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The Timing of Endoscopic Evaluation of Anti-TNFα Therapy Patients with Ulcerative Colitis

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Abstract

Anti-TNFα Therapy are used to induce remission and as maintenance therapy in refractory ulcerative colitis (UC) to achieve mucosal healing (MH). However, the time at which mucosal healing should be assessed is unclear. We retrospectively examined the optimal timing for colonoscopy and the criteria to determine the need for the continuation of treatment. We evaluated 44 UC patients that were treated with anti-TNFα Therapy and categorized them into the following groups according to the degree of MH within 12 months: MH and non-MH/NMH, early-MH (EMH, healing within three months), and slow MH/SMH (healing between 4-12 months). We compared the Mayo Endoscopic Subscore (MES) between the MH vs. NMH and SMH vs. NMH groups. The Lichtiger index and blood test results were investigated as predictive factors of MH. MH was defined as an MES of ≤ 1. The MES was significantly lower in the MH group at 3, 6, and 12 months, compared to the NMH group. Significant changes were observed in the platelet counts, the Lichtiger index, the levels of C-reactive protein (lower), and hemoglobin (higher) in the MH group at 3- and 6-months

following treatment. However, the only significant difference between the SMH and NMH groups was in the endoscopic findings at 6- or 12-months post-treatment. Colonoscopy should be performed three months after treatment with anti-TNFα Therapy. The treatment should be continued in patients who do not achieve mucosal healing at 3-months, and colonoscopy should be repeated at 6- or 12-months to assess the outcomes.

Keywords
Ulcerative colitis; anti-TNFα therapy; infliximab; adalimumab; timing for colonoscopy

1. Introduction

Ulcerative colitis (UC) is the most common intractable disease in Japan, with over 200,000 individuals affected in 2017 [1]. The Japanese National Health Insurance System (as of 2017) covers the use of cytapheresis (CAP), anti-TNFα therapy (infliximab [IFX] and adalimumab [ADA]), and prednisolone (PSL) alternatives such as tacrolimus (TAC) as remission induction therapy for UC [2, 3]. Mucosal healing (MH) is the goal for induction of remission and is associated with decreased recurrence and bowel resection [4-6]. Anti-TNFα therapy is effective in the treatment of refractory UC for the induction of remission and as maintenance therapy [7-10]. However, the timing of confirmation of MH by colonoscopy, following anti-TNFα therapy, varies among patients. Thus, there is currently no consensus regarding the exact time of evaluation of MH by colonoscopy in patients subjected to anti-TNFα therapy.

Clinical evidence indicates that patients with UC can be categorized as those who demonstrate improvements in endoscopic findings within several weeks after anti-TNFα therapy and those who gradually show improvement over several months [10, 11]. Patients in the latter category may not show any signs of improvement on colonoscopy performed soon after the initiation of treatment. As a result, decision-making regarding the continuation of treatment and the exact time for the evaluation of the therapeutic effects of anti-TNFα therapy remains unclear. Moreover, no studies have examined the optimal timing of colonoscopy in patients who gradually achieve MH. Therefore, it is difficult to decide whether to continue or change treatment. Herein, we performed a retrospective study to determine the optimal timing for a post-anti-TNFα therapy colonoscopy and investigated the criteria to decide on the continuation of treatment in patients with UC.

2. Patients and Methods

Data from 44 patients with UC that had been subjected to anti-TNFα therapy (IFX, n = 27; ADA, n = 17) at our hospital from June 2009 to March 2017 were included in this study. All patients were steroid-resistant or steroid-dependent. The sample included 23 (52.3%) men and 21 (47.7%) women, with a median age of 36.5 years (16-78 years). We categorized the 44 patients into two groups based on the patients that had achieved MH within 12 months after the start of anti-TNFα therapy (MH group, n = 20) and those who did not (non-MH [NMH] group, n = 24). The patients that required changes in therapy within the 12 months were classified into the NMH group.

Colonoscopy was performed at 1, 3, 6, and 12 months after the initiation of treatment to determine the optimal timing. We further categorized the patients in the MH group as those who

had achieved mucosal healing within 3-months (early-MH [EMH], n = 11) and those between 4- and 12-months (slow MH [SMH], n = 9). We compared the SMH patients with NMH ones to determine the predictors of the possibility of continued treatment. Besides, we also examined the predictors of recurrence in EMH.

Outcomes were compared between the groups based on the colonoscopy findings (endoscopic scores), clinical assessments, and the results of the blood tests (Figure 1).

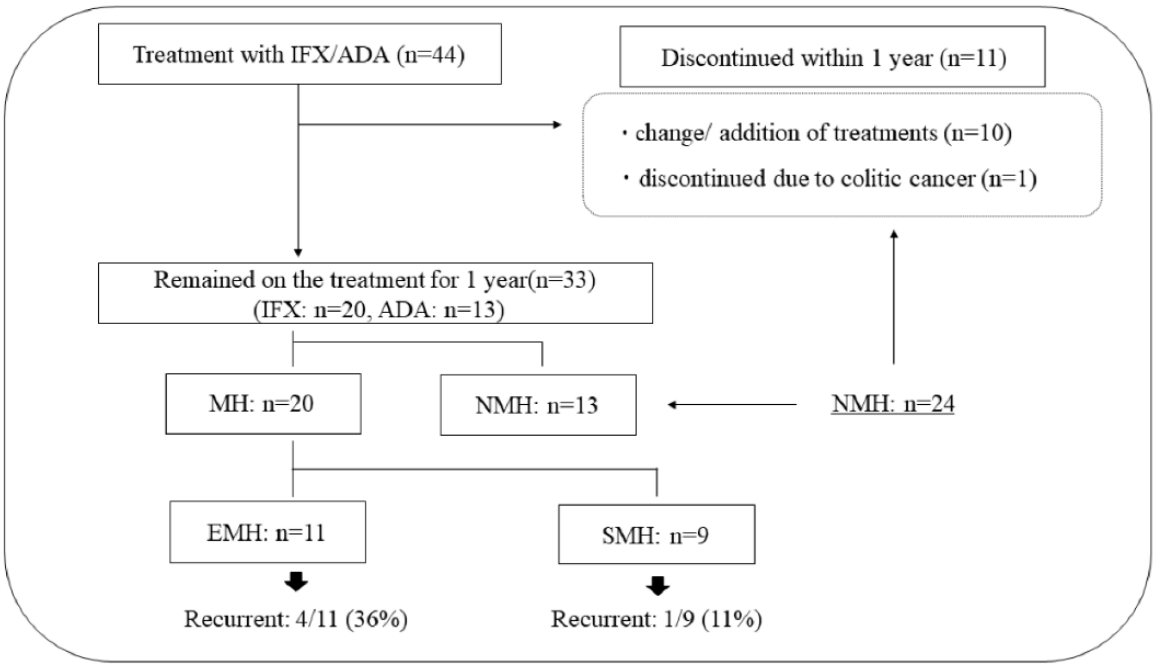

Figure 1 Clinical course of all 44 patients with UC. Patients flow. Forty-four UC patients received anti-TNFα therapy (IFX/ADA). Thirty-three of the 44 patients received anti-TNFα therapy for 12 months. MH was achieved in 20 out of 33 patients (EMH: n = 11, SMH: n = 9). IFX, Infliximab; ADA, Adalimumab; MH, mucosal healing; NMH, Non-mucosal healing; EMH, Early-mucosal healing; SMH, Slow-mucosal healing; UC, ulcerative colitis.

In the MH group, colonoscopy was performed in ten cases after 1 month, in 13 cases after 3 months, in eight cases after 6 months, and in 14 cases after 12 months. In the NMH group, colonoscopy was performed in nine cases after 1 month, five cases after 3 months, 10 cases after 6 months, and nine cases after 12 months. The mean colonoscopy time was 26.7 ± 14.7 days (1 month), 87.1 ± 21.7 days (3 months), 194 ± 35.3 days (6 months), and 416 ± 85.3 days (12 months).

We selected the Mayo Endoscopic Subscore (MES) for the evaluation of MH, as it is the gold standard for endoscopic measures [12]. MH was defined as an MES of ≤1 [13, 14] and endoscopic recurrence as an MES ≥2 during the follow-up period. Clinical assessments were performed based on the Lichtiger index [15].

We first compared the MES values between the MH and NMH groups and then between the SMH and NMH groups to determine the optimal timing of colonoscopy. The Lichtiger index and the blood parameters such as white blood cell count [WBC] (/μL), hemoglobin [Hb] (g/dL), platelet count [Plt] ($x10^4$/μL), C-reactive protein [CRP] (mg/dL), and albumin [Alb] (g/dL) were also compared between the MH and NMH groups, as well as the SMH and NMH groups. This was done to establish the

optimal timing and criteria to determine the need for continuation of treatment with anti-TNFα agents.

2.1 Statistical Analyses

The data are presented as the number of cases and median (min-max). The Wilcoxon signed-rank test was used to compare the results between two groups, and a p-value of ≤0.05 was considered statistically significant. All the analyses were performed using the statistical program JMP Pro12 (Statistical Discover, SAS, Cary, NC).

2.2 Ethical Considerations

The protocol of this study was reviewed and approved by the Ethics Review Committee of Tokyo Women's Medical University (approval number: 5174). Informed consent was obtained from all the patients.

3. Results

3.1 Patient Characteristics and Clinical Course

The patients' characteristics are summarized in Table 1. There were 20 patients (45.5%) in the MH group and 24 (54.5%) in the NMH group, and their characteristics were not significantly different. Similarly, there were no significant differences between patients in the SMH (n = 9, 20.5%) and NMH groups (n = 24, 54.5%) (Table 1 and Table 2).

Table 1 Characteristics of patients in the MH and NMH groups.

	MH group n = 20	**NMH group n = 24**	**p-value**
IFX/ADA	11/9	16/8	0.4287
Male/female	11/9	12/12	0.7409
Age at disease onset, yrs	28.5 (15-75)	20.5 (10-61)	0.1006
Age at the time of treatment, yrs	36.5 (23-78)	34.5 (16-71)	0.5876
Time since diagnosis, days	2963 (60-9200)	3302 (111-14911)	0.8412
Steroid-dependent /steroid-resistant	17/3	18/6	0.4129
Disease type pancolitis/left-sided	16/4	21/3	0.4982
AZA, n (%)	8 (40%)	12 (50%)	0.5071

The data indicate the number of patients (median: min-max). ADA, Adalimumab; AZA, azathioprine; IFX, Infliximab; MH, Mucosal healing; NMH, Non-mucosal healing; yrs, years.

Table 2 Characteristics of patients in the SMH and NMH groups.

	SMH group n = 9	**NMH group n = 24**	**p-value**

IFX/ADA	5/4	16/8	0.5546
Male/female	4/5	12/12	0.7761
Age at disease onset, yrs	29 (15-44)	20.5 (10-61)	0.2921
Age at the time of treatment, yrs	36 (23-58)	34.5 (16-71)	0.4422
Time since diagnosis, days	2822 (60-9200)	3302 (111-14911)	0.8241
Steroid-dependent /steroid-resistant	8/1	18/6	0.3847
Disease type pancolitis/left-sided	8/1	21/3	0.9133
AZA, n (%)	3 (33%)	12 (50%)	0.3918

The data indicate the number of patients (median: min-max). ADA, Adalimumab; AZA, azathioprine; IFX, Infliximab; NMH, Non-mucosal healing; SMH, Slow-mucosal healing; yrs, years.

In 33 of the 44 patients, treatment with an anti-TNFα agent was continued for 12 months, of which 20 patients were treated with IFX and 13 with ADA. Treatment with IFX was discontinued in one patient on day-109 due to the occurrence of colitic cancer. The treatments were modified in ten patients (addition or an increased dose of PSL, addition of CAP, a change in the anti-TNFα therapy regimen, addition of TAC, or surgery) due to insufficient treatment response or worsening of symptoms. The treatments were modified in six patients within 3-months of initiation (IFX: n = 3, ADA: n = 3), in two patients between 4- and 6-months (IFX: n = 1, ADA: n = 1), and in two patients between 7- and 12-months (IFX: n = 2). Four patients (36%, IFX: n = 2, ADA: n = 2) in the EMH group and one patient (11%, IFX: n = 1) in the SMH group had endoscopic recurrence within 12-months (Figure 1).

3.2 Findings of Colonoscopy of the UC Patients After Treatment with Anti-TNFα Agents

3.2.1 Comparison between the MH and NMH Groups

The MES values of the MH and NMH groups did not vary significantly before treatment and after the completion of 1-month. Subsequently, the MES was significantly lower ($p<0.05$) in the MH group compared to the NMH group at 3-months (MH: 1 [0-3], NMH: 2 [2-3], p = 0.0219), 6-months (MH: 1 [0-2], NMH: 2 [2-3], p = 0.0019), and 12-months (MH: 1 [0-2], NMH: 2 [2-3], p = 0.0012). These findings indicated that colonoscopy should be performed during the third month or later after the initiation of treatment (Table 3, Figures 2A-E).

Table 3 Comparison of the clinical course between the MH and NMH groups.

	MH group n = 20	**NMH group n = 24**	**p-value**
MES, points:			
Pre	3 (1-3)	3 (2-3)	0.7334
1 mo. post	2 (0-2)	2 (2-3)	0.1081
3 mos. post	1 (0-3)	2 (2-3)	0.0219
6 mos. post	1 (0-2)	2 (2-3)	0.0019

12 mos. post	1 (0-2)	2 (2-3)	0.0012
Lichtiger index, points:			
Pre	8 (3-15)	7 (3-13)	0.3104
1 mo. post	4 (2-9)	4 (2-11)	0.3018
3 mos. post	2.5 (1-8)	5 (2-10)	0.0016
6 mos. post	2.5 (1-9)	3 (2-11)	0.2629
12 mos. post	2.5 (1-10)	3 (1-7)	0.2003
WBC,/μL:			
Pre	6300 (4570-9500)	7160 (3500-11570)	0.3052
1 mo. post	6265 (3630-14150)	6610 (3010-12030)	0.6177
3 mos. post	6450 (4040-12720)	7390 (3960-13350)	0.3050
6 mos. post	6230 (3440-10400)	6550 (3880-10190)	0.2934
12 mos. post	5070 (4020-9440)	6130 (4020-10220)	0.4014
Hb, g/dL:			
Pre	13.0 (9.2-15.5)	12.2 (8.5-15.1)	0.0425
1 mo. post	13.0 (9.5-14.9)	12.7 (7.9-16.2)	0.3179
3 mos. post	13.7 (11.7-15.7)	12.4 (10-16)	0.0719
6 mos. post	13.8 (11.1-15.4)	12.4 (9.9-15.4)	0.0192
12 mos. post	13.8 (10.6-15.5)	12.7 (8.4-15.3)	0.1592
Plt, ×104/μL:			
Pre	26.5 (13.3-47.4)	31.4 (19.8-54.2)	0.0518
1 mo. post	25.1 (13.2-45.9)	28.2 (16.8-60.9)	0.0540
3 mos. post	22.8 (14.7-42)	30.2 (16.3-63.3)	0.0176
6 mos. post	23.3 (11.2-48.4)	32.6 (18.1-57.1)	0.0370
12 mos. post	22.8 (13.3-88.6)	32.9 (20.8-69.5)	0.0574
CRP, mg/dL:			
Pre	0.21 (0.03-4.55)	0.45 (0.02-7.5)	0.5167
1 mo. post	0.09 (0-2.77)	0.12 (0-10.46)	0.4280
3 mos. post	0.05 (0-0.33)	0.12 (0.02-2.06)	0.0425
6 mos. post	0.05 (0-1.11)	0.11 (0.02-1.55)	0.0707
12 mos. post	0.10 (0-1.23)	0.2 (0-4.87)	0.2771
Alb, g/dL:			
Pre	4 (3.1-4.6)	3.6 (3-4.5)	0.1426
1 mo. post	4.2 (2.8-4.7)	4.1 (2.4-4.8)	0.7023
3 mos. post	4.4 (3.8-4.9)	4.2 (3.4-4.7)	0.3927
6 mos. post	4.3 (3.5-5.2)	4.3 (3.6-4.7)	1.0000
12 mos. post	4.2 (3-4.5)	4.4 (3.3-4.8)	0.3714

Alb, albumin; CRP, C-reactive protein; Hb, hemoglobin; MES, Mayo endoscopic sub-score; MH, Mucosal healing; mo, month; NMH, Non-mucosal healing; Plt, Platelets; WBC, White blood cell.

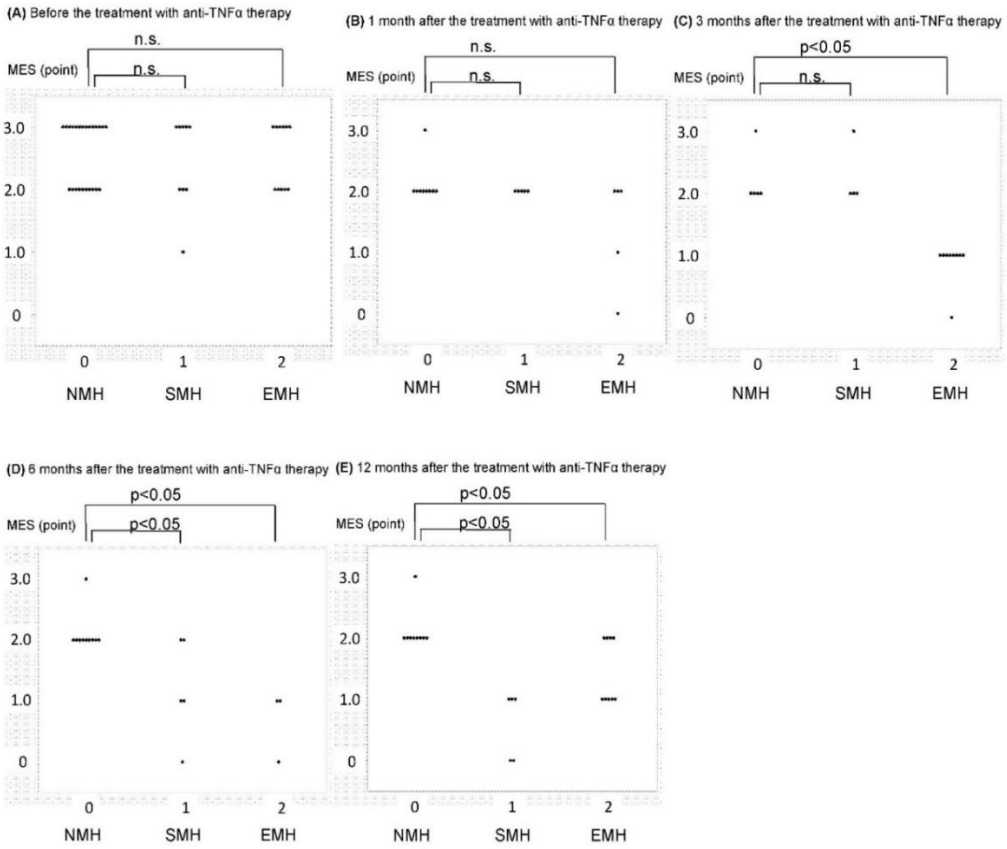

Figure 2 Findings of colonoscopy of the UC patients after treatment with anti-TNFα agents. Comparison between the NMH and SMH groups, as well as the NMH and MH groups. The MES values were significantly lower ($p<0.05$) in the MH group compared to the NMH group at 3-months. MES, Mayo endoscopic sub-score; UC, ulcerative colitis; MH, mucosal healing; NMH, Non-mucosal healing; EMH, Early-mucosal healing; SMH, Slow-mucosal healing.

3.2.2 Comparison between the SMH and NMH Groups

The MES of the SMH and NMH groups did not vary significantly before treatment, at 1-month, and at 3-months after the initiation of treatment with anti-TNFα agents (Table 4, Figures 2A-E). There were significant differences in the MES ($p<0.05$) between the SMH and NMH groups at 6-months (SMH: 1 [0-2], NMH: 2 [2-3], $p = 0.0011$) and 12-months (SMH: 1 [0-1], NMH: 2 [2-3], $p = 0.0026$). These findings indicated that the distinction between SMH and NMH should be made by performing a colonoscopy at 6- or 12-months after the initiation of treatment.

Table 4 Comparison of the clinical course between the SMH and NMH groups.

	SMH group n = 9	**NMH group n = 24**	**p-value**
MES, points:			
Pre	3 (1-3)	3 (2-3)	0.7261
1 mo. post	2 (2-2)	2 (2-3)	0.5510

3 mos. post	2 (2-3)	2 (2-3)	1.0000
6 mos. post	1 (0-2)	2 (2-3)	0.0011
12 mos. post	1 (0-1)	2 (2-3)	0.0026
Lichtiger index, points:			
Pre	10 (4-14)	7 (3-13)	0.1418
1 mo. post	4.5 (3-9)	4 (2-11)	0.5674
3 mos. post	3.5 (2-8)	5 (2-10)	0.1002
6 mos. post	3 (2-9)	3 (2-11)	0.7217
12 mos. post	2.5 (1-5)	3 (1-7)	0.7468
WBC,/μL:			
Pre	6635 (5430-9500)	7160 (3500-11570)	0.7010
1 mo. post	9570 (3630-14150)	6610 (3010-12030)	0.5025
3 mos. post	6370 (4040-12720)	7390 (3960-13350)	0.3016
6 mos. post	6735 (3740-10400)	6550 (3880-10190)	0.8429
12 mos. post	5895 (4590-8010)	6130 (4020-10220)	1.0000
Hb, g/dL:			
Pre	13.6 (11.2-15.5)	12.2 (8.5-15.1)	0.0275
1 mo. post	14.2 (9.5-14.9)	12.7 (7.9-16.2)	0.2850
3 mos. post	13.6 (11.7-15)	12.4 (10-16)	0.3624
6 mos. post	14.1 (11.3-14.7)	12.4 (9.9-15.4)	0.0836
12 mos. post	14.3 (11.9-15.5)	12.7 (8.4-15.3)	0.1465
Plt, ×104/μL:			
Pre	25.7 (13.3-40.6)	31.4 (19.8-54.2)	0.2175
1 mo. post	25.5 (13.8-35.7)	28.2 (16.8-60.9)	0.4462
3 mos. post	24.6 (14.9-35.8)	30.2 (16.3-63.3)	0.1683
6 mos. post	23.9 (14.7-31.3)	32.6 (18.1-57.1)	0.1335
12 mos. post	20.6 (17.5-31.5)	32.9 (20.8-69.5)	0.1743
CRP, mg/dL:			
Pre	0.21 (0.06-4.55)	0.45 (0.02-7.5)	0.5991
1 mo. post	0.14 (0.03-2.77)	0.12 (0-10.46)	0.9833
3 mos. post	0.05 (0-0.2)	0.12 (0.02-2.06)	0.1454
6 mos. post	0.06 (0-0.2)	0.11 (0.02-1.55)	0.1056
12 mos. post	0.17 (0.01-0.87)	0.2 (0-4.87)	0.9278
Alb, g/dL:			
Pre	4.1 (3.6-4.6)	3.6 (3-4.5)	0.1312
1 mo. post	4.4 (2.8-4.7)	4.1 (2.4-4.8)	0.5042
3 mos. post	4.3 (3.8-4.8)	4.2 (3.4-4.7)	0.8965
6 mos. post	4.3 (4.1-4.8)	4.3 (3.6-4.7)	0.9130
12 mos. Post	4.3 (4-4.5)	4.4 (3.3-4.8)	0.5154

Alb, albumin; CRP, C-reactive protein; Hb, hemoglobin; MES, Mayo endoscopic sub score; mo, month; NMH, Non mucosal healing; Plt, Platelets; SMH, Slow mucosal healing; WBC, White blood cell.

3.2.3 Factors Predicting MH

The Lichtiger index, platelets, and CRP values at three months were significantly lower in the MH group compared to the NMH group ($p<0.05$) (Table 3). The platelet counts were significantly lower, and Hb values were significantly higher in the MH group at 6-months post-treatment ($p<0.05$). Moreover, the pre-treatment Hb values were significantly higher in the MH group ($p<0.05$). Similarly, a comparison between the SMH and NMH groups revealed that the Hb values before treatment were significantly higher in the SMH group ($p<0.05$) (Table 4). There were no significant differences in the Lichtiger index, WBC, Hb, platelets, CRP, or Alb values at 1, 3, 6, and 12 months after the initiation of treatment with anti-TNFα agents. The Lichtiger index improved after 1-month in both the SMH and NMH groups. Thus, the Lichtiger index alone was not sufficient to predict MH.

3.2.4 Comparison of the Recurrence and Non-Recurrence Groups in the EMH Group

A comparison of the four out of 11 patients in the EMH group who had relapsed (recurrence group), with the seven who did not show significant differences in the pre-treatment levels of Hb and Alb (non-recurrence group), is presented in Table 5. The recurrence group had lower pre-treatment Hb and Alb ($p<0.05$). There was also a significant difference in the levels of Hb and MES after 12 months of treatment ($p<0.05$). This suggests that pre-treatment levels of Hb and Alb may be predictors of relapse in the EMH group.

Table 5 Comparison of the recurrence and non-recurrence groups in the EMH group.

	Recurrence group n = 4	**Non-recurrence group n = 7**	**p-value**
MES, points:			
Pre	3 (2-3)	2 (2-3)	0.3827
1 mo. post	0 (0-0)	2 (1-2)	0.2357
3 mos. post	0 (0-1)	1 (1-1)	0.2386
6 mos. post	-	1 (0-1)	-
12 mos. Post	2 (2-2)	1 (1-1)	0.0072
Lichtiger index, points:			
Pre	7 (6-15)	8 (3-14)	0.9239
1 mo. post	2 (2-6)	2 (2-4)	1.0000
3 mos. post	2 (1-4)	2 (1-4)	1.0000
6 mos. post	2 (1-5)	2 (1-7)	0.6995
12 mos. Post	2 (1-4)	2 (1-4)	1.0000
WBC,/μL:			
Pre	9090 (5600-4570)	5820 (5240-6830)	0.7055
1 mo. post	6090 (4620-6910)	5230 (3770-14150)	0.6366
3 mos. post	7130 (5930-8450)	6340 (4110-9900)	0.7768
6 mos. post	5660 (4470-7930)	6170 (3440-7480)	0.9247
12 mos. Post	5440 (4450-8240)	4570 (4020-6410)	0.2703

Hb, g/dL:			
Pre	11 (9.2-12.7)	13.7 (12-15.5)	0.0298
1 mo. post	12.5(10.9-13)	13.1 (12.2-14.9)	0.1849
3 mos. post	13.4(13.1-14.9)	14.1 (12.5-15.7)	0.4487
6 mos. post	12.9(11.1-14.5)	14.2 (13.1-15.4)	0.1082
12 mos. Post	11.4(10.6-12.1)	14.1 (13.8-15.2)	0.0195
Plt, ×104/μL:			
Pre	33.85 (20.6-47.4)	27.1 (14.2-30.2)	0.5074
1 mo. post	23.25 (14.8-37.6)	25.0 (13.2-27.1)	0.6366
3 mos. post	25.95 (15.4-36.3)	21.7 (14.7-27.4)	0.5083
6 mos. post	25.35 (11.2-48.4)	22.1 (13.3-28.8)	0.8498
12 mos. Post	31.05 (13.3-47.6)	22.8 (16-23.3)	0.2683
CRP, mg/dL:			
Pre	0.905 (0.04-1.95)	0.24 (0.03-1.02)	0.2151
1 mo. post	0.135 (0-1.28)	0.06 (0-0.25)	0.7048
3 mos. post	0.1 (0-0.33)	0.05 (0-0.17)	0.5681
6 mos. post	0.13 (0-0.33)	0.05 (0.02-1.11)	0.9240
12 mos. Post	0.165 (0-0.53)	0.04 (0.03-0.1)	0.3832
Alb, g/dL:			
Pre	3.5 (3.1-3.6)	4.1 (3.6-4.4)	0.0166
1 mo. post	4.2 (3.7-4.5)	4.05 (3.9-4.4)	0.7476
3 mos. post	4.4 (4.1-4.9)	4.4 (3.8-4.6)	1.0000
6 mos. post	4.3 (3.5-4.7)	4.0 (3.8-5.2)	1.0000
12 mos. Post	4.0 (3.7-4.3)	4.25 (4-4.4)	0.3065

Alb, albumin; CRP, C-reactive protein; EMH, Early mucosal healing; Hb, hemoglobin; MES, Mayo endoscopic sub score; mo, month; NMH, Non mucosal healing; Plt, Platelets; WBC, White blood cell.

4. Discussion

Anti-TNFα therapy is often used in the treatment of refractory UC, and several studies have demonstrated MH [16]. However, there is no consensus regarding the timing of performing a colonoscopy to evaluate the effects of treatment in patients with UC. When anti-TNFα therapy was used for the induction of remission, the effects were typically assessed at 8, 30, or 52-54 weeks after the initiation of treatment [7, 9, 17-19]. In the present study, we compared the outcomes between the MH and NMH groups, as well as the SMH and NMH groups, to determine the optimal timing to perform a colonoscopy to assess the effects of two anti-TNFα therapies (IFX and ADA). We also investigated the criteria to determine the need for continuation of treatment with anti-TNFα therapy. To address these questions, we performed colonoscopy at 1, 3, 6, and 12 months after the completion of treatment in 44 patients with UC.

4.1 Colonoscopy Timing for Anti-TNFα Therapy Treated UC Patients

4.1.1 Comparison between the MH and NMH Groups

The MES in the MH group was significantly lower at 3, 6, and 12 months after the treatment ($p<0.05$). These findings suggested that colonoscopy should be performed at 3, 6, or 12 months after treatment to determine the degree of MH to assess the effects of treatment. Our study also revealed that some patients with NMH findings at 3-months could achieve MH after 4-months. UC patients treated with anti-TNFα agents can be classified as those who achieve MH at an early stage and those who heal gradually.

4.1.2 Comparison between SMH and NMH Patients

To establish the appropriate usage criteria for anti-TNFα therapy, we further categorized the patients into SMH and NMH groups and determined the optimal timing to evaluate the effect of treatment in SMH patients, as well as to distinguish between SMH and NMH patients. While the EMH group can be determined to show MH by colonoscopy at an early stage, the SMH group does not show MH at the same time; therefore, it is difficult to decide whether to continue or change treatment. By comparing SMH and NMH, we expect to make appropriate treatment decisions by accurately predicting the difference between the SMH and NMH groups in which anti-TNFα agents work slowly. In the comparison of the biomarkers studied for SMH and NMH, significant differences in Hb levels were observed before treatment ($p<0.05$). The causes of anemia in UC have been implicated in iron-deficiency anemia that is associated with bleeding from inflamed mucosa, reduced iron absorption, and anemia associated with chronic inflammation (ACD: anemia of chronic disease). We believe that a higher pre-treatment Hb level may lead to SMH, even if MH is not achieved early [20, 21]. As the present results did not examine the etiology of anemia, further studies are required. The MES values in the SMH group were significantly lower at 6 and 12 months ($p<0.05$). These findings suggested that in SMH patients, colonoscopy should be performed at 6 or 12 months to determine the effect of treatment with anti-TNFα agents.

4.2 Factors Predicting MH and Relapsing EMH

The Lichtiger index, platelets, and CRP values were significantly lower in the MH group than in the NMH group at 3-months. This suggested that patients with improvements in the Lichtiger index, platelets, and CRP at 3-months were likely to achieve MH within 12 months and that these may be considered to be predictive factors in UC patients treated with anti-TNFα agents.

Comparison between the SMH and NMH groups revealed that while the colonoscopy findings differed, there were no significant differences in the Lichtiger index or hematological parameters (WBC, Hb, platelets, and Alb) at any time point. This indicated that colonoscopy is necessary to evaluate the treatment effects in SMH and NMH patients. There was no significant difference in the Lichtiger index between the SMH and NMH groups. In 13 of the 24 NMH patients, although an improvement in the Lichtiger index was observed, the treatment with anti-TNFα agents was continued for 12 months. In contrast, in patients who demonstrated no MH without improvement in their Lichtiger index, the treatment was discontinued. Our study revealed the possibility that a subset of patients who do not achieve MH within 3-months might do so within 12-months if

treatment with anti-TNFα therapy is continued. Thus, colonoscopy should be performed at 6- and 12-months after the initiation of treatment to account for patients who may demonstrate SMH. MH is an important goal in the treatment of UC apart from clinical remission; therefore, the optimal criteria and timing for the evaluation of MH should be identified during treatment.

Comparison of the relapse and non-relapse groups in the EMH group showed significant differences in the levels of Hb and Alb before treatment and Hb and MES after 12-months of treatment. This suggests that pre-treatment levels of Hb and Alb may be predictors of relapse in the EMH group.

This study has some limitations. First, the sample size was not very large (n = 44). Moreover, all the patients could not be subjected to multiple endoscopies simultaneously, and the study design was retrospective. A prospective multicenter study is necessary to further explore the issues examined herein.

The strength of our study is that by dividing MH into EMH and SMH, we observed that only the Lichtiger index and blood test parameters during treatment could not predict future MH. Furthermore, we also found the involvement of pre-treatment levels of Alb and Hb as predictors of EMH relapse.

5. Conclusion

Colonoscopy performed 3-months after the initiation of treatment with anti-TNFα agents is effective in the assessment of treatment response in patients with UC. Treatment with anti-TNFα agents should be continued in the subset of patients who do not demonstrate MH at 3-months but possibly heal gradually, based on clinical data and symptoms. Colonoscopy should be repeated at 6- or 12-months in such patients to re-evaluate the treatment response.

Author Contributions

HK, AI and KT: study concept and design; HK, AI and TO: data acquisition; HK: statistical analysis and drafting of the first version of the manuscript; HK, AI, TO, SN, and KT: critical revision and approval of the final version of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Japan Intractable Diseases Information Center: Japan Intractable Diseases Research Foundation. 2020. Available from: http://www.ibdjapan.org/patient/pdf/01.pdf.
2. Faubion Jr WA, Loftus Jr EV, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: A population-based study. Gastroenterology. 2001; 121: 255-260.
3. Khan N, Abbas A, Williamson A, Balart L. Prevalence of corticosteroids use and disease course after initial steroid exposure in ulcerative colitis. Dig Dis Sci. 2013; 58: 2963-2969.
4. Hanauer SB, Kirsner JB. Treat the patient or treat the disease? Dig Dis. 2012; 30: 400-403.
5. Frøslie KF, Jahnsen J, Moum BA, Vatn MH, IBSEN Group. Mucosal healing in inflammatory bowel

disease: Results from a Norwegian population-based cohort. Gastroenterology. 2007; 133: 412-422.
6. Ardizzone S, Cassinotti A, Duca P, Mazzali C, Penati C, Manes G, et al. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. Clin Gastroenterol Hepatol. 2011; 9: 483-489.
7. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005; 353: 2462-2476.
8. Armuzzi A, Pugliese D, Danese S, Rizzo G, Felice C, Marzo M, et al. Long-term combination therapy with infliximab plus azathioprine predicts sustained steroid-free clinical benefit in steroid-dependent ulcerative colitis. Inflamm Bowel Dis. 2014; 20: 1368-1374.
9. Sandborn WJ, Van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012; 142: 257-265.
10. Colombel JF, Sandborn WJ, Ghosh S, Wolf DC, Panaccione R, Feagan B, et al. Four-year maintenance treatment with adalimumab in patients with moderately to severely active ulcerative colitis: Data from ULTRA 1, 2, and 3. Am J Gastroenterol. 2014; 109: 1771-1780.
11. Suzuki Y, Motoya S, Hanai H, Hibi T, Nakamura S, Lazar A, et al. Four-year maintenance treatment with adalimumab in Japanese patients with moderately to severely active ulcerative colitis. J Gastroenterol. 2017; 52: 1031-1040.
12. Meucci G, Fasoli R, Saibeni S, Valpiani D, Gullotta R, Colombo E, et al. Prognostic significance of endoscopic remission in patients with active ulcerative colitis treated with oral and topical mesalazine: A prospective, multicenter study. Inflamm Bowel Dis. 2012; 18: 1006-1010.
13. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N Engl J Med. 1987; 317: 1625-1629.
14. Colombel JF, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011; 141: 1194-1201.
15. Lichtiger S, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med. 1994; 330: 1841-1845.
16. Harbord M, Eliakim R, Bettenworth D, Karmiris K, Katsanos K, Kopylov U, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: Current management. J Crohns Colitis. 2017; 11: 769-784.
17. Barreiro M, Lorenzo A, Mera J, Dominguez-Munoz E. W1262 prospective, open pilot study for evaluating the clinical efficacy and mucosal healing rate of infliximab in steroid-dependent ulcerative colitis. Gastroenterology. 2008; 134: A-667.
18. Kobayashi T, Suzuki Y, Motoya S, Hirai F, Ogata H, Ito H, et al. First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis-results from a multicenter prospective randomized controlled trial and its post hoc analysis. J Gastroenterology. 2016; 51: 241-251.
19. Afif W, Leighton JA, Hanauer SB, Loftus Jr EV, Faubion WA, Pardi DS, et al. Open-label study of adalimumab in patients with ulcerative colitis including those with prior loss of response or intolerance to infliximab. Inflamm Bowel Dis. 2009; 15: 1302-1307.
20. Dignass AU, Gasche C, Bettenworth D, Birgegård G, Danese S, Gisbert JP, et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory

bowel diseases. J Crohns Colitis. 2015; 9: 211-222.
21. Weiss G, Gasche C. Pathogenesis and treatment of anemia in inflammatory bowel disease. Haematologica. 2010; 95: 175-178.