

Serum PR3-ANCA Is a Predictor of Primary Nonresponse to Anti-TNF- α Agents in Patients with Ulcerative Colitis

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Keywords

Inflammatory bowel disease · Primary failure · Infliximab · Adalimumab · Golimumab

Abstract

Background: Anti-tumor necrosis factor- α (TNF- α) agents are effective for moderately to severely active ulcerative colitis (UC). Nonetheless, a proportion of patients fail to respond to these agents as therapy for induction of remission. Recent studies indicated that perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) may predict response to anti-TNF- α agents in UC patients. However, whether PR3-ANCA can predict primary nonresponse (PNR) to anti-TNF- α agents has not yet been evaluated. The aim of this study was to examine whether PR3-ANCA can predict PNR to anti-TNF- α in UC patients. **Methods:** This was a single-center retrospective study. Data were extracted from 50 patients with UC who had measurements of PR3-ANCA and received anti-TNF- α agents for the first time as induction therapy. The primary endpoint of this study was a proportion of patients with PNR stratified by PR3-ANCA positivity. PNR to anti-TNF- α agents was defined as failure to achieve reduction in partial Mayo score by 2 or more points and change to other therapeutics within 6 weeks. **Results:** Fourteen (28%) of the 50 patients

were PR3-ANCA positive. Seventeen (34%) of the 50 patients demonstrated PNR. Eleven (78.6%) of the 14 PR3-ANCA-positive patients demonstrated PNR, while 6 (16.7%) of the 36 PR3-ANCA-negative patients demonstrated PNR. Multivariate analysis demonstrated that PR3-ANCA positivity was associated with PNR to anti-TNF- α agents (odds ratio 19.29, 95% CI: 3.30–172.67; $p = 0.002$). **Conclusion:** PR3-ANCA positivity can predict PNR to anti-TNF- α agents in UC patients.

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon and rectum with repeated cycles of remission and relapse [1]. UC and Crohn's disease (CD) are the 2 major forms of inflammatory bowel disease (IBD). The etiology of UC remains unknown. Treatment is determined according to disease extent and activity. First-line therapy for patients with mild-to-moderate activity is 5-aminosalicylic acid (5-ASA). Corticosteroids are used for patients who are refractory to 5-ASA or who have moderate-to-severe activity. However, roughly half of patients are resistant to or dependent on corticosteroids. Anti-tumor necrosis factor-alpha (TNF- α) agents are indi-

cated for treatment of patients with moderate-to-severe UC that is refractory to corticosteroids [2–5]. Despite the efficacy of anti-TNF- α agents, 30–40% of patients do not respond to initial induction dosing of anti-TNF- α agents, known as primary nonresponse (PNR). Several predictors of PNR, including disease activity and serum albumin levels, have been reported. However, none have sufficient predictive capacity for clinical use [6].

Anti-neutrophil cytoplasmic antibodies (ANCA) are autoantibodies to antigens localized in the cytoplasm of neutrophils [7]. ANCA is classified into 2 types according to staining patterns on indirect immunofluorescence (IIF): cytoplasmic ANCA (c-ANCA), whereby neutrophil cytoplasm is stained granularly, and perinuclear ANCA (p-ANCA), whereby antigens around the nucleus are stained [8, 9]. The target antigens of p-ANCA and c-ANCA were subsequently identified: myeloperoxidase for p-ANCA and protease-3 (PR-3) for c-ANCA. These antigens can be measured using enzyme-linked immunosorbent assay (ELISA) or chemiluminescent enzyme immunoassay (CLEIA), which are more specific and sensitive than IIF.

ANCA are diagnostic markers for ANCA-associated vasculitis (AAV). In addition to AAV, ANCA positivity is observable in patients with various immunological disorders such as rheumatoid arthritis and primary biliary cholangitis [10]. P-ANCA positivity was also reported in approximately 10–80% of UC patients not complicated with AAV and can be used as a diagnostic marker for UC [10–13]. A meta-analysis demonstrated the sensitivity and specificity of p-ANCA positivity were 55.3 and 88.5%, respectively, in the differential diagnosis of UC and CD [12]. Interestingly, several recent studies reported that p-ANCA can also serve as a predictor of PNR to anti-TNF- α agents in UC patients [14–19].

PR3-ANCA positivity, corresponding to c-ANCA, is also observable in UC patients and was reported to have a sensitivity of 58% and a specificity of 93% in the differential diagnosis of UC and CD [20]. However, whether PR3-ANCA can predict PNR to anti-TNF- α agents in UC patients has not yet been examined. The aim of this study was to investigate whether PR3-ANCA is a predictor of PNR to anti-TNF- α agents in UC patients.

Materials and Methods

Study Design

This was a retrospective cohort study conducted at a regional IBD center in Japan.

Patients

We included UC patients who received anti-TNF- α agents (infliximab [IFX], adalimumab [ADA], and golimumab [GLM]) for the first time between January 2012 and December 2019 and had available data on serum PR3-ANCA. Diagnosis of UC was made in accordance with Japanese practice guidelines [21].

Treatment

We administered anti-TNF- α agents at standard dose regimens: IFX was administered at 5 mg/kg at 0, 2, and 6 weeks and every 8 weeks thereafter; ADA was administered at 160 mg at week 0, 80 mg at week 2, and then 40 mg biweekly; and GLM was administered at 200 mg at week 0, 100 mg at week 2, and then at 100 mg every 4 weeks.

Data Collection

We extracted the following data from medical charts: age, sex, body mass index (BMI), disease extent, disease duration, Mayo score [22], serum albumin levels, hemoglobin (Hb) levels, serum C-reactive protein (CRP) levels, serum PR3-ANCA levels, smoking history, and concomitant medications. PR3-ANCA was measured using CLEIA (Hoken Kagaku, Inc., Yokohama, Japan). PR3-ANCA positivity was defined as 3.5 U/mL or higher.

Outcome Measurements

The primary outcome of this study was proportion of patients with PNR to anti-TNF- α agents stratified by PR3-ANCA positivity. PNR was defined as failure to achieve reduction in partial Mayo score by 2 or more points and change to other therapies within 6 weeks. Patients whose treatment was changed because of intolerance to anti-TNF- α agents were excluded from analysis. As predictive factors for PNR, we examined age, sex, disease duration, disease extent, BMI, Mayo score, endoscopic Mayo subscore, albumin, Hb, CRP, smoking habit, and concomitant medications.

Statistical Analysis

Normally distributed continuous variables are presented as mean \pm SD, and nonparametric variables are presented as median (interquartile range [IQR]). Normality was assessed with the Shapiro-Wilk test. For statistical analyses, each explanatory variable was compared between those with and without PNR using Student's *t* test, the χ^2 test, or the Wilcoxon rank-sum test. Factors contributing to PNR to anti-TNF- α agents were also analyzed using logistic regression analysis with explanatory variables. PNR prediction performance (sensitivity and specificity) was evaluated for significant factors. For these analyses, we used R functions. *p* values <0.05 were considered statistically significant.

Results

Patient Demographics

During the study period, 88 patients received anti-TNF- α agents for the first time (IFX: *n* = 51 [58%]; ADA: *n* = 28 [32%]; and GLM: *n* = 9 [10%]). Data on PR3-ANCA were available in 51 (58%) patients. For most patients, PR3-ANCA was measured for differential diagno-

Table 1. Characteristics of patients enrolled in this study ($N = 50$)

Age, years, mean \pm SD	46.3 \pm 19.4
Male, n (%)	29 (58)
Disease duration, years, mean \pm SD	11.3 \pm 9.5
Disease extent: extensive, left-sided, and proctitis, n (%)	39 (78), 11 (22), 0 (0)
BMI, mean \pm SD	21.7 \pm 3.3
Mayo score, median (IQR)	9 (8–10)
eMayo 0, n (%)	0 (0)
eMayo 1, n (%)	0 (0)
eMayo 2, n (%)	21 (42)
eMayo 3, n (%)	29 (58)
Alb, g/dL, mean \pm SD	3.3 \pm 0.7
Hb, g/dL, mean \pm SD	11.7 \pm 1.7
CRP, mg/dL, mean \pm SD	2.8 \pm 3.5
Smoking: current, ex-smoker, and nonsmoker, n (%)	9 (18), 3 (6), 38 (76)
Concomitant medication	
5-ASA, n (%)	32 (64)
Steroids, n (%)	25 (50)
PSL \geq 20 mg/day, n (%)	10 (20)
PSL <20 mg/day, n (%)	15 (30)
Thiopurines, n (%)	38 (76)
IFX, ADA, and GLM, n (%)	33 (66), 13 (26), 4 (8)
Time between PR3-ANCA measurement and anti-TNF- α initiation, days, median (range)	170 (–1,579~2,076)

SD, standard deviation; IQR, interquartile range; BMI, body mass index; eMayo, endoscopic Mayo subscore; Alb, albumin; Hb, hemoglobin; CRP, C-reactive protein; 5-ASA, 5-aminosalicylic acid; PSL, prednisolone; IFX, infliximab; ADA, adalimumab; GLM, golimumab; ANCA, anti-neutrophil cytoplasmic antibody.

sis at UC onset. One patient was excluded from analysis because of intolerance to anti-TNF- α agents.

Baseline parameters of the 50 patients are shown in Table 1. The mean age was 46.3 \pm 19.4 years, 29 (58%) were male, and 39 (78%) had extensive colitis. Most patients had moderate colitis with a median Mayo score of 9 (IQR: 8–10). This study did not include UC cases with vasculitis-related extraintestinal symptoms.

Predictors of PNR

Seventeen (34%) of the 50 patients demonstrated PNR at week 6. Univariate analysis revealed significant differences between patients with and without PNR in Hb (mean [SD]: 10.9 [1.8] vs. 12.0 [0.7], $p = 0.039$), smoking cessation history (36% [$n = 6$] vs. 9% [$n = 3$], $p = 0.044$), and PR3-ANCA positivity (65% [$n = 11$] vs. 9% [$n = 3$], $p < 0.001$) (Table 2). Other factors, including age, sex, disease duration, Mayo score, or CRP, were not significantly different between patients with and without PNR (Table 2). Multivariate analysis using logistic regression analysis showed PR3-ANCA positivity was significantly associated with PNR (odds ratio 19.29, 95% confidence interval [CI]: 3.30–

172.67; $p = 0.002$). No other factors, including BMI, Mayo score, Hb levels, or smoking cessation history, were significantly associated with PNR (Table 3).

Rates of PNR

Eleven (78.6%) of the 14 patients with PR3-ANCA positivity demonstrated PNR, while 6 (16.7%) of the 36 patients with PR3-ANCA negativity demonstrated PNR ($p = 0.0001$, using the χ^2 test).

Performance of PR3-ANCA for Predicting PNR

We examined the performance of PR3-ANCA for predicting PNR: the sensitivity was 64.7%, specificity was 90.9%, positive predictive value was 78.6%, and negative predictive value was 83.3%. The area under the curve of receiver operating characteristics (ROC) analysis was 0.82 (95% CI: 0.69–0.96). PNR diagnostic performance with best accuracy (threshold 2.45 U/mL) obtained by using Youden's method showed that the sensitivity was 82.4%, specificity was 84.8%, positive predictive value was 74.0%, and negative predictive value was 90.3%, respectively.

Table 2. Characteristics of patients with primary nonresponse and those without

	Primary nonresponse (n = 17)	Primary response (n = 33)	p value
Age, years, mean ± SD	45.2±21.5	46.8±18.6	0.801*
Male, n (%)	10 (59)	19 (58)	0.933**
Disease duration, years, median (IQR)	10 (3–14)	8 (6–17)	0.831***
Disease extent: extensive, left-sided, and proctitis, n (%)	13 (76), 4 (24), 0 (0)	26 (79), 7 (21), 0 (0)	0.851**
BMI, median (IQR)	19.6 (18.9–23.1)	21.9 (20.0–23.2)	0.073***
Mayo score, median (IQR)	9 (9–10)	9 (8–10)	0.120***
eMayo 0, n (%)	0 (0)	0 (0)	
eMayo 1, n (%)	0 (0)	0 (0)	
eMayo 2, n (%)	5 (29)	16 (48)	0.196**
eMayo 3, n (%)	12 (71)	17 (52)	0.364**
Alb, g/dL, mean ± SD	3.2±0.7	3.3±0.7	0.843*
Hb, g/dL, mean ± SD	10.9±1.8	12.0±0.7	0.039*
CRP, mg/dL, median (IQR)	0.96 (0.41–6.00)	1.02 (0.25–3.65)	0.594***
Smoking: current, ex-smoker, and nonsmoker, n (%)	6 (36), 0 (0), 11 (64)	3 (9), 3 (9), 27 (82)	0.044**
Concomitant medication			
5-ASA, n (%)	13 (76)	19 (58)	0.187**
Steroids, n (%)	8 (47)	17 (52)	0.765**
PSL ≥20 mg/day, n (%)	3 (18)	7 (21)	0.765**
PSL <20 mg/day, n (%)	5 (29)	10 (30)	0.948**
Thiopurines, n (%)	12 (71)	26 (79)	0.520**
IFX, ADA, and GLM, n (%)	8 (47), 6 (35), 3 (18)	25 (78), 7 (21), 1 (1)	0.072**
Time between PR3-ANCA measurement and anti-TNF-α initiation, days, median (range)	226 (–1,579~2,076)	115 (–566~375)	0.413***
PR3-ANCA +, n (%)	11 (65)	3 (9)	0.000**

SD, standard deviation; IQR, interquartile range; BMI, body mass index; eMayo, endoscopic Mayo subscore; Alb, albumin; Hb, hemoglobin; CRP, C-reactive protein; 5-ASA, 5-aminosalicylic acid; PSL, prednisolone; IFX, infliximab; ADA, adalimumab; GLM, golimumab; ANCA, anti-neutrophil cytoplasmic antibody. Bold indicates statistical significance. * *t* test. ** χ^2 test. *** Wilcoxon rank-sum test.

Table 3. The association between primary nonresponse to anti-TNF-α agents and explanatory variables

	Odds ratio	95% confidence interval	p value
Sex (female)	0.53	0.06–3.60	0.535
BMI	0.86	0.62–1.13	0.321
Mayo score at baseline	0.93	0.44–1.86	0.847
Hemoglobin	0.92	0.53–1.54	0.756
Disease duration	1.02	0.93–1.10	0.650
Smoking cessation	4.88	0.57–51.02	0.154
PR3-ANCA	19.29	3.30–172.67	0.002

BMI, body mass index; ANCA, anti-neutrophil cytoplasmic antibody. Bold indicates statistical significance.

Discussion

Herein, we demonstrated PR3-ANCA as a predictor of PNR to anti-TNF-α agents in UC patients. Several studies showed that p-ANCA can predict early clinical response to anti-TNF-α agents in UC patients [14–19]. A meta-analysis demonstrated that p-ANCA-negative patients

had an almost two-fold higher response rate to anti-TNF-α agents than those positive for p-ANCA. The positive predictive value of p-ANCA for PNR was 41.1% when p-ANCA was positive, and the positive predictive value of p-ANCA for primary response was 74.0% when p-ANCA was negative [15]. However, p-ANCA is measured using IIF, sometimes making judgments about positivity and

negativity difficult. Therefore, judgment often differs depending on measurement facilities. In contrast, PR3-ANCA has an advantage over p-ANCA regarding measurement methods. PR3-ANCA is measured using ELISA and CLEIA, which are more sensitive and quantitative than IIF, used to measure p-ANCA [10, 12, 13]. In the present study, we showed the positive predictive value of PR3-ANCA for PNR was 78.6%, while the negative predictive value was 83.3%. The predictive capacity of PR3-ANCA appears sufficient for clinical use. Overall, in clinical practice, PR3-ANCA should be a more useful predictor of PNR to anti-TNF- α in UC patients than p-ANCA.

In the present study, univariate analysis revealed that lower Hb levels and smoking cessation were associated with PNR. A multicenter retrospective study showed that low Hb levels correlated with PNR to anti-TNF- α agents in UC patients [23]. Several studies reported that smoking habit is associated with PNR [24]. Furthermore, it was reported that nonsmoking increases the rates of c-ANCA positivity in patients with vasculitis [25]. Given these observations, low Hb levels and smoking cessation may have confounded with PR3-ANCA in this study. However, multivariate analysis demonstrated PR3-ANCA as a predictor of PNR with high odds ratio, suggesting PR3-ANCA is an independent predictor of PNR.

There are reports of effectiveness for anti-TNF- α agents in other ANCA-positive diseases. In AAV, anti-TNF- α agents, in addition to standard care, did not affect induction rate, adverse events, activity score, relapse rate, and biomarker levels [26]. In this previous report, anti-TNF- α agents had no effect on AAV. In ANCA-positive patients, the mechanism of nonresponse to anti-TNF- α agents is unknown.

This study had several limitations. First, only 14 patients were PR3-ANCA positive, and this small sample size may have been insufficient for multivariate analysis. Second, because of the retrospective nature of this study, we could not exclude the effects of other possible confounding factors on PNR to anti-TNF- α agents. Third, this was a single-center study and the external validity of our findings is unknown. Fourth, the timing of PR3-ANCA measurement varied among subjects. Finally, our study population consisted of patients in whom PR3-ANCA was measured primarily for differential diagnosis of UC. In total, 28% of patients were PR3-ANCA positive, which was consistent with previously reported positivity rates in UC patients [27]. While this observation suggests our study population was representative of the general UC population, it is unclear whether our findings can be applied to this population. To overcome these limitations, our findings must be

validated in prospective large multicenter studies. Despite these limitations, this is the first study to demonstrate that PR3-ANCA can serve as a predictive factor for PNR to anti-TNF- α agents in UC patients.

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Statement of Ethics

We conducted this study in compliance with the latest version of the Declaration of Helsinki. The study was approved by the institutional ethics committee (the ethics committee of Ofuna Chuo Hospital, No. 2018-011). Patient consent was waived because of the retrospective and observational nature of the study.

Conflict of Interest Statement

A.Y. received personal fees from Mitsubishi Tanabe Pharma, Janssen Pharmaceutical K.K., and AbbVie Inc. K.M. received personal fees from Mitsubishi Tanabe Pharma, Janssen Pharmaceutical K.K., AbbVie Inc., EA Pharma Co., Ltd., Pfizer Inc., Mochida Pharmaceutical Co., Ltd., Alfresa Pharma Co., and Thermo Fisher Scientific K.K.; and research grants from Mitsubishi Tanabe Pharma, Janssen Pharmaceutical K.K., AbbVie Inc., EA Pharma Co., Ltd., Mochida Pharmaceutical Co., Ltd., and Nippon Kayaku Co., Ltd. F.U. received personal fees from Mitsubishi Tanabe Pharma, Janssen Pharmaceutical K.K., AbbVie Inc., and EA Pharma Co., Ltd. Y.E. received personal fees from Mitsubishi Tanabe Pharma, Janssen Pharmaceutical K.K., AbbVie Inc., and EA Pharma Co., Ltd. T.H. received personal fees from Aspen Japan K.K., JIMRO, Mitsubishi Tanabe Pharma, Janssen Pharmaceutical K.K., and Takeda Pharma Co., Ltd.; and research grants from Zeria Pharmaceutical Co., Ltd. T.M. has no conflicts of interest to declare. However, none of the above is relevant to this article.

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Author Contributions

A. Yoshida, K. Matsuoka, and F. Ueno designed the study. Data were collected by A. Yoshida, T. Morizane, and Y. Endo. T. Morizane analyzed the data. A. Yoshida and K. Matsuoka drafted the manuscript and interpreted the data. T. Hibi and K. Matsuoka made critical revisions to the manuscript. All authors reviewed and approved the final version of the manuscript.

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