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Factors associated with changes in tacrolimus blood concentration after food initiation in patients with ulcerative colitis

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The therapeutic effect of tacrolimus against ulcerative colitis (UC) is correlated with its trough blood concentration. Conventionally, oral tacrolimus for the treatment of UC is initiated under fasting conditions; once the symptoms improve, food intake is resumed. Tacrolimus blood concentration decreases with food intake compared with that under fasting conditions. The aim of this study was to explore the characteristics of patients with UC whose tacrolimus blood concentrations tended to decrease after food initiation. Medical data of 13 patients with UC and treated with tacrolimus were retrospectively obtained. The participant characteristics associated with the changes in tacrolimus blood concentrations after food initiation were analyzed using regression analysis based on the rate of decrease in the concentration/dose (C/D) ratio after food initiation. Single regression analysis showed that the number of days required from tacrolimus initiation to food resumption (P = 0.0071) and individual differences in the increase in tacrolimus blood concentration after administration (P = 0.0247) were significantly associated with the rate of decrease in the C/D ratio after food initiation. Furthermore, multiple regression analysis showed a significant effect of the number of days to food resumption (P = 0.0004) and individual differences in the increase in tacrolimus blood concentration after administration (P = 0.0012). The results suggest that the degree of change in blood tacrolimus concentration after food initiation may be related to the severity of the symptoms and pathology of UC. Early identification of participant characteristics may help control tacrolimus blood concentration fluctuations after food initiation.

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by hematochezia, diarrhea, tenesmus, and constitutional symptoms such as weight loss and fever during disease flare (Dulai and Jairath 2018). The severity of the disease varies widely, with 20–30% of patients with UC requiring hospitalization at some point during the course of the disease because of severe acute flares (Dulai and Jairath 2018). Most patients with UC can be successfully managed with corticosteroids or 5-aminosalicylic acid alone. However, calcineurin inhibitors, such as tacrolimus, and tumor necrosis factor-alpha inhibitors, such as infliximab, can be used as secondary therapies to avoid immediate surgical treatment in case of corticosteroid resistance. Tacrolimus is widely recognized as an anti-rejection agent because of its immunosuppressive characteristics; it binds to the immunophilin FK-binding protein (FKBP) and thus to calcineurin, and inhibits its activity (Plosker and Foster 2000; Scalea et al. 2016; Thomson, Bonham, and Zeevi 1995). Studies have demonstrated its efficacy in corticosteroid-refractory UC (Ogata et al. 2012).

The therapeutic effect of tacrolimus against UC correlates with its trough blood concentration (Ogata et al. 2006, 2012). However, tacrolimus has a narrow therapeutic range; moreover, tacrolimus shows inter-individual pharmacokinetic variability (Kuypers 2020). Several factors affect trough blood concentration of tacrolimus. First, fasting can affect the pharmacokinetics of tacrolimus. Its C_{max} is approximately four times higher under fasting conditions than under feeding conditions (Lainesse et al. 2008). Second, genetic background may influence the pharmacokinetics of tacrolimus (Hirai et al. 2014; Yoshikawa et al. 2021). Tacrolimus is metabolized primarily by cytochrome P450 (CYP) 3A4 and 3A5 enzymes and is a substrate for P-glycoprotein, a drug efflux pump encoded by *ABCB1*. Third, red blood cell concentration or hematocrit can affect the trough blood concentration of tacrolimus. As tacrolimus is primarily distributed in red blood cells, anemia and blood transfusion can cause fluctuations in tacrolimus blood concentrations (Yoshikawa et al. 2020; Yoshikawa et al. 2020). Among these factors, fasting has a unique effect on UC treatment. Generally, tacrolimus treatment is initiated via oral administration under fasting conditions for UC treatment; once the condition improves, food intake is resumed. It has been reported and often experienced in real-world clinical practice that tacrolimus blood concentration decreases with food intake compared with that under fasting conditions (Bekersky et al. 2001; Gustavsen et al. 2020; Tagui et al. 2016). However, in some cases, the tacrolimus blood concentration does not decrease even after food resumption. Deviation of tacrolimus blood concentration from the target range owing to pharmacokinetic changes is detrimental to patients; therefore, changes in tacrolimus blood concentrations following food initiation must be monitored appropriately. Therefore, in this study, we analyzed and explored the characteristics of patients with UC whose tacrolimus blood concentrations tended to decrease after food initiation based on historical information to control tacrolimus blood concentration fluctuations associated with food initiation.

2. Investigations and results

2.1. Participant characteristics

During the study period, tacrolimus was used to treat UC in 20 patients, 7 of whom met the exclusion criteria; therefore, 13 patients were finally included in the analysis. Participant characteristics at tacrolimus initiation and during tacrolimus treatment are presented in Tables 1 and 2, respectively.

Table 1: Participants' characteristics at treatment initiation

Characteristic	Data
Sex (male/female)	9/4
Age (years)	40 (21–63)
Height (cm)	167.5 (148.4–180.3)
Body weight (kg)	59.9 (29.2–85.2)
Body mass index	22.5 (13.3–28.3)
Serum AST (U/L)	14 (6–31)
Serum ALT (U/L)	13 (5–101)
Serum γ-GTP (U/L)	20 (11–121)
Serum total bilirubin (mg/dL)	0.5 (0.2–1.3)
Serum albumin (g/dL)	3.44 (2.03–4.08)
Serum K (mmol/L)	3.8 (3.3–4.6)
Serum Na (mmol/L)	137 (133–142)
Serum glucose (mg/dL)	104 (75–202)
Serum creatinine (mg/dL)	0.72 (0.51–1.52)
eGFR (mL/min/1.73 m^2)	92.04 (39.05–134.11)
Red blood cell (×10^6/μL)	4.40 (2.59–5.67)
Hemoglobin (g/dL)	12.9 (8.2–16.3)
Defecation frequency (count) [a)]	5 (3–15)
Bloody stool frequency (count) [a)]	5 (0–15)
Dietary intake (%) [a)]	0.0

Median (minimum-maximum)
[a)] At tacrolimus initiation
AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: gamma-glutamyl transpeptidase, eGFR: estimated glomerular filtration rate

Table 2: Participants' characteristics during the treatment

Characteristic	Data
C/D ratio ([ng/mL]/[mg/kg]) [a)]	137.8 (56.6–505.4)
First TDM (day)	3 (2–5)
First Tac concentration (ng/mL)	6.6 (1.2–20.2)
Days to food resumption (day)	15 (5–21)
Receipt of lansoprazole (%)	23.1
Receipt of other PPI (%)	23.1
Receipt of amlodipine (%)	7.7
Receipt of other CCB (%)	0.0
Receipt of azole antifungal agent (%)	0.0
Receipt of metabolic enzyme inducers (%)	0.0

Median (minimum-maximum)
[a)] Immediately before food initiation.
C/D: concentration/dose, Tac: tacrolimus, TDM: therapeutic drug monitoring, PPI: proton pump inhibitor, CCB: calcium channel blocker

2.2. Major factors associated with changes in tacrolimus blood concentrations

Patient characteristics at tacrolimus initiation and during tacrolimus treatment, which may be associated with the changes in tacrolimus blood concentration following food initiation, were analyzed using regression analysis based on the rate of decrease in the C/D ratio after food initiation (Table 3).

First, single regression analysis showed that the number of days required from tacrolimus initiation to food resumption ($P = 0.0071$) and α value ($P = 0.0247$), an index of individual differences in the increase in tacrolimus blood concentration after administration, were significantly associated with the rate of decrease in C/D ratio after food initiation. Furthermore, multiple regression analysis showed a significant influence of the days to food resumption ($P = 0.0004$) and α value ($P = 0.0012$).

The relationship between the number of days required from tacrolimus initiation to food resumption and the rate of decrease in the C/D ratio after food initiation showed that the longer the duration

Table 3: Regression analysis for the association of patient characteristics with the changes in tacrolimus blood concentration after food initiation

Factor	Single regression			Multiple regression		
	Estimate	95% CI	P	Estimate	95% CI	P
Age (years)	-0.008	-0.021 to 0.005	0.2207	-	-	-
Sex (male/female)	0.126	-0.300 to 0.552	0.5287	-	-	-
Body weight (kg)	-0.001	-0.016 to 0.013	0.8321	-	-	-
Body mass index	0.001	-0.054 to 0.056	0.9622	-	-	-
Serum AST (U/L)	0.002	-0.029 to 0.032	0.9125	-	-	-
Serum ALT (U/L)	-0.001	-0.009 to 0.007	0.8555	-	-	-
Serum γ-GTP (U/L)	-0.001	-0.008 to 0.006	0.7017	-	-	-
Serum total bilirubin (mg/dL)	0.176	-0.409 to 0.760	0.5218	-	-	-
Serum K (mmol/L)	-0.145	-0.717 to 0.427	0.5886	-	-	-
Serum Na (mmol/L)	0.027	-0.049 to 0.103	0.4526	-	-	-
Serum albumin (g/dL)	-0.004	-0.370 to 0.363	0.9833	-	-	-
Days to food resumption (day)	-0.045	-0.074 to -0.015	0.0071	-0.043	-0.061 to -0.024	0.0004
Red blood cell (×10^6/μL)	-0.093	-0.334 to 0.148	0.4138	-	-	-
α	-0.448	-0.828 to -0.068	0.0247	-0.422	-0.631 to -0.212	0.0012
C/D ratio before food initiation ([ng/mL]/[mg/kg])	-0.001	-0.002 to 0.001	0.2172	-	-	-
Defecation frequency (count)	-0.011	-0.057 to 0.035	0.6095	-	-	-

CI: confidence interval, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: gamma-glutamyl transpeptidase, eGFR: estimated glomerular filtration rate, C/D: concentration/dose

None of the patients had severe hepatic impairment at tacrolimus initiation. Although the symptoms of UC varied among the patients, tacrolimus was initiated under fasting conditions in all patients. The time required for patients to resume food intake was five days in early cases and 21 days in late cases after tacrolimus initiation.

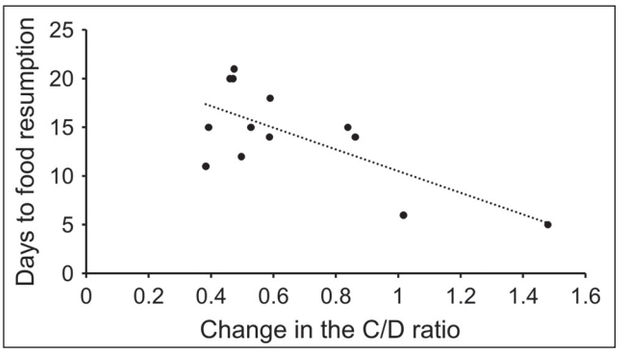

Fig. 1: Scatterplot of the relationship between the number of days required from tacrolimus initiation to food resumption and the change in the C/D ratio after food initiation. Dotted lines are regression lines; C/D: concentration/dose.

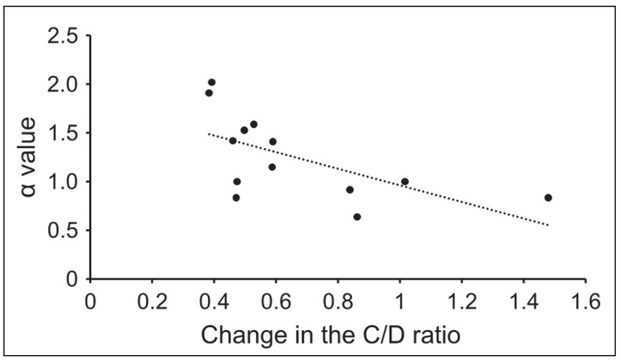

Fig. 2: Scatterplot of the relationship between α value and the change in the C/D ratio after food initiation. Dotted lines are regression lines; α = [Maximum C/D ratio] / ([C/D ratio on day X of treatment] × (6/X)), X = 3–5; C/D: concentration/dose

Table 4: Cutoff values for the number of days to food resumption, leading to a specific reduction in the C/D ratio of tacrolimus

	20% reduction	30% reduction	40% reduction	50% reduction
Specificity	0.50	0.50	0.50	1.00
Sensitivity	1.00	1.00	1.00	0.50
Cutoff value	11	11	11	20
AUC (95% CI)	0.819 (0.562–1.000)	0.819 (0.562–1.000)	0.819 (0.562–1.000)	0.714 (0.396–1.000)

C/D: concentration/dose, AUC: area under the curve, CI: confidence interval

Table 5: Cutoff values for α leading to a specific reduction in the C/D ratio of tacrolimus

	20% reduction	30% reduction	40% reduction	50% reduction
Specificity	1.00	1.00	1.00	0.86
Sensitivity	0.78	0.78	0.78	0.67
Cutoff value	1.15	1.15	1.15	1.42
AUC (95% CI)	0.917 (0.764–1.000)	0.917 (0.764–1.000)	0.917 (0.764–1.000)	0.738 (0.439–1.000)

C/D: concentration/dose, AUC: area under the curve, CI: confidence interval

of food resumption, the greater the rate of decrease in the C/D ratio after food initiation (Fig. 1). In addition, receiver operating characteristic (ROC) analysis indicated that the condition for the C/D ratio to decrease beyond a certain level was 11 days or longer duration to food resumption (Table 4).

The relationship between α value and the rate of decrease in the C/D ratio after food initiation showed that the higher the α value, the greater the rate of decrease in the C/D ratio after food initiation (Fig. 2). In addition, the ROC analysis indicated that at an α value of 1.15 or higher, the C/D ratio decreased beyond a certain level (Table 5).

3. Discussion

With early identification of UC cases in which tacrolimus blood concentrations decline after food initiation, it will be possible to determine whether tacrolimus dosage should be adjusted at food initiation. In this study, patients with UC whose tacrolimus blood concentrations tended to decrease after food initiation were characterized by "a longer time required for blood concentrations to stabilize after tacrolimus initiation" and "a higher number of days required from tacrolimus initiation to food resumption." However, as this was a single-center study, the hospital's treatment policy might have affected the course of UC treatment. In addition, the available data of all participants were limited owing to the retrospective nature of the study, and patients with missing information were excluded; therefore, the number of participants included was small. Notably, tacrolimus blood concentrations were measured only a few times per week and not daily.

In this study, the longer the duration between tacrolimus initiation and food resumption, the greater the rate of decrease in the C/D ratio after food initiation. The longer time to food resumption might explain the greater intractability of UC symptoms, although individual differences in tacrolimus responsiveness should be considered. Severe UC is a potentially life-threatening disease, and all patients with >6–10 bloody stool events per day along with fever, dehydration, tachycardia, malaise, and/or elevated C-reactive protein are eligible for inpatient treatment (Van Assche et al. 2008). Dehydration is closely related to the effect of food on drug absorption in the gastrointestinal tract. In general, the presence of food in the gastrointestinal tract leads to a decrease in water and fluid volumes, leading to a decrease in drug disintegration and dissolution (Schiller et al. 2005). In addition, the presence of food in the gastrointestinal tract leads to a reduction in the excretion rate of gastric contents and a decrease in drug absorption (Hénin et al. 2016). As tacrolimus is highly liposoluble, it easily passes through the gastrointestinal mucosa. However, the dispersion and solubility of the drug in the gastrointestinal tract deteriorate with reduced water content, leading to decreased absorption of tacrolimus. Therefore, it is assumed that patients who are dehydrated and with decreased fluid volume due to long-term UC symptoms are more likely to experience decreased absorption of oral tacrolimus after food intake. In Japan, trough blood concentrations should be maintained at a high level (10–15 ng/mL) for two weeks after tacrolimus initiation and at the maintenance level (5–10 ng/mL) after two weeks (Kawakami et al. 2015; Ogata et al. 2006). In the present study, the ROC analysis revealed that patients showing early remission two weeks after tacrolimus initiation, that is, patients who were in the high blood concentration phase and had resumed food intake, will not present a decrease in the C/D ratio after food initiation.

In this study, a higher α value (an index of increase in blood concentration) after tacrolimus initiation indicated a greater decrease in the

C/D ratio after food initiation. Alpha (α) is the original index used for evaluating blood concentration changes in this study, and a higher α value indicates a higher C/D ratio and suggests that a longer time is needed for the stabilization of blood concentration. In other words, patients with a high α value have a low ability to eliminate (metabolize) drugs. Hepatic CYP expression decreases at the onset of UC (Kusunoki et al. 2014). In addition, the suppression of CYP mRNA in the liver correlates with cytokine levels (Kusunoki et al. 2015). Thus, patients with low hepatic CYP expression and less ability to metabolize drugs may experience more severe UC. Dehydration has been presumed to occur in these severe cases of UC, resulting in decreased absorption of tacrolimus after food intake, as described above. An α value greater than 1 indicates that the tacrolimus blood concentrations increased after the first six days of treatment. Here, the ROC analysis indicated that the C/D ratio decreased by more than 20% after food initiation at an α value of more than 1.15. In addition, the C/D ratio decreased by more than 50% at an α value of 1.42 or higher, indicating an additional 1.4-fold increase in tacrolimus blood concentration after the first six days of treatment. Our previous study demonstrated that patients with low tacrolimus metabolic ability take a longer time to attain a steady state and have a 2-fold higher C/D ratio than patients with high tacrolimus metabolic ability (Yoshikawa et al. 2021). To the best of our knowledge, this is the first study to predict the changes in drug blood concentrations after food resumption based on the index of increase in drug blood concentration.

The study findings suggest that the degree of change in tacrolimus blood concentration after food initiation may be related to the severity of UC symptoms and pathology. Early prediction of cases in which the tacrolimus blood concentration decreases after food initiation based on these characteristics will allow to control the changes in blood concentration associated with food initiation by adjusting tacrolimus dosage at the time of food initiation.

4. Experimental

4.1. Study design and setting

We conducted a single-center, observational, cross-sectional study to determine factors associated with the changes in tacrolimus blood concentration after food initiation in patients with UC. This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Review Committee of the Faculty of Medicine at the University of Miyazaki, Japan (O-1117).

4.2. Selection of participants

This study included patients with UC receiving tacrolimus at the University of Miyazaki Hospital between April 2018 and March 2021. The selection criteria were 1) age ≥ 20 years, 2) tacrolimus blood concentration monitoring, and 3) continuation of tacrolimus until food resumption. Patients who were consuming food at the time of tacrolimus initiation were excluded from this study.

4.3. Variables and data sources

Patient information (age, sex, height, body weight, clinical laboratory data, dietary intake, defecation, tacrolimus blood concentration monitoring, and medication use) was collected from electronic medical records. UC status was assessed based on the frequency of defecation and bloody stools. Whole blood tacrolimus concentrations were measured using the ARCHITECT i1000SR system (Abbott, Tokyo, Japan). Tacrolimus blood concentration (ng/mL) was divided by the dose per body weight (mg/kg) to calculate the C/D ratio. The change in the C/D ratio of tacrolimus owing to food initiation was calculated as the ratio of the lowest C/D ratio after food initiation to that immediately before food initiation. In this study, the α value was established to indicate the increase in tacrolimus blood concentration after tacrolimus initiation. The C/D ratio stabilized to a steady state in approximately half of the participants on day 6 of tacrolimus administration, whereas it increased after day six in the remaining half of the participants. Therefore, the α value was calculated using the following formula to identify patients whose C/D ratio increased on or after day six of tacrolimus administration and to indicate the rate of increase in the C/D ratio on day 6 of tacrolimus administration.

$$\alpha = [\text{Maximum C/D ratio}] / ([\text{C/D ratio on day X of treatment}] \times (6/X))$$

X = 3–5.

Thus, the magnitude of α indicates the duration required to reach a steady state of tacrolimus blood concentration.

4.4. Statistical methods

Representative values for continuous variables of the participants' characteristics are presented as median and range. The participants' characteristics associated with changes in tacrolimus blood concentrations after food initiation were analyzed using a single regression analysis based on the rate of decrease in the C/D ratio after food initiation. Factors considered significant by the single regression analysis were analyzed for their respective effects using a multiple regression analysis. For each of these factors, cutoff values were determined using ROC analysis for each level of decrease in tacrolimus blood concentration after food initiation.

R version 4.1.2 (R. Available online: https://www.r-project.org/) was used for statistical analysis. $P < 0.05$ indicated statistical significance.

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Competing interests: The authors declare no conflict of interest.

Ethical approval: This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Review Committee of the Faculty of Medicine at the University of Miyazaki, Japan (O-1117).

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