의학석사 학위논문

궤양성 대장염 환자에서 항 TNF 제제에 대한 경과 예측에 혈청 알부민 및 C-반응 단백질 조기 변화의 임상적 의의

The clinical significance of early change of serum albumin and C-reactive protein for predicting outcomes of anti-TNF therapy in patients with ulcerative colitis

울 산 대 학 교 대 학 원
의 학 과
이 선 호

궤양성 대장염 환자에서 항 TNF 제제에 대한 경과 예측에 혈청 알부민 및 C-반응 단백질 조기 변화의 임상적 의의

지 도 교 수　　예 병 덕

이 논문을 의학석사 학위 논문으로 제출함

2018 년 06 월

울 산 대 학 교 대 학 원
의　　학　　과
이 선 호

이선호의 의학석사학위 논문을 인준함

심사위원	변 정 식	(인)
심사위원	예 병 덕	(인)
심사위원	황 성 욱	(인)

울 산 대 학 교 대 학 원

2018 년 06 월

Abstract

Background: The aim of this study was to investigate novel predictors of clinical and endoscopic outcomes in anti-TNF-naïve ulcerative colitis (UC) patients initiating anti-TNF treatment.

Methods: A total of 210 UC patients who started treatment with infliximab or adalimumab from June 2009 and December 2016 in Asan Medical Center, Korea (male 62.4%, median age at diagnosis of UC 37.9 years [interquartile range (IQR), 25.5-48.9], and median duration of follow-up 3.3 years [IQR, 1.9-5.0]) were retrospectively analyzed. Predictors of primary non-response to anti-TNF treatment (PNR) and endoscopic outcomes were identified using logistic regression. Cumulative event-free survival of colectomy and anti-TNF failure were estimated by Kaplan-Meir curves and predictors were investigated using log-rank test and Cox hazard regression.

Results: Forty-one patients (19.5%) showed PNR. Serum albumin week 2/week 0 ratio (W2/W0) $\leq$ 0.96 (adjusted OR[aOR] 2.76, 95% confidence interval [CI] 1.30-6.10) and C-reactive protein (CRP) W2/W0 $\geq$ 1.35 (aOR 2.39, 95% CI 1.14-5.08) were significant predictors of PNR. Furthermore, serum albumin W2/W0>0.96 significantly predicted mucosal healing (Mayo endoscopic subscore 0-1) (aOR 2.56, 95% CI 1.38-4.85) and endoscopic response at week 8-14 (aOR 2.71, 95% CI 1.49-4.98), respectively. During the entire study period, serum albumin W2/W0 $\leq$ 0.96 significantly predicted risk of colectomy (aHR 2.67, 95% CI 1.00-7.11) and anti-TNF failure (aHR 1.96, 95% CI 1.32-2.92), respectively, whereas CRP W2/W0 $\geq$ 1.35 significantly predicted anti-TNF failure (aHR 1.80, 95% CI 1.05-2.30).

Conclusion: The early change of serum albumin and CRP in the first two weeks after starting anti-TNF treatment significantly predicts PNR. Furthermore, W2/W0 of serum albumin significantly predicts short-term endoscopic outcomes, cumulative colectomy-free survival, and cumulative anti-TNF failure-free survival. Based on these novel markers, anti-TNF treatment could be optimized as early as 2 weeks to improve clinical and endoscopic outcomes.

Key words: Ulcerative colitis, Infliximab, Adalimumab, albumin, C-reactive protein

Table of contents

List of Tables and Figures

Introduction

Ulcerative colitis (UC) is considered a chronic inflammatory disease characterized by courses of relapse and remission.[1] In recent years, anti-tumor necrosis factor-α (anti-TNF) monoclonal antibodies has been used more frequently and earlier in patients with UC.[2-4] Both infliximab (IFX) and adalimumab (ADA) have been reported to be more efficacious in moderate to severe UC patients than placebo with early clinical response rates up to 64.0% and 50.4%, respectively in clinical trials.[5-7] Moreover, mucosal healing at week 8 was more frequently achieved in patients treated with IFX and ADA compared to placebo, with rates of 62% and 46.9%, respectively, in clinical trials.[5, 7, 8] However, despite the efficacy of anti-TNF treatment, a substantial proportion of patients with UC up to 30-60% eventually failed to treatment with anti-TNF agents according to retrospective studies.[9-11] Primary failure to anti-TNF agents has been reported in 22-30% of UC patients and among responders to induction therapy, up to 33.7% of patients experienced anti-TNF failure at 1-year.[10, 11] Therefore, if predictors of response and failure to anti-TNF therapy in the early treatment course are established, anti-TNF therapy could be optimized depending on the predictors. However, studies investigating early predictors of poor clinical and endoscopic outcomes after starting anti-TNF treatment remain limited.

We studied a cohort of moderate to severe UC patients naïve to anti-TNF treatment who started IFX or ADA at our center and assessed clinical and endoscopic outcomes. Our focus was to identify early predictors of clinical and endoscopic outcomes. In addition, the value of those early predictors for long-term clinical outcomes were also investigated. In our study, early change of biochemical markers such as serum albumin and C-reactive protein (CRP) in the first two weeks after anti-TNF treatment was of interest.

Methods

Study population

Among UC patients managed at Asan Medical Center, a tertiary hospital in Seoul, Korea, a total of 210 consecutive patients who started treatment with IFX or ADA between June 2009 and December 2016 were retrospectively analyzed. Referred patients who received the first anti-TNF dosing at another institution were excluded from our study. Patient demographics and clinical data were collected from the electronic medical records and the Asan Inflammatory Bowel Disease Registry, which has been prospectively maintained and updated since 1997 as previously described.[2, 12] Diagnosis of UC was based on history of diarrhea, blood or pus in stool for at least 4 weeks in addition to distinctive endoscopic features of diffusely granular, friable, or ulcerated mucosa and characteristic histopathological evidence of chronic inflammation.[12-16] Data including birthdate, sex, date of UC diagnosis, smoking history, disease extent, Mayo score at initiation of anti-TNF agents, and previous and concurrent medications were collected.[17] This study was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB No. 2018-0565).

Anti-TNF administration

Anti-TNF treatment was initiated in moderate to severe UC patients who did not respond to conventional corticosteroids and/or immunomodulator therapy. Intravenous infusion of IFX (dose of 5 mg/kg body weight at week 0, 2, 6 for induction and every 8 weeks thereafter for maintenance therapy) or subcutaneous injection of ADA (160 mg at week 0, 80 mg at week 2, 40 mg at week 4, 6, and 8 for induction and every 2 weeks thereafter for maintenance therapy) were applied. Anti-TNF maintenance therapy was indicated for those with clinical response to induction therapy.

Study outcomes

The study patients were followed from the initiation of IFX or ADA until withdrawal of anti-TNF therapy due to colectomy or non-response, patient preference to stopping anti-TNF agents, adverse events resulting in withdrawal of anti-TNF agents (i.e. infusion reactions, infections), or end of follow-up period (April 2018).

Clinical response was defined as a decrease of at least 3 points and 30% of Mayo score and decrease of rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0-1.[5] Primary non-response to anti-TNF treatment (PNR) was defined as withdrawal of anti-TNF agents due to colectomy or no clinical response in the induction phase. Cumulative colectomy-free survival and cumulative anti-TNF failure-free survival were investigated in the entire study period. Colectomy cases due to dysplasia or cancer were excluded from the colectomy outcome. Anti-TNF failure was defined as any one of the followings: (1) withdrawal of anti-TNF agents due to colectomy or loss of response; (2) use of rescue corticosteroids after the induction period.

Endoscopic outcomes were evaluated among 194 patients (92.4%) who had undergone both baseline and follow-up (at week 8-14) endoscopy. Two certified endoscopists (B.D.Y and S.W.H) independently graded the endoscopic images using Mayo endoscopic subscore (MES) and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score.[17, 18] In case of disagreement of the endoscopic scores, the final score was recorded based on a consensus between two reviewers as described in our previous study.[19] Mucosal healing (MH) was defined as Mayo endoscopic subscore of 0-1. Endoscopic response (ER) was defined as decrease of MES ≥ 1 or UCEIS ≥ 2 based on the recent international consensus by International Organization for the Study of Inflammatory Bowel Disease (IOIBD).[20]

Predictors of clinical and endoscopic outcomes were analyzed considering the following variables; sex, age at anti-TNF initiation, disease duration at anti-TNF initiation, previous thiopurine use within 1

month, concomitant (prescriptions within 30 days before and/or after anti-TNF initiation) thiopurine use, remote (within 4-12 months) and recent (within 3 months) corticosteroid use, concomitant corticosteroid use, extensive disease (according to Montreal Classification)[21] and severe disease (Mayo score≥11) at anti-TNF initiation, current smoking, perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) positivity, recent combined cytomegalovirus (CMV) colitis within 3 months. The following biochemical variables were also included for analysis: anemia at baseline (hemoglobin<13 g/dL in male, <12 g/dL in female), leukocytosis at baseline (white blood cell count>10,000/mm^3), low serum albumin (≤3.4 g/d) and elevated CRP (≥0.6 mg/dl) at baseline. We also investigated week 2/week 0 ratio (W2/W0) of serum albumin and CRP as a predictor for analysis. Patients who were given intravenous albumin infusions in the first 2 weeks after starting anti-TNF treatment were excluded from this study. Normal range of serum chemistry values (Cobas 8000 modular analyzer, Roche Diagnostics, Basel, Switzerland; AU5800 Beckman Coulter, Brea, CA) were as follows; CRP (<0.6 mg/dL), and serum albumin (3.5–5.2 g/dL).

Statistical analysis

Continuous variables were reported as medians with interquartile ranges (IQR), whereas categorical variables were reported as numbers and percentages. Logistic regression with backward elimination was used to determine odds ratios (OR) with 95% confidence intervals (CI) for predictors of time-independent outcomes (PNR and endoscopic outcomes). Novel markers were dichotomized based on cut-off levels for predicting PNR. Delong's test was used to measure the cut-off level with optimal sensitivity and specificity of novel markers for predicting PNR. These novel markers according to pre-defined cut-off levels of PNR were then investigated for predicting endoscopic outcomes and long-term cumulative event-free survival of colectomy and anti-TNF failure. Cumulative event-free survival was estimated by Kaplan-Meier curves. Predictors for cumulative event-free survivals were evaluated using log-rank test (univariable analysis) and Cox proportional hazard regression (multivariable analysis). Also, when analyzing predictors for cumulative event-free survivals, the exposure to thiopurine or

methotrexate after starting anti-TNF treatment was modeled as a time-dependent covariate to avoid the potential bias related with those medications. Basal serum albumin and CRP levels were missing in only 2 patients and week 2 serum albumin and CRP levels were missing in 2 and 5 patients, respectively. When evaluating these markers as predictors, only patients with available data were analyzed. *P* values <0.05 were regarded as statistically significant. R software (version 3.4.3; available: http://cran.r-project.org/) was used for statistical analysis.

Results

Baseline characteristics

During the study period, a total of 210 patients started anti-TNF treatment at our hospital; 182 (86.7%) started infliximab and 28 (13.3%) started adalimumab. Median disease duration at baseline was 4.4 years (IQR 1.7-8.5), and median follow-up duration after anti-TNF initiation was 3.3 years (IQR 1.9-5.0). Among all patients, 131 patients (62.4%) were male and the median age at UC diagnosis was 37.9 years (IQR 25.5-48.9). Median Mayo score was 9.0 (IQR 8.0-10.0) and 131 patients (62.4%) had extensive colitis at baseline. Baseline characteristics of the study patients are summarized in Table 1.

Clinical and endoscopic outcomes

The flow chart of clinical outcomes of the study patients are presented in Figure 1. Among the 210 UC patients who received anti-TNF treatment, forty one patients (19.5%) were deemed primary anti-TNF non-response; 17 (8.1%) stopped anti-TNF treatment to receive colectomy and 24 (11.4%) stopped anti-TNF treatment due to no clinical response. A total of six patients (2.6%) stopped anti-TNF treatment during induction phase due to adverse events; Two patients had infusion reaction, 2 patients were suspected to have *pneumocystis jirovecii* pneumonia, 1 patient had suspected IFX-associated pneumonitis, and 1 patient developed thrombocytopenia after IFX.

A total of 163 patients (77.6%) continued maintenance anti-TNF treatment after the induction phase. Among those patients, 14 patients (6.7%) stopped treatment due to loss of response, 5 patients (2.4%) underwent colectomy due to UC exacerbation, and 44 (21.0%) used rescue corticosteroids. Fourteen patients (6.7%) stopped receiving anti-TNF treatment for other reasons including adverse events in 4 patients and patient preference to stopping treatment in 9 patients. A total of 130 patients (61.9%) continuously received anti-TNF maintenance treatment regardless of rescue corticosteroid use at the

end of the study period.

Table 1. Demographics and clinical characteristics of study patients

	N=210
Anti-TNF agent	
Infliximab	182 (86.7%)
Adalimumab	28 (13.3%)
Male	131 (62.4%)
Age at diagnosis (years)	37.9 (25.5-48.9)
Age at baseline (years)	43.6 (32.0-55.9)
Disease duration at baseline (years)	4.4 (1.7-8.5)
Follow-up duration (years)	3.3 (1.9-5.0)
Previous and concomitant[a] use of medication	
Previous thiopurine use within 1 month	102 (48.6%)
Concomitant[a] thiopurine use	117 (55.7%)
Remote corticosteroid use (within 4-12 months)	111 (52.9%)
Recent corticosteroid use (within 3 months)	119 (52.4%)
Concomitant[a] corticosteroid use	176 (83.8%)
Recent combined CMV colitis within 3 months	81 (38.6%)
p-ANCA positivity	108 (51.4%)
Disease extent at baseline	
Left-sided colitis	79 (37.6%)
Extensive colitis	131 (62.4%)
Mayo score at baseline	9.0 (8.0-10.0)
Partial Mayo score at baseline	6.0 (5.0-7.0)
Mayo endoscopic subscore at baseline	3.0 (3.0-3.0)
UCEIS score at baseline	5.0 (5.0-6.0)
Baseline serum albumin (g/dL)	3.2 (2.7-3.8)
Baseline CRP (mg/dL)	0.90 (0.29-2.40)

[a]Concomitant was defined as prescriptions within 30 days before and/or after anti-TNF initiation

CMV, cytomegalovirus; CRP, C-reactive protein; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; TNF, tumor necrosis factor; UCEIS, ulcerative colitis endoscopic index of severity

Continuous values are expressed as medians with interquartile ranges; categorical values are expressed as numbers with percentages.

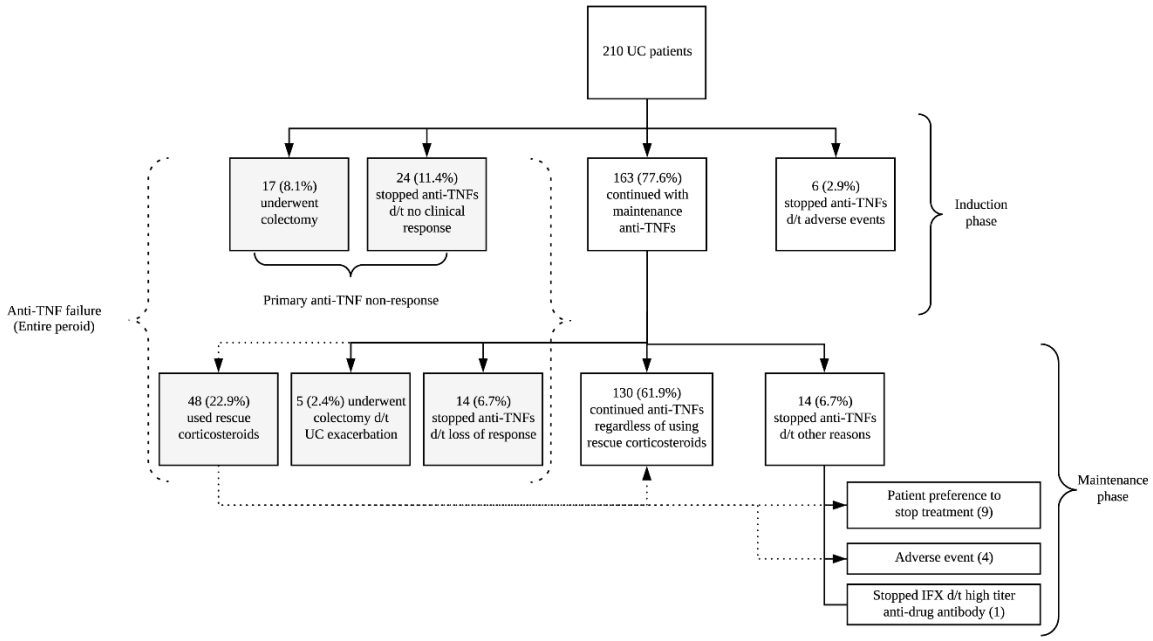

Figure 1. Flow chart of clinical outcomes after anti-TNF treatment of the study patients
IFX, infliximab; TNF, tumor necrosis factor; UC, ulcerative colitis

Twenty-two patients (10.5%) underwent colectomy over a median follow-up duration of 3.06 years (IQR 1.78-5.00) and 108 patients (51.4%) stopped anti-TNF treatment due to colectomy or no clinical response or rescue corticosteroid therapy (anti-TNF failure) over a median duration of 1.50 years (IQR 0.21-3.40).

Among the 194 patients who underwent both baseline and follow-up (week 8-14) endoscopy, mucosal healing was achieved in 80 (41.2%) patients and endoscopic response was identified in 107 (55.2%) patients.

Novel predictors for clinical and endoscopic outcomes

Predictors of PNR are shown in Table 2. Among the markers investigated for predicting PNR, disease duration at baseline (adjusted OR [aOR] 0.89, 95% CI 0.80-0.97), serum albumin W2/W0 $\leq$ 0.96 (aOR 2.76, 95% CI 1.30-6.10) and CRP W2/W0 $\geq$ 1.35 (aOR 2.39, 95% CI 1.14-5.08) were identified as significant predictors.

Predictors of mucosal healing and endoscopic response are shown in Table 3 and Table 4. For mucosal healing, female gender (aOR 0.43, 95% CI 0.23-0.79 [*vs.* male]), age at baseline (aOR 0.97, 95% CI 0.95-0.99), and serum albumin W2/W0>0.96 (aOR 2.56, 95% CI 1.38-4.85) were significant predictors after multivariable analysis. Regarding endoscopic response, only serum albumin W2/W0>0.96 (aOR 2.71, 95% CI 1.49-4.98) was a significant predictor after multivariable analysis.

Kaplan-Meier curves based on predefined cut-off levels of novel markers for predicting cumulative event-free survivals of colectomy and anti-TNF failure are shown in Figure 2. Analyses regarding predictors of cumulative colectomy-free survival and anti-TNF failure-free survival are shown in Table 5 and Table 6. For predicting colectomy during the entire study period, recent combined CMV colitis within 3 months (aHR 2.51, 95% CI 1.04-6.05), severe disease (Mayo score $\geq$ 11) at baseline (aHR 2.78,

95% CI 1.19-6.47) and serum albumin W2/W0 ≤ 0.96 (aHR 2.67, 95% CI 1.00-7.11) were identified as significant predictors. Regarding anti-TNF failure, both novel markers, serum albumin W2/W0 ≤ 0.96 (aHR 1.96, 95% CI 1.32-2.92) and CRP W2/W0 ≥ 1.35 (aHR 1.55, 95% CI 1.05-2.30) were significant predictors.

Subgroup analysis based on disease severity for predicting endoscopic outcomes

In the subgroup analysis based on disease severity according to Mayo score (severe disease defined as Mayo score ≥ 11), serum albumin W2/W0>0.96 significantly predicted mucosal healing (MES 0-1) and endoscopic response regardless of disease severity as shown in Table 7.

Table 2. Predictors of primary anti-TNF non-response

	Univariable analysis		Multivariable analysis[d]		
	OR	***p***	**aOR**	**95% CI**	***p***
Male	1.38	0.385			
Age at baseline	1.00	0.783			
Disease duration at baseline	0.88	0.010	0.89	0.80-0.97	0.017
Previous thiopurine use within 1 month	1.65	0.157			
Concomitant[a] thiopurine use	1.69	0.148			
Remote corticosteroid use (within 4-12 months)	1.18	0.643			
Recent corticosteroid use (within 3 months)	0.92	0.864			
Concomitant[a] corticosteroids use	0.76	0.500			
Current smoker	1.21	0.373			
Recent combined CMV colitis within 3 months	1.64	0.157			
p-ANCA positivity	0.88	0.705			
Extensive colitis at baseline	1.38	0.385			
Anemia[b] at baseline	1.35	0.438			
Severe disease (Mayo score≥11) at baseline	1.64	0.207			
Leukocytosis (>10,000/mm^3) at baseline	0.70	0.361			
Hypoalbuminemia (≤3.4 g/dl)at baseline	1.36	0.402			
Elevated CRP (≥0.6 mg/dl) at baseline	1.05	0.898			
Serum albumin W2/W0≤0.96[c]	2.78	0.005	2.76	1.30-6.10	0.009
Serum CRP W2/W0≥1.35[c]	2.97	0.002	2.39	1.14-5.08	0.022

[a]Concomitant was defined as prescriptions within 30 days before and/or after anti-TNF initiation.

[b]Defined as hemoglobin<13 g/dL in male, <12 g/dL in female

[c]Based on cut-off level for primary anti-TNF non-response

[d]Patients with both serum albumin and CRP data at week 0 and 2 were analyzed in the final model (N=203)

aOR, adjusted odds ratio; CI, confidence interval; CMV, cytomegalovirus; CRP, C-reactive protein; OR, odds ratio; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; TNF, tumor necrosis factor; UCEIS, ulcerative colitis endoscopic index of severity; W2/W0, week 2/week 0 ratio

Table 3. Predictors of mucosal healing at week 8-14

	Univariable analysis		Multivariable analysis[d]		
	OR	***p***	**aOR**	**95% CI**	***p***
Male	0.46	0.010	0.43	0.23-0.79	0.008
Age at baseline	0.97	0.008	0.97	0.95-0.99	0.013
Disease duration at baseline	1.03	0.360			
Previous thiopurine use within 1 month	0.56	0.049	Not included in the final model		
Concomitant[a] thiopurine use	0.76	0.360			
Remote corticosteroid use (within 4-12 months)	0.70	0.217			
Recent corticosteroid use (within 3 months)	1.00	0.994			
Concomitant[a] corticosteroids use	1.00	0.992			
Current smoker	0.81	0.284			
Recent combined CMV colitis within 3 months	0.80	0.450			
p-ANCA positivity	0.84	0.547			
Extensive colitis at baseline	1.17	0.602			
Anemia[b] at baseline	0.85	0.583			
Severe disease (Mayo score≥11) at baseline	1.41	0.321			
Leukocytosis (>10,000/mm^3) at baseline	1.34	0.347			
Hypoalbuminemia (≤3.4 g/dl)at baseline	1.55	0.145			
Elevated CRP (≥0.6 mg/dl) at baseline	0.91	0.747			
Serum albumin W2/W0>0.96[c]	2.74	0.001	2.56	1.38-4.85	0.003
Serum CRP W2/W0<1.35[c]	1.49	0.197			

[a]Concomitant was defined as prescriptions within 30 days before and/or after anti-TNF initiation.

[b]Defined as hemoglobin<13 g/dL in male, <12 g/dL in female

[c]Based on cut-off level for primary anti-TNF non-response

[d]Patients with both serum albumin and CRP data at week 0 and 2 together with endoscopic data were analyzed in the final model (N=187)

aOR, adjusted odds ratio; CI, confidence interval; CMV, cytomegalovirus; CRP, C-reactive protein; OR, odds ratio; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; TNF, tumor necrosis factor; UCEIS, ulcerative colitis endoscopic index of severity; W2/W0, week 2/week 0 ratio

Table 4. Predictors of endoscopic response at week 8-14

	Univariable analysis		Multivariable analysis[d]		
	OR	***p***	**aOR**	**95% CI**	***p***
Male	0.64	0.134			
Age at baseline	0.98	0.029	0.98	0.96-1.00	0.068
Disease duration at baseline	1.02	0.487			
Previous thiopurine use within 1 month	0.52	0.024	0.58	0.32-1.05	0.074
Concomitant[a] thiopurine use	0.60	0.082			
Remote corticosteroid use (within 4-12 months)	0.71	0.231			
Recent corticosteroid use (within 3 months)	1.11	0.775			
Concomitant[a] corticosteroids use	1.17	0.642			
Current smoker	0.97	0.876			
Recent combined CMV colitis within 3 months	0.71	0.258			
p-ANCA positivity	0.90	0.716			
Extensive colitis at baseline	1.04	0.890			
Severe disease (Mayo score≥11) at baseline	1.23	0.551			
Anemia[b] at baseline	1.14	0.669			
Leukocytosis (>10,000/mm^3) at baseline	0.66	0.107			
Hypoalbuminemia (≤3.4 g/dl)at baseline	1.57	0.129			
Elevated CRP (≥0.6 mg/dl) at baseline	0.92	0.774			
Serum albumin W2/W0 >0.96[c]	2.91	<0.001	2.71	1.49-4.98	0.001
Serum CRP W2/W0<1.35[c]	1.83	0.047	Not included in the final model		

[a]Concomitant was defined as prescriptions within 30 days before and/or after anti-TNF initiation.

[b]Defined as hemoglobin<13 g/dL in male, <12 g/dL in female

[c]Based on cut-off level for primary anti-TNF non-response

[d]Patients with both serum albumin and CRP data at week 0 and 2 together with endoscopic data were analyzed in the final model (N=187)

aOR, adjusted odds ratio; CI, confidence interval; CMV, cytomegalovirus; CRP, C-reactive protein; OR, odds ratio; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; TNF, tumor necrosis factor; UCEIS, ulcerative colitis endoscopic index of severity; W2/W0, week 2/week 0 ratio

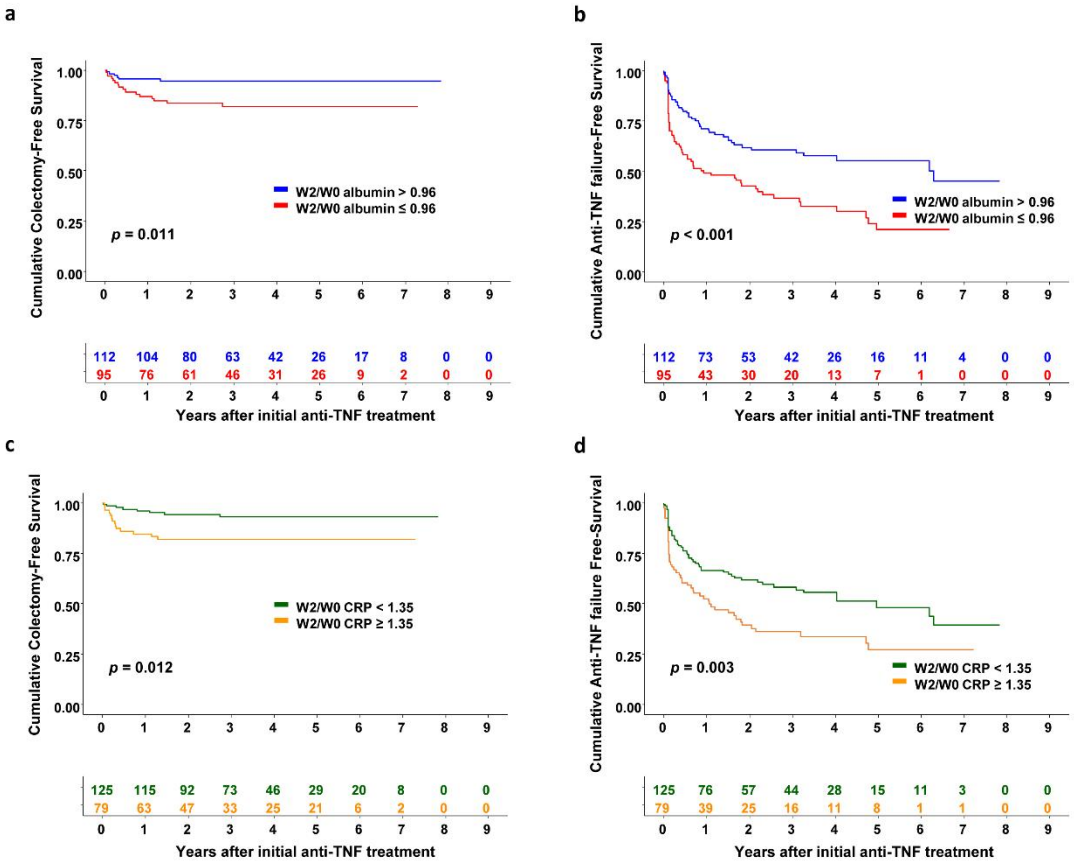

Figure 2. Cumulative event-free survival curves based on predefined cut-off levels of serum albumin W2/W0 regarding a) colectomy; b) anti-TNF failure. Cumulative event-free survival curves based on predefined cut-off levels of C-reactive protein W2/W0 regarding c) colectomy; d) anti-TNF failure.

TNF, tumor necrosis factor; W2/W0, week 2/week 0 ratio; CRP, C-reactive protein

Table 5. Predictors of risk of colectomy

	Univariable analysis		Multivariable analysis[d]		
	HR	***p***	**aHR**	**95% CI**	***p***
Male	1.69	0.273			
Age at baseline	1.03	0.052			
Disease duration at baseline	0.94	0.250			
Previous thiopurine use within 1 month	0.59	0.227			
Concomitant[a] thiopurine use	0.81	0.621			
Remote corticosteroid use (within 4-12 months)	1.59	0.294			
Recent corticosteroid use (within 3 months)	1.24	0.731			
Concomitant[a] corticosteroids use	1.34	0.600			
Thiopurine add-on after anti-TNF treatment[e]	1.10	0.843			
Methotrexate add-on after anti-TNF treatment[e]	1.08	0.960			
Current smoker	1.54	0.089			
Recent combined CMV colitis within 3 months	2.86	0.018	2.51	1.04-6.05	0.041
p-ANCA positivity	0.96	0.929			
Extensive colitis at baseline	2.16	0.130			
Severe disease (Mayo score≥11) at baseline	2.99	0.011	2.78	1.19-6.47	0.018
Anemia[b] at baseline	2.21	0.150			
Leukocytosis (>10,000/mm^3) at baseline	1.19	0.699			
Hypoalbuminemia (≤3.4 g/dl)at baseline	2.36	0.091			
Elevated CRP (≥0.6 mg/dl) at baseline	1.84	0.201			
Serum albumin W2/W0≤0.96[c]	3.39	0.011	2.67	1.00-7.11	0.049
Serum CRP W2/W0≥1.35[c]	3.05	0.012	2.09	0.84-5.24	0.114

[a]Concomitant was defined as prescriptions within 30 days before and/or after anti-TNF initiation.

[b]Defined as hemoglobin<13 g/dL in male, <12 g/dL in female

[c]Based on cut-off level for primary anti-TNF non-response

[d]Patients with both serum albumin and CRP data at week 0 and 2 were analyzed in the final model (N=203)

[e]Time-dependent covariable

aHR, adjusted hazard ratio; CI, confidence interval; CMV, cytomegalovirus; CRP, C-reactive protein; HR, hazard ratio; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; TNF, tumor necrosis factor; UCEIS, ulcerative colitis endoscopic index of severity; W2/W0, week 2/week 0 ratio

Table 6. Predictors of risk of anti-TNF failure

	Univariable analysis		Multivariable analysis[d]		
	HR	***p***	**aHR**	**95% CI**	***p***
Male	0.98	0.929			
Age at baseline	1.01	0.386			
Disease duration at baseline	0.96	0.088			
Previous thiopurine use within 1 month	0.91	0.636			
Concomitant[a] thiopurine use	0.93	0.725			
Remote corticosteroid use (within 4-12 months)	1.44	0.062			
Recent corticosteroid use (within 3 months)	1.68	0.090			
Concomitant[a] corticosteroids use	1.55	0.083			
Thiopurine add-on after anti-TNF treatment[e]	0.80	0.252			
Methotrexate add-on after anti-TNF treatment[e]	0.78	0.726			
Current smoker	0.87	0.283			
Recent combined CMV colitis within 3 months	1.39	0.093			
p-ANCA positivity	1.12	0.570			
Extensive colitis at baseline	1.15	0.486			
Severe disease (Mayo score≥11) at baseline	1.21	0.388			
Anemia[b] at baseline	0.88	0.523			
Leukocytosis (>10,000/mm^3) at baseline	0.96	0.858			
Hypoalbuminemia (≤3.4 g/dl)at baseline	1.14	0.516			
Elevated CRP (≥0.6 mg/dl) at baseline	0.86	0.437			
Serum albumin W2/W0≤0.96[c]	2.11	<0.001	1.96	1.32-2.92	0.001
Serum CRP W2/W0≥1.35[c]	1.80	0.003	1.55	1.05-2.30	0.027

[a]Concomitant was defined as prescriptions within 30 days before and/or after anti-TNF initiation.

[b]Defined as hemoglobin<13 g/dL in male, <12 g/dL in female

[c]Based on cut-off level for primary anti-TNF non-response

[d]Patients with both serum albumin and CRP data at week 0 and 2 were analyzed in the final model (N=203)

[e]Time-dependent covariable

aHR, adjusted hazard ratio; CI, confidence interval; CMV, cytomegalovirus; CRP, C-reactive protein; HR, hazard ratio; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; TNF, tumor necrosis factor; UCEIS, ulcerative colitis endoscopic index of severity; W2/W0, week 2/week 0 ratio

Table 7. Subgroup analysis of the novel markers for predicting endoscopic outcomes based on disease severity

	Mucosal healing[b]		**Endoscopic response[b]**	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Severe disease (Mayo score≥11)				
Serum albumin W2/W0>0.96[a]	4.06 (1.16-15.75)	0.034	5.20 (1.44-21.42)	0.016
Serum CRP W2/W0<1.35[a]	4.87 (1.31-21.49)	0.024	3.04 (0.86-11.44)	0.089
Moderate disease (6≤Mayo score<11)				
Serum albumin W2/W0>0.96[a]	2.50 (1.26-5.10)	0.010	2.57 (1.32-5.11)	0.006
Serum CRP W2/W0<1.35[a]	1.05 (0.53-2.09)	0.895	1.56 (0.79-3.07)	0.200

[a]Based on cut-off level for primary anti-TNF non-response

[b]Patients with both serum albumin and CRP data at week 0 and 2 together with endoscopic data were analyzed (N=187)

CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; W2/W0, week 2/week 0 ratio

Discussion

Based on investigation of our real-life UC cohort, we identified serum albumin and CRP W2/W0 ratio as significant markers to predict both clinical and endoscopic outcomes after starting anti-TNF treatment in anti-TNF-naïve UC patients.

In the management of patients with moderate to severe UC, anti-TNF therapy is currently the mainstay of medical treatment. However, a substantial proportion of UC patients shows PNR or secondary loss of response to anti-TNF therapy. There have been several real-life studies on the genetic, clinical, serological, or biochemical markers at initiation of anti-TNF agents for predicting poor response to anti-TNF therapy, such as high genetic risk score,[22] primary failure to previous anti-TNF agent,[23] intolerance as the reason for the first anti-TNF discontinuation,[24] previous treatment with cyclosporine and/or corticosteroids,[11, 25] ex-smoking,[26] recent history of CMV colitis,[27, 28] obesity at baseline,[29] severe diseases,[23, 27] ANCA positivity,[30] positive antibody to *Escherichia Coli* outer membrane porin,[31] high CRP at baseline,[11, 25, 32] anemia at baseline,[11] and low serum albumin.[33] Besides baseline characteristics and laboratory values, we hypothesized that early change of serum biomarkers could predict the short-term clinical and endoscopic response after anti-TNF therapy in patients with UC. However, only few studies have investigated the early change of biochemical markers including serum albumin and CRP as predictors of outcomes after starting IFX.[33, 34]

In the study by Morita et al, among UC patients treated with IFX or ADA, CRP levels at week 2 were significantly higher in non-responders compared with responders at week 8.[33] However, independent association between CRP levels at week 2 and clinical response at week 8 was not investigated.[33] Moreover, serum albumin at week 2 and change of CRP and albumin compared with baseline values were not investigated in their study.[33] Iwasa et al first investigated W2/W0 ratio of CRP as a predictor for clinical outcomes at week 14 in UC patients starting IFX.[34] They found significant differences in W2/W0 ratio of CRP when comparing responders and partial responders, as well as between responders

and non-responders.[34] The cut-off value of 0.19 for W2/W0 CRP ratio could predict a partial response to IFX with a 79.1% sensitivity and 75.9% specificity, having the area under the receiver operating characteristics curve of 0.799.[34] During follow-up of 72 patients for average 39.5 months, cumulative probabilities of colectomy were significantly different between two groups divided based on the cut-off value of 0.19 for W2/W0 CRP ratio ($P = 0.0391$).[34] However, the independent statistical significance of W2/W0 CRP ratio, endoscopic outcomes, and W2/W0 albumin ratio were not investigated.[34] Moreover, both studies were limited with small number of study subjects.[33, 34] We therefore, aimed to investigate the early change of both serum albumin and CRP in the first two weeks after starting anti-TNF treatment as predictors for short-term clinical and endoscopic outcomes in a relatively large cohort of Asian UC patients.

In our study, both serum albumin W2/W0 ratio and CRP W2/W0 ratio significantly and independently predicted PNR, but only serum albumin W2/W0 ratio, not CRP W2/W0 ratio predicted mucosal healing and endoscopic response at week 8-14. Serum albumin W2/W0 ratio could also predict cumulative colectomy-free survival and anti-TNF failure-free survival. However, serum CRP W2/W0 ratio failed to predict cumulative colectomy-free survival.

Serum albumin and CRP levels are known to represent the inflammatory burden of UC.[35, 36] Moreover, according to previous studies, these markers reflect IFX concentration, IFX clearance and half-life of drug after starting IFX.[37-39] Based on our study results, the early change of serum albumin and CRP levels after only the first dose of anti-TNF administration seems to capture enough signal to predict early clinical and endoscopic outcomes in patients with UC. In our study, the W2/W0 ratio of serum albumin seemed to have an advantage over the W2/W0 CRP ratio in that it could significantly predict short-term endoscopic outcomes and also the cumulative colectomy-free survival, although no direct head-to-head comparison between two markers was performed. One possible reason for the advantage of the albumin ratio over the CRP ratio might be related to the inter-individual variability of serum albumin. Serum albumin is known to be affected by multiple factors including patient and disease

characteristics.[38] The W2/W0 ratio of serum albumin, but not the single value at week 2 might overcome the inter-individual variability of albumin and other factors that tend to change over time, possibly better reflecting more acute changes during the first two weeks. Furthermore, this marker was able to predict endoscopic outcomes regardless of UC severity at baseline.

In this study, primary anti-TNF failure was observed in 19.5% of patients. This was comparable to or slightly lower than the rates of previous studies.[9-11] Moreover, this seemed to be lower compared to the 29.7% of a previous study from our center.[28] Exclusion of referred patients who started anti-TNF treatment at other centers and inclusion of only anti-TNF-naïve patients may have influenced these results. Furthermore, more severe patients with low serum albumin levels who were given intravenous albumin infusions during the first 2 weeks were also excluded from our study. Therefore, caution is warranted when interpreting our results on PNR, nevertheless, our current study design might overcome the referral bias and might reflect the real-life practice better.

Our study also showed the association between recent CMV colitis and the risk of colectomy as well as the association between severe disease activity and the risk of colectomy, both of which are consistent with our previous reports.[27, 28]

Recently, there has been a paradigm shift in treating patients with inflammatory bowel disease (IBD). Previously, symptom-based treatment strategy with loose monitoring was regarded as enough for management of IBD. However, this strategy is currently considered not to be preventive of disease progression and bowel damage in patients with IBD, which are progressive in a substantial proportion of patients.[40, 41] According to the recent STRIDE consensus, mucosal healing was recommended as a target for UC therapy together with symptomatic remission and biomarkers such as CRP and fecal calprotectin. These biomarkers were regarded as adjunctive measures of inflammation for monitoring disease acitivity.[42] In the recently published CALM study, biomarkers such as CRP and fecal calprotectin were utilized for deciding treatment escalation, which proved to be effective in achieving

better clinical and endoscopic outcomes than symptom-driven decisions alone.[43] In this sense, the objective biomarkers could play an important role in guiding treatment of UC. Our study supports this concept, providing evidence for the usefulness of serum biomarker change in predicting response to anti-TNF therapy in UC. Moreover, serum albumin and CRP are frequently used in daily clinical practice and are easy to check.

We had several limitations in our study. First, trough levels of anti-TNFs and levels of anti-drug antibody were not evaluated in our study. To have a better understanding of our novel markers, the association between markers with anti-TNF trough levels/anti-drug antibodies should be elucidated in future studies. Second, among the study patients, two patients had compensated liver cirrhosis and one patient had previous history of liver transplantation due to combined primary sclerosing cholangitis. The low serum albumin levels in these patients may have influenced our results, however, use of ratio rather than absolute levels may have reduced the inter- and intra-individual variability among individuals. Third, our study had the limitations of a retrospective design and was based on a single tertiary referral center. However, homogeneous and standardized treatment strategy can be applied in the single center setting, thereby minimizing variabilities depending on physicians. Fourth, the definition of anti-TNF failure was not identical to other studies. In fact, there have been various definitions of clinical outcomes in retrospective studies. Regarding the definition of anti-TNF failure, we did not account for adverse events (mostly infection) and/or patient preference, as it seemed irrelevant to predict these reasons with biomarkers. Accordingly, the clinical outcomes of our study should be interpreted cautiously.

Conclusions

The early change of serum albumin and CRP in the first two weeks after starting IFX or ADA significantly predicts primary anti-TNF non-response. Furthermore, W2/W0 ratio of serum albumin significantly predicts endoscopic outcomes and cumulative colectomy-free and anti-TNF failure-free survival as well. This marker predicts endoscopic outcomes regardless of disease severity at baseline. Based on these novel markers, anti-TNF treatment could be optimized as early as 2 weeks to improve clinical and endoscopic outcomes. External validation of these markers is warranted in future studies.

References

1. Ordas I, Eckmann L, Talamini M, et al. Ulcerative colitis. Lancet 2012;380:1606-19.
2. Lee HS, Park SH, Yang SK, et al. Long-term prognosis of ulcerative colitis and its temporal change between 1977 and 2013: a hospital-based cohort study from Korea. J Crohns Colitis 2015;9:147-55.
3. Rungoe C, Langholz E, Andersson M, et al. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979-2011. Gut 2014;63:1607-16.
4. Choi CH, Moon W, Kim YS, et al. Second Korean guidelines for the management of ulcerative colitis. Intest Res 2017;15:7-37.
5. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462-76.
6. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut 2011;60:780-7.
7. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012;142:257-65 e1-3.
8. Cholapranee A, Hazlewood GS, Kaplan GG, et al. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. Aliment Pharmacol Ther 2017;45:1291-1302.
9. Arias MT, Vande Casteele N, Vermeire S, et al. A panel to predict long-term outcome of infliximab therapy for patients with ulcerative colitis. Clin Gastroenterol Hepatol 2015;13:531-8.
10. Murthy SK, Greenberg GR, Croitoru K, et al. Extent of Early Clinical Response to Infliximab Predicts Long-term Treatment Success in Active Ulcerative Colitis. Inflamm Bowel Dis 2015;21:2090-6.
11. Oussalah A, Evesque L, Laharie D, et al. A multicenter experience with infliximab for ulcerative

colitis: outcomes and predictors of response, optimization, colectomy, and hospitalization. Am J Gastroenterol 2010;105:2617-25.

12. Park SH, Yang SK, Park SK, et al. Long-term prognosis of crohn's disease and its temporal change between 1981 and 2012: a hospital-based cohort study from Korea. Inflamm Bowel Dis 2014;20:488-94.

13. Binder V, Both H, Hansen PK, et al. Incidence and prevalence of ulcerative colitis and Crohn's disease in the County of Copenhagen, 1962 to 1978. Gastroenterology 1982;83:563-8.

14. Garland CF, Lilienfeld AM, Mendeloff AI, et al. Incidence rates of ulcerative colitis and Crohn's disease in fifteen areas of the United States. Gastroenterology 1981;81:1115-24.

15. Tysk C, Jarnerot G. Ulcerative proctocolitis in Orebro, Sweden. A retrospective epidemiologic study, 1963-1987. Scand J Gastroenterol 1992;27:945-50.

16. Yang SK, Hong WS, Min YI, et al. Incidence and prevalence of ulcerative colitis in the Songpa-Kangdong District, Seoul, Korea, 1986-1997. J Gastroenterol Hepatol 2000;15:1037-42.

17. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625-9.

18. Travis SP, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut 2012;61:535-42.

19. Lee SH, Kim MJ, Chang K, et al. Fecal calprotectin predicts complete mucosal healing and better correlates with the ulcerative colitis endoscopic index of severity than with the Mayo endoscopic subscore in patients with ulcerative colitis. BMC Gastroenterol 2017;17:110.

20. Vuitton L, Peyrin-Biroulet L, Colombel JF, et al. Defining endoscopic response and remission in ulcerative colitis clinical trials: an international consensus. Aliment Pharmacol Ther 2017;45:801-813.

21. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19 Suppl A:5A-36A.

22. Burke KE, Khalili H, Garber JJ, et al. Genetic Markers Predict Primary Nonresponse and Durable Response to Anti-Tumor Necrosis Factor Therapy in Ulcerative Colitis. Inflamm Bowel Dis (in press).

23. Iborra M, Perez-Gisbert J, Bosca-Watts MM, et al. Effectiveness of adalimumab for the treatment of ulcerative colitis in clinical practice: comparison between anti-tumour necrosis factor-naive and non-naive patients. J Gastroenterol 2017;52:788-799.

24. Martineau C, Flourie B, Wils P, et al. Efficacy and safety of golimumab in Crohn's disease: a French national retrospective study. Aliment Pharmacol Ther 2017;46:1077-1084.

25. Ferrante M, Vermeire S, Fidder H, et al. Long-term outcome after infliximab for refractory ulcerative colitis. J Crohns Colitis 2008;2:219-25.

26. Ribaldone DG, Dileo I, Pellicano R, et al. Severe ulcerative colitis: predictors of response and algorithm proposal for rescue therapy. Ir J Med Sci 2018;187:385-392.

27. Park SH, Yang SK, Hong SM, et al. Severe disease activity and cytomegalovirus colitis are predictive of a nonresponse to infliximab in patients with ulcerative colitis. Dig Dis Sci 2013;58:3592-9.

28. Seo H, Chang K, Lee SH, et al. Long-term outcomes of infliximab treatment and predictors of response in 195 patients with ulcerative colitis: a hospital-based cohort study from Korea. Scand J Gastroenterol 2017;52:857-863.

29. Madsen KG, Pottegard A, Hallas J, et al. Treatment failure of TNF-alpha inhibitors in obese patients with inflammatory bowel disease-A cohort study. Inflamm Bowel Dis 2018 (in press).

30. Yoon SM, Haritunians T, Chhina S, et al. Colonic phenotypes are associated with poorer response to anti-TNF therapies in patients with IBD. Inflamm Bowel Dis 2017;23:1382-1393.

31. Kevans D, Waterman M, Milgrom R, et al. Serological markers associated with disease behavior and response to anti-tumor necrosis factor therapy in ulcerative colitis. J Gastroenterol Hepatol 2015;30:64-70.

32. O'Connell J, Rowan C, Stack R, et al. Golimumab effectiveness and safety in clinical practice for moderately active ulcerative colitis. Eur J Gastroenterol Hepatol 2018 (in press).

33. Morita Y, Bamba S, Takahashi K, et al. Prediction of clinical and endoscopic responses to anti-tumor necrosis factor-alpha antibodies in ulcerative colitis. Scand J Gastroenterol 2016;51:934-41.

34. Iwasa R, Yamada A, Sono K, et al. C-reactive protein level at 2 weeks following initiation of infliximab induction therapy predicts outcomes in patients with ulcerative colitis: a 3 year follow-up study. BMC Gastroenterol 2015;15:103.

35. Solem CA, Loftus EV, Jr., Tremaine WJ, et al. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflamm Bowel Dis 2005;11:707-12.

36. Wetterfors J, Liljedahl SO, Plantin LO, et al. Hypoalbuminaemia in ulcerative colitis and certain forms of enteritis. Clinical and pathophysiological aspects. Acta Med Scand 1963;174:529-49.

37. Brandse JF, Mathot RA, van der Kleij D, et al. Pharmacokinetic features and presence of antidrug antibodies associate with response to infliximab induction therapy in patients with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol 2016;14:251-8 e1-2.

38. Fasanmade AA, Adedokun OJ, Olson A, et al. Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. Int J Clin Pharmacol Ther 2010;48:297-308.

39. Kevans D, Murthy S, Mould DR, et al. Accelerated clearance of infliximab is associated with treatment failure in patients with corticosteroid-refractory acute ulcerative colitis. J Crohns Colitis 2018 (in press).

40. Pariente B, Cosnes J, Danese S, et al. Development of the Crohn's disease digestive damage score, the Lemann score. Inflamm Bowel Dis 2011;17:1415-22.

41. Torres J, Billioud V, Sachar DB, et al. Ulcerative colitis as a progressive disease: the forgotten evidence. Inflamm Bowel Dis 2012;18:1356-63.

42. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): Determining therapeutic goals for treat-to-target. Am J Gastroenterol 2015;110:1324-38.

43. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet 2018;390:2779-2789.

국문요약

목적: 본 연구의 목적은 항 TNF 제제의 치료 경험이 없는 궤양성 대장염 환자에서 항 TNF 제제의 투여 후 임상 및 내시경 반응에 대한 새로운 예측인자를 규명하는 것이다.

방법: 본 연구에서는 2009 년 6 월부터 2016 년 12 월까지 서울아산병원에서 infliximab 또는 adalimumab 치료를 시작한 궤양성 대장염 환자 210 명 (남성 62.4%, 궤양성 대장염 진단 시 나이의 중앙값 37.9 세 [사분위수 범위, 25.5-48.9], 추적 기간의 중앙값 3.3 년 [사분위수 범위, 1.9-5.0])을 후향적으로 분석하였다. 로지스틱 회귀분석을 통해 항 TNF 제제에 대한 일차 무반응 및 내시경 결과를 예측하는 인자를 규명하였다. Kaplan-Meier 분석을 통해 대장절제술 무발생 및 항 TNF 제제 실패 무발생 누적생존율을 계산하였고, 로그순위검정법 및 콕스 비례위험 회귀분석 모형을 통해 대장절제술 및 항 TNF 제제 실패의 예측인자를 규명하였다.

결과: 총 41 명 (19.5%)이 항 TNF 제제에 일차 무반응을 보였다. 혈청 알부민 2 주/0 주 비 ≤0.96 (보정된 교차비 2.76, 95% 신뢰구간 1.30-6.10) 및 C-반응 단백질 2 주/0 주 비≥1.35 (보정된 교차비 2.39, 95% 신뢰구간 1.14-5.08)가 항 TNF 제제에 대한 일차 무반응의 의미있는 예측인자였다. 또한, 혈청 알부민 2 주/0 주 비>0.96 는 8-14 주째 점막치유 (mucosal healing) (Mayo endoscopic subscore 0-1) (보정된 교차비 2.56, 95% 신뢰구간 1.38-4.85) 및 내시경 반응 (보정된 교차비 2.71, 95% 신뢰구간 1.49-4.98)을 의미있게 예측하였다. 혈청 알부민 2 주/0 주 비≤0.96 는 대장절제술 (보정된 위험비 2.67, 95% 신뢰구간 1.00-7.11) 및 항 TNF 제제 실패 (보정된 위험비 1.96, 95% 신뢰구간 1.32-2.92)를 의미있게 예측한 반면, C-반응 단백질 2 주/0 주 비≥1.35 는 항 TNF 제제 실패 (보정된 위험비 1.80, 95% 신뢰구간 1.05-2.30)만 의미있게 예측하였다.

결론: 항 TNF 제제 치료 후 혈청 알부민과 C-반응 단백질의 첫 2 주간 변화는 항 TNF 제제에 대한 일차 무반응을 의미있게 예측하였다. 특히, 혈청 알부민 2 주/0 주 비는 단기 내시경 반응과 대장절제술 무발생 및 항 TNF 제제 실패 무발생 누적생존을 의미있게 예

측하였다. 이러한 새로운 예측인자들을 바탕으로, 치료 시작 2 주째에 항 TNF 제제 투여를 최적화함으로써, 임상 및 내시경 반응의 향상에 기여할 수 있을 것이다.

중심단어: 궤양성 대장염, Infliximab, Adalimumab, 알부민, C-반응 단백질