjects were identified and then reviewed to confirm cases as defined below. This study was approved by both the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Adults eighteen years or older, who provided research authorization, were identified based on the presence of diarrhea (greater than three loose stools in 24 hours), normal endoscopic colonic appearance, and histopathologic evidence of CC or LC (10). Individuals who did not have diarrhea, who had an alternative explanation for their diarrhea, such as an infectious etiology or inflammatory bowel disease, or who had no evidence of microscopic colitis on review of their biopsies were excluded. From confirmed cases, we identified those who were treated with corticosteroids (either budesonide or prednisone). Demographic and clinical information was abstracted by chart review, including initial corticosteroid start and stop

date, type of corticosteroid and dose, response, the date of recurrence, and the need for corticosteroid maintenance.

Response was defined as improvement in bowel movements during the initial course of corticosteroid treatment (within the first 8 weeks). Complete response was defined as resolution of diarrhea, whereas partial response was defined as at least 50% improvement in number of bowel movements. Improvement of less than 50% was considered non-response. Recurrence was defined as the recurrence of diarrhea after improvement during the first treatment course of corticosteroids. Long-term corticosteroid maintenance was defined as restarting this treatment for microscopic colitis after a recurrence. The duration of follow up was determined from the date of corticosteroid initiation to the date of last follow up.

There were seven patients who treated with prednisone for other conditions; one each for aortitis, polymyalgia rheumatica, chronic obstructive pulmonary disease, chronic urticaria, and sacroiliitis, and two with undifferentiated connective tissue disease. These patients were included in our analyses as we were able to determine the effect of corticosteroid therapy on their colitis symptoms.

Statistical analyses were performed using JMP version 9.0.1. Differences in treatment response at 8 weeks were compared using chi squared analysis. Cox proportional hazard analysis was used to compare time to recurrence in patients treated with prednisone to those treated with budesonide.

Results

Of 315 Olmsted County residents diagnosed with microscopic colitis from 1986 to 2010, 80 patients (25.4%) were treated with corticosteroids. The median age at the time of microscopic colitis diagnosis was 66.5 years (range, 16 – 95) and 78.7% were female. Forty patients (50%) had LC and 40 (50%) had CC. The percentage treated with corticosteroids increased from 0% from 1986 – 1990 to 10% from 1996–2000, 26.5% from 2001 to 2005, and 62.5% from 2006 – 2010 (p=0.005). Of the 80 patients treated with corticosteroids, 17 (21.3%) were treated with prednisone and 63 (78.7%) were treated with budesonide. The median dose of budesonide was 9 mg (range, 6 – 9 mg) and the median dose of prednisone was 25 mg (range, 7 – 40 mg).

Six patients were lost to follow-up. The remaining 74 patients had a median duration of follow-up of 4 years (range 0.2 – 14 years); 56 (75.6%) had complete response and 15 (20.3%) had partial response. Of those treated with prednisone, 9/17 (52.9%) had a complete response, 7/17 (41.2%) had a partial response, and 1/17 (5.9%) had no response. Of those treated with budesonide, 47/57 (82.5%) had a complete response, 8/57 (14.0%) had a partial response, and 2/57 (3.5%) had no response. The rate of complete response was higher in patients treated with budesonide compared to those treated with prednisone (82.5% vs 52.9%, p=0.02; odds ratio 4.2, 95% CI 1.3 – 13.5). The rate of complete response to corticosteroid therapy was similar in patients with LC and CC (77.8% vs 73.4%, p=0.68; odds ratio 1.25, 95% CI 0.43–3.63).

Patients treated with budesonide were less likely to recur than those treated with prednisone (hazard ratio, 0.38; 95% CI 0.18 – 0.85; p=0.02). The median time to recurrence after stopping prednisone was 21.0 days, which was significantly shorter than after stopping budesonide (63.5 days, p=0.02).

Of the three patients who did not respond to corticosteroids, one was lost to follow up after failing budesonide, one was maintained on diphenoxylate after failing sulfasalazine, bismuth

subsalicylate, and budesonide, and one was maintained on a restricted diet and diphenoxylate after failing budesonide.

Of the 71 patients who responded, 50 (70.4%) had a recurrence after steroid discontinuation. After 397 person-years of follow-up in the 73 patients with long-term data, 47 (64.4%) required maintenance with corticosteroids. Three other patients with a recurrence were maintained on loperamide, bismuth subsalicylate, and mesalamine, respectively. In the remaining 23 patients who did not have a recurrence, 6 (26%) remained in remission on no medications while 17 (74%) were maintained with an alternative therapy, typically antidiarrheal drugs, even though they did not have symptomatic recurrence.

Discussion

In this population-based cohort study, the use of corticosteroid therapy increased significantly, from 0% from 1986 – 1990 to 62.5% from 2006 – 2010. Budesonide was used more commonly than prednisone, and was more effective in terms of a higher response rate, a lower rate of recurrence, and a longer time to recurrence. Prior studies assessing budesonide therapy have mostly included patients with collagenous colitis (2–7), while our study had equal numbers of patients with LC and CC.

Randomized controlled trials evaluating budesonide in the treatment of microscopic colitis have shown a high response rate as well as a high rate of relapse. In CC, response rates have ranged from 57% to 100%, with a recurrence rate of 80% (2, 3, 7). In LC, response to budesonide was seen in 86% versus 48% with placebo (p=0.010), with 44% of patients experiencing a recurrence after discontinuation of budesonide after a mean follow up of two months (10). Similarly, our study demonstrated a response rate to budesonide of 83% and a recurrence rate of 70%.

Two randomized controlled maintenance trials have demonstrated that budesonide is superior to placebo for maintaining remission, at least through 6 months, although the relapse rate was still high after discontinuation of prolonged therapy (5, 6). In one study, patients received open-label budesonide induction and were then randomized to maintenance therapy with budesonide 6 mg per day or placebo. Of the patients treated with budesonide, 76.5% (13/17) remained in remission at 24 weeks versus 12% (2/17) treated with placebo (5). In a similar study, 65% of patients (15/23) treated with budesonide maintained remission compared to 26% (6/23) treated with placebo (6). Our experience was similar to these results, with a majority of our patients being maintained on budesonide therapy.

In keeping with the availability of budesonide and clinical trials demonstrating its effectiveness in microscopic colitis, we saw a decrease in the use of prednisone over the study period while the use of budesonide increased. Budesonide demonstrated a better response rate and lower recurrence rate than prednisone, although these results should be interpreted with caution as patients were not randomized to treatment, and in some patients the dose of prednisone was relatively low.

Budesonide has fewer corticosteroid-related adverse effects than prednisone, although the risk of side effects may be increased in those with liver disease or those who drink grapefruit juice (11). In patients on long term budesonide, monitoring of bone density, blood pressure, and blood glucose is recommended (11).

In conclusion, the overall use of corticosteroids has become increasingly common in patients with microscopic colitis. Patients treated with corticosteroids for microscopic colitis have a high response rate and a significant risk of recurrence after corticosteroid withdrawal, often

requiring long-term corticosteroid maintenance treatment. Budesonide had a higher response rate than prednisone, a lower risk of recurrence, and a longer time to recurrence.

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Study Highlights

1. What is current knowledge:
    a. Several options exist for the treatment of microscopic colitis
    b. Corticosteroid therapy appears to be effective
    c. Recurrence is common after discontinuing corticosteroid treatment
2. What is new here:
    a. Corticosteroid use has increased significantly over time
    b. Budesonide is more effective than prednisone
    c. Budesonide has a lower risk of recurrence and a longer time to recurrence