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Importance of eosinophilic infiltration of the colonic mucosa in ulcerative colitis patients who are refractory to maintenance therapy

A prospective, single-center study

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Abstract

Eosinophilic infiltration is sometimes observed histologically in ulcerative colitis (UC), but the effect of the degree of infiltration on the treatment course for UC is not completely understood. We investigated whether short-term steroid administration in UC patients refractory to maintenance therapy, with high eosinophilic infiltration in the colonic mucosa, contributed to the clinical and endoscopic improvement. Ten patients with endoscopically active and pathologically high eosinophilic infiltration, based on pathological examination using endoscopic biopsy, were examined for the clinical background when starting steroid treatment. The clinical and endoscopic improvement before and after steroid use were assessed prospectively. The average initial steroid dosage and duration of use were 21.0 mg and 102.7 days, respectively. The mean values before and after steroid use of the clinical activity index, the Mayo endoscopic subscore, and the UC endoscopic index of severity were 2.4 and 1.0, 1.8 and 0.7, and 3.9 and 1.1, respectively. All scores improved significantly after steroid use ($P = .042$, $P = .002$, $P = .002$, respectively). Steroids were discontinued in all patients; no patients required steroid re-administration. There may be cases of UC with eosinophilic infiltration into the colonic mucosa and resistance to maintenance treatment, suggesting that short-term steroid administration may contribute to clinical and endoscopic improvements.

Abbreviations: CAI = clinical activity index, IL = interleukin, MES = Mayo endoscopic subscore, NK = natural killer, Th1 = T-helper-1 cells, TNFα = tumor necrosis factor alpha, UC = ulcerative colitis, UCEIS = ulcerative colitis endoscopic index of severity, WBC = white blood cell.

Keywords: clinical remission, endoscopic remission, eosinophil, steroids, maintenance therapy, observational study, ulcerative colitis

1. Introduction

Ulcerative colitis (UC) is a gastrointestinal disorder of unknown pathogenesis that causes inflammatory lesions in the large intestine.[1] Corticosteroid treatment is the first-line treatment option in patients with moderate-to-severe UC, but there are patients who show steroid dependence or resistance to steroids, and approximately 20% to 30% of patients do not improve with steroid treatment.[2,3] Advanced therapies such as biologics and calcineurin inhibitors are administered in such patients as medical treatment to replace steroids, but if none of these advanced treatments are successful, colectomy must eventually be performed.

The pathophysiology of UC includes activation of immunocompetent cells due to disruption of the mucosal defense mechanism in the large intestinal mucosa, and CD4-positive T cells play a major role among these immunocompetent cells. However, in recent years, it has been reported that the pathophysiology of refractory UC is associated with interleukin (IL)-33 produced by damaged colonic epithelial cells and eosinophils induced by IL-33.[4,5] Recent studies have reported that the mucosa of intractable UC lesions has a large amount of eosinophilic infiltration,[6] and the eosinophilic infiltration of the colonic mucosa is an indicator of treatment resistance to vedolizumab.[7]

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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We recently reported that benralizumab, an anti-IL-5 receptor antibody, was used in patients with asthma and UC, which showed an improvement in coexisting UC.[8] Benralizumab is known to directly eliminate eosinophils by inducing apoptosis by directly binding to IL-5 receptor α on the surface of eosinophils and inducing natural killer cells by antibody-dependent cellular cytotoxicity.[9] It was also reported that administration of steroids in patients with anti-tumor necrosis factor alpha (TNFα) antibody-resistant UC combined with eosinophilic gastroenteritis resulted in prominent improvement in eosinophilic infiltration and improvement in UC activity.[10] However, in cases where inflammation is prolonged despite maintenance treatment for UC, such as biologics, the relationship between the degree of eosinophilic infiltration as a histological finding in the colonic mucosa and the disease state has not been thoroughly investigated. In addition, the role of removal of eosinophils by short-term steroid administration in the pathophysiology of refractory UC is not elucidated.

Here, we investigated whether short-term steroid administration contributes to clinical and endoscopic improvement in patients with UC who have endoscopic disease activity despite maintenance treatment and with high eosinophilic infiltration on endoscopic biopsy.

2. Methods

2.1. Patients and study design

This study included patients with UC who were undergoing maintenance therapy and showed endoscopic disease activity by colonoscopy at Hamamatsu University School of Medicine between August 2017 and December 2018. Ten patients with conspicuous eosinophilic infiltration (≥20 cells/high-power field) were selected for pathological examination of biopsy specimens, and short-term administration of 0.6 mg/kg of steroids was started in these patients. The dose of steroid was gradually reduced by 5 mg every 2 weeks, and steroid administration was discontinued for approximately 2 months. Endoscopy was repeated within 2 weeks to 2 months after discontinuation of steroids, and the endoscopic activity, mucosal eosinophil count, and pathological activity were evaluated. These patients were diagnosed with UC according to the established criteria of the current UC based on typical clinical symptoms, endoscopic findings, and histological evaluation.[11] They were excluded from IBD such as indeterminate colitis and/or inflammatory bowel disease that was unclassified at the time of diagnosis. This was a single-center observational study.

The primary endpoint of this study was the change in the number of infiltrative eosinophils in the colonic mucosa before and after short-term steroid administration. The secondary endpoints were changes in clinical, endoscopic, and pathological activities.

2.2. Disease assessment

Clinical disease activity was assessed using the clinical activity index (CAI) by Rachmilewitz.[12] The criteria for Mayo endoscopic subscore (MES) were as follows: normal or inactive disease; mild disease with erythema, decreased vascular pattern, and mild friability; moderate disease with marked erythema, absence of vascular patterns, friability, and erosions; and severe disease with spontaneous bleeding and ulceration.[13] The ulcerative colitis endoscopic index of severity (UCEIS) score was calculated by summing the scores of the three descriptors: vascular pattern (scores 0–2), bleeding (scores 0–3), and erosions and ulcers (scores 0–3).[14] Serum C-reactive protein, albumin, hemoglobin, and white blood cell levels were measured by the clinical laboratory department of Hamamatsu University School of Medicine.

2.3. Measurement of the number of eosinophils infiltrating the colonic mucosa

The biopsy specimens collected during colonoscopy were formalin-fixed, paraffin-embedded, and hematoxylin and eosin-stained. The sample was used to measure the number of eosinophils infiltrating the colonic mucosa. Using the specimen of the part with the highest inflammation endoscopically, the part with the highest inflammation was selected by pathological diagnosis, and the eosinophil count was measured in the high-power field. Pathological activity scores were also calculated using Geboes biopsy histology scores.[15] All specimens were evaluated by two experienced pathologists who were blinded to the patient's background.

2.4. Statistical analysis

Statistical analysis was performed using SPSS for Windows, Version 26.0 (SPSS Inc., Chicago, Illinois) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). Continuous variables are presented as mean ± standard deviation or mean ± standard error of the mean, and groups were compared using the Student's t test or Mann–Whitney U test, unless stated otherwise. Categorical variables are presented as percentages and were analyzed using Fisher's exact test. Statistical significance was set at $P < .05$.

2.5. Ethical statement

Prior to the commencement of the present study, the protocol was reviewed and approved by the Ethics Committee of Hamamatsu University School of Medicine (number 15-222). All enrolled patients agreed to participate after being informed of the study purpose, and written informed consent was obtained. All investigations were conducted in accordance with the Good Clinical Practice Guidelines involving human subjects. The study adhered to the Declaration of Helsinki.

3. Results

3.1. Background of enrolled patients

The characteristics of the ten patients with UC are shown in Table 1. There were six men and four women, with an average age of 44.5 years and an average illness duration of 10 years. The disease types were total colitis, left-sided colitis, and proctitis in seven, two, and one patients, respectively. At the time of initial colonoscopy, the mean CAI, MES, and UCEIS scores were 3.0, 2.0, and 4.2, respectively. Prior to colonoscopy, 90% of patients received 5-aminosalicylic acid/salazosulfapyridine, 40% received anti-TNFα preparations, 20% received immunomodulators, and 10% received steroid enemas. The treatments administered at the start of the first steroid were 5-aminosalicylic acid/salazosulfapyridine in 80% of the patients, anti-TNFα antibody preparation in 40% of the patients, and immunomodulatory drug in 20% of the patients. The average amount of initial steroid usage was 21.0 mg, and the average duration of use was 102.7 days.

3.2. Changes in mucosal infiltrative eosinophil counts due to steroid administration

We examined the changes in mucosal infiltrative eosinophil counts before and after short-term steroid administration (Fig. 1). The mean eosinophil counts before and after steroid administration were 79.2 ± 20.6 and 56.8 ± 20.2, respectively, showing a statistically significant decrease in the eosinophil count ($P = .02$). Nine of the ten patients showed a decrease in mucosal infiltrative eosinophil counts due to steroid administration, while one patient showed an increase in the mucosal infiltrative eosinophil count after steroid administration.

Table 1

Baseline characteristics.

Characteristics	N = 10
Age (yr), mean (range) ± SD	44.5 (23–62) ± 11.8
Male/Female	6/ 4
Disease extent, n (%)	
Extensive colitis	7 (70.0)
Left-sided colitis	2 (20.0)
Proctitis	1 (10.0)
Disease duration (yr), mean (range) ± SD	10.0 (0–26) ± 8.3
CAI (Rachmilewitz index), mean (range) ± SD	3.0 (0–7) ± 2.3
MES, mean (range) ± SD	2.0 (1–3) ± 04
UCEIS, mean (range) ± SD	4.2 (2–6) ± 1.2
Induction dose of steroid (mg), mean (range) ± SD	21.0 (20–25) ± 2.0
Duration of steroid administration (days) ± SD	102.7 (63–161) ± 28.1
Medication before steroid induction, n (%)	
5-ASA/SASP	9 (90.0)
Anti TNFα antibody	4 (40.0)
Immunomodulators	2 (20.0)
Suppository steroids	1 (10.0)
Medication after steroid induction, n (%)	
5-ASA/SASP	8 (80.0)
Anti TNFα antibody	4 (40.0)
Immunomodulators	2 (20.0)
Suppository steroids	0 (0.0)

5-ASA = 5-aminosalicylic acid, CAI = clinical activity index, MES = Mayo endoscopic subscore, SASP = salazosulfapyridine, SD = standard deviation, TNFα = tumor necrosis factor alfa, UCEIS = ulcerative colitis endoscopic index of severity.

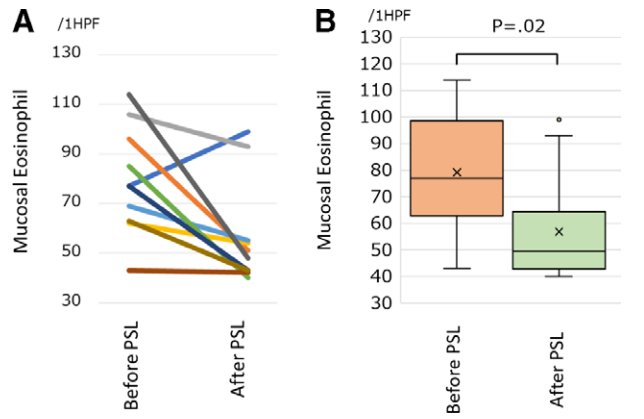

Figure 1. The changes in mucosal infiltrative eosinophil counts before and after short-term steroid administration. (a) Changes in the number of eosinophils infiltrating the mucosa before and after steroid administration in each case. (b) The average mucosal eosinophilic infiltration decreased statistically significantly before and after steroid administration. HPF = high power field, PSL = prednisolone.

3.3. Changes in pathological activity due to steroid administration

We then examined the changes in the Geboes score before and after short-term steroid administration (Fig. 2). The mean Geboes scores before and after steroid administration were 4.6 ± 0.5 and 2.5 ± 1.1, respectively, showing a statistically significant decrease in the Geboes score ($P < .001$).

3.4. Changes in clinical and endoscopic activity due to steroid administration

We investigated the changes in clinical and endoscopic activity due to steroid administration (Fig. 3). The average CAI before and after steroid administration was 3.0 ± 2.3 and 1.0 ± 0.9, respectively, showing a statistically significant decrease in CAI

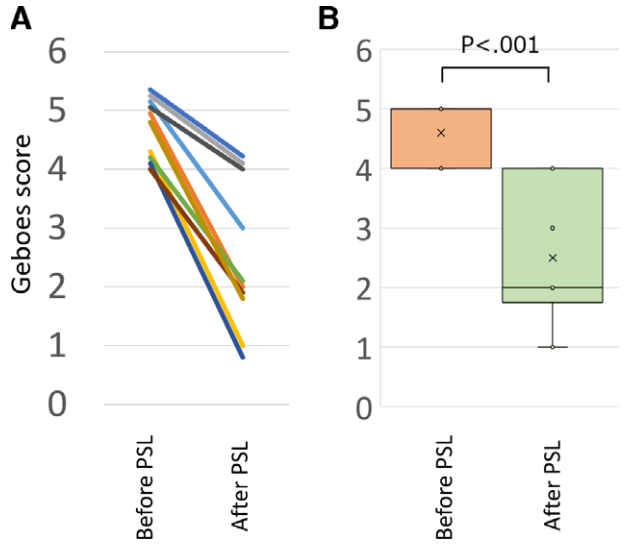

Figure 2. The changes in the Geboes score before and after short-term prednisolone (PSL) administration. (a) The change in Geboes score before and after PSL administration in each case. (b) The Geboes score showed a statistically significant decrease before and after PSL administration.

($P = .042$). Endoscopic activity was assessed using two endoscopic scoring systems: MES and UCEIS. The mean MES changed from 2.0 ± 0.4 to 0.7 ± 0.5 before and after steroid administration, showing a statistically significant difference ($P = .002$). The mean UCEIS score changed from 4.2 ± 1.2 to 1.1 ± 0.8, which was also statistically significant ($P = .002$). Therefore, clinical, endoscopic, and pathological improvements can be achieved with a decrease in the number of eosinophils infiltrating the large intestinal mucosa by short-term steroid administration. A typical case is shown in Figure 4.

3.5. Changes in blood biomarkers due to steroid administration

We also investigated changes in blood biomarkers due to steroid administration (Fig. 5). White blood cell, hemoglobin, albumin, and C-reactive protein levels were investigated as blood biomarkers, but none of the biomarkers showed statistically significant changes due to steroid administration.

4. Discussion

In this study, we derived the following new findings: first, if inflammation is not properly controlled by UC maintenance therapy, the number of infiltrating eosinophils in the colonic mucosa can increase; second, short-term steroid administration significantly reduced the number of infiltrating eosinophils in the colonic mucosa; and third, when the number of eosinophils in the mucosa of the large intestine decreased, there was also a significant decrease in clinical and endoscopic activities.

Cytokine imbalance is involved in the pathophysiology of IBD. It is generally known that T-helper-1 cells (Th1) and Th17 cytokines act as exacerbating factors in Crohn's disease,[16,17] and UC is considered to be Th2-predominant.[18–25] However, recent studies have revealed that UC also exhibits various cytokine patterns, such as Th1, Th17, and Th9.[26] Therefore, it is ideal to select a therapeutic agent suitable for the diverse cytokine patterns of patients with UC, but there are currently no useful biomarkers to determine the cytokine patterns in patients.

Currently, advanced therapies such as anti-cytokine preparations, anti-integrin preparations, and small molecule compounds, such as Janus kinase inhibitors, are considered as

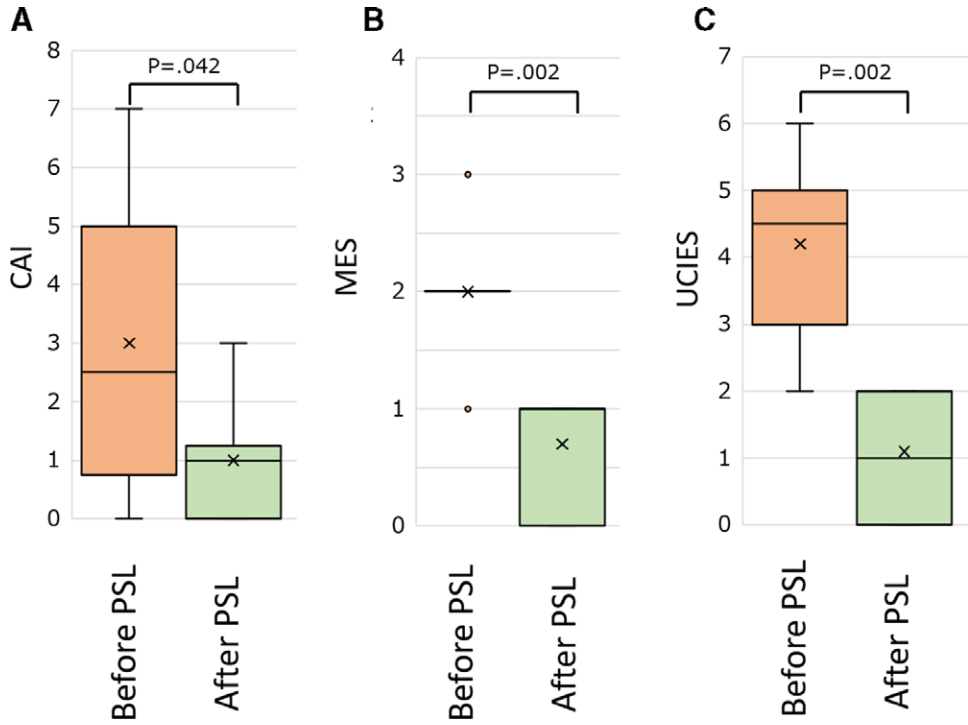

Figure 3. The changes in clinical activity before and after short-term prednisolone (PSL) administration. Clinical activity index (CAI) (a) score statistically significantly decreased before and after PSL administration. The same was statistically significant for Mayo endoscopic subscore (MES) (b) and ulcerative colitis endoscopic index of severity (UCEIS) score (c).

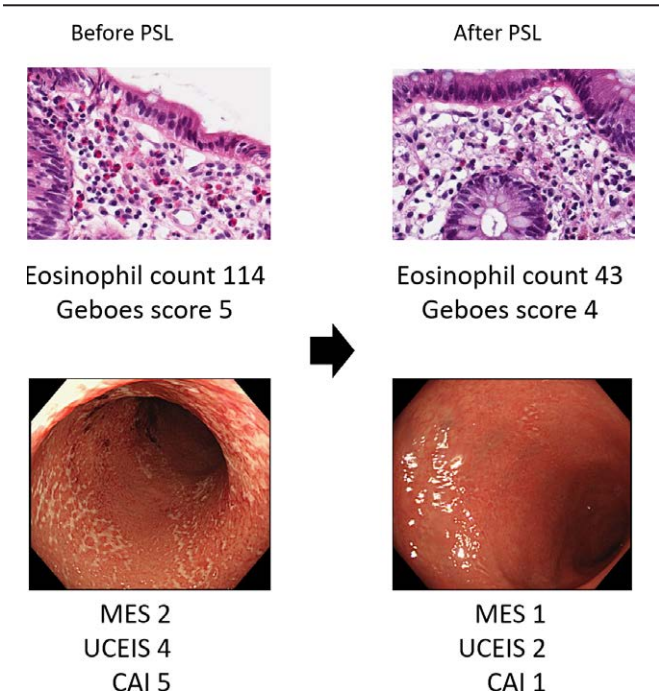

Figure 4. A typical case of endoscopic, clinical, and pathological changes before and after short-term steroid administration. Geboes score mildly improved, but mucosal eosinophils are reduced. The Mayo endoscopic subscore (MES), ulcerative colitis endoscopic index of severity (UCEIS), and clinical activity index (CAI) scores improved.

therapeutic agents for UC. For pathophysiological conditions in which Th1 and Th17 are predominant, anti-TNFα and anti-IL-12/IL-23 antibody preparations are effective. On the other hand, there is currently no useful advanced therapy that selectively inhibits Th2; therefore, we still have to rely on steroids for Th2-dominant pathophysiology. In our study, it is highly possible that Th2 was dominant because eosinophilic infiltration was high in many cases in which inflammation could not be controlled, even with the use of anti-TNFα preparations, and steroids were also significantly effective.

IL-4, IL-5, and IL-13 play a major role in Th2-associated inflammation, and IL-5 is known to induce eosinophils.[27] Recent reports have shown that it is associated with eosinophilic infiltration of the colonic mucosa in patients with UC who are refractory to standard existing treatments.[6] In addition, Griseri et al showed that removal of neutrophils with an anti-IL6G antibody did not improve intestinal inflammation in an IL-23-driven chronic colitis model, but removal of eosinophils with anti-IL-5 antibody or anti-Sigiec-F serum improved the intestinal inflammation, indicating that eosinophils are highly involved in the worsening of IBD disease.[5] We encountered a case in which the use of benralizumab, an anti-IL-5 receptor antibody, in an asthmatic patient resulted in improvement of coexistent UC,[8] demonstrating the possibility that there is a pathogenesis of UC in which removal of eosinophils improves disease activity. As clinical trials of anti-IL-13 antibody preparations against UC have failed,[28] there are still no therapeutic agents targeting Th2. The reason is that the target patients of clinical trials for Th2-targeted therapeutic agents were all UC patients with various cytokine patterns, and the results of clinical trials would likely have been different if only UC patients with Th2-dominant cytokine patterns were included. The development of therapeutic agents targeting Th2, including IL-5, in UC patients with Th2-dominant cytokine patterns, is awaited.

Currently, there are no clinically usable biomarkers that can determine the cytokine patterns in patients with UC. Although it would be ideal to biopsy the mucosa of the inflamed area of a UC patient under endoscopy and examine the cytokine pattern by polymerase chain reaction and/or other tests, these methods are complicated and require time and manpower, making it impractical in clinical practice. However, if the pathological

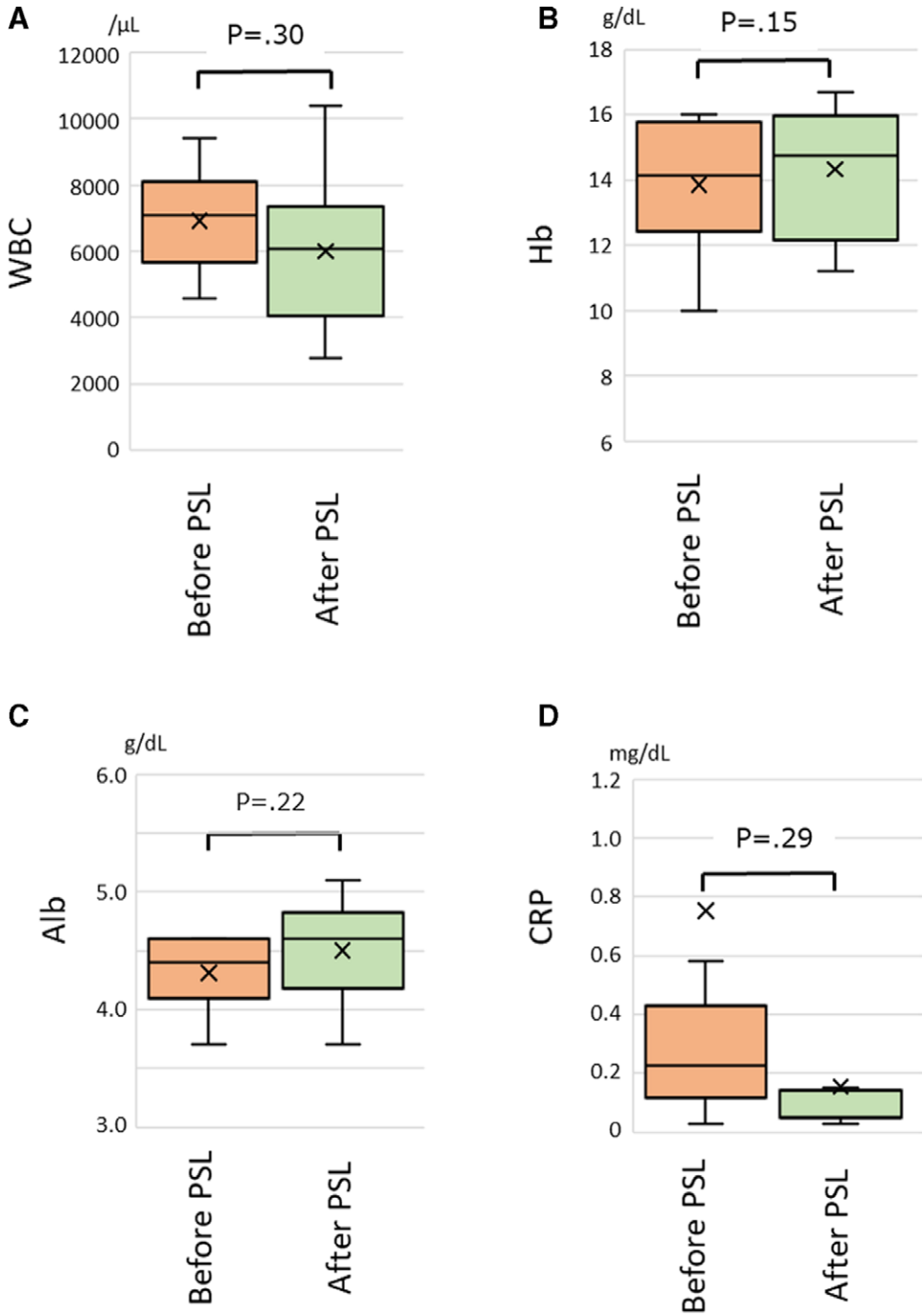

Figure 5. The changes in blood biomarker before and after short-term prednisolone (PSL) administration. There was no significant difference in the white blood cell count (WBC) (a) before and after PSL administration. Similar results were observed in hemoglobin (Hb) (b), albumin (Alb) (c), and C-reactive protein (CRP) (d).

diagnosis of biopsy specimens shows a large number of eosinophils infiltrating the colonic mucosa, it can be concluded that UC patients have a Th2-dominant disease. Pathological assessment of the degree of eosinophilic infiltration compared with polymerase chain reaction is feasible in routine clinical practice. Therefore, it is possible to use steroids for a short duration in refractory UC patients who are Th2-dominant, leading to stable maintenance treatment thereafter. Eosinophilic infiltration of the colonic mucosa has also been reported to be an indicator of resistance to treatment with vedolizumab,[7] and α4β7, the target molecule of vedolizumab, is expressed on the surface of eosinophils.[29] Therefore, one treatment strategy may be to control inflammation more efficiently by first eliminating eosinophils in the local mucosal area by administering steroids and simultaneously inhibiting the migration of eosinophils from the blood to the mucosal inflammatory area by administering vedolizumab.

This study has several limitations. First, this was a single-center, prospective, observational study. Although the data on detailed blood tests and pathological findings could be easily extracted, the number of enrolled patients was small. Second, there was no comparator in the steroid group. Third, no studies have examined stool biomarkers, such as calprotectin, before and after steroid treatment. However, despite the small number of patients in our study, statistically significant improvements in clinical, endoscopic, and pathological scores were achieved.

These results support the idea that there is a subgroup of UC patients who are refractory to maintenance therapy but have a large amount of eosinophilic infiltration in the colonic mucosa and who may benefit considerably from short-term steroid therapy.

In conclusion, in patients with an endoscopically active and high eosinophilic infiltrate in the colonic mucosa despite maintenance therapy, short-term steroid therapy was shown to improve clinical, endoscopic, and pathologic outcomes. In the future, it will be necessary to clarify the cytokine patterns of these patients and determine the type of maintenance treatment that is useful after steroid withdrawal.

Author contributions

TM contributed to this work; TM, KS, and NI designed the study; TM, NI, and S. Tamura collected the data; S. Tani, MY, MI, and YH analyzed the data; TM and KS wrote the manuscript; SO, SB and TF provided critical insights with respect to manuscript preparation.

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