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Risk Factors for Nephrotoxicity due to Tacrolimus Therapy for Ulcerative Colitis

Satoshi Nakata Kazuki Kakimoto Keijiro Numa Naohiko Kinoshita Yuka Kawasaki Yoshihiro Tatsumi Hideki Tawa Ryoji Koshiba Yuki Hirata Kazuhiro Ota Naokuni Sakiyama Yuichi Kojima Hiroki Nishikawa Takuya Inoue Toshihisa Takeuchi Shinya Fukunishi Takako Miyazaki Shiro Nakamura Kazuhide Higuchi

2nd Department of Internal Medicine, Osaka Medical and Pharmaceutical University, Takatsuki, Japan

Keywords
Tacrolimus · Ulcerative colitis · Nephrotoxicity · Renal impairment · Risk factor

Abstract
Background and Aims: The calcineurin inhibitor tacrolimus is reportedly effective for moderate/severe ulcerative colitis (UC); however, it is also reportedly associated with nephrotoxicity. We investigated the risk factors for tacrolimus-induced nephrotoxicity and whether renal impairment adversely affected the outcomes of tacrolimus treatment in patients with UC. ***Methods:*** We conducted a retrospective study of 93 patients with UC who were administered tacrolimus leading to high trough levels (10–15 ng/mL) for 2 weeks and low trough levels (5–10 ng/mL) for 3 months. ***Results:*** Acute kidney injury (AKI) occurred in 44 patients (47.3%) during tacrolimus treatment. Of these patients, 34 (36.6%) developed AKI during the high trough phase and 17 (18.3%) developed AKI when the trough value exceeded the original target value of 15 ng/mL. Multivariate logistic regression analysis revealed that the male sex was significantly associated with AKI (p = 0.002, AOR = 4.38, 95% CI [1.69–11.3]). Clinical remission rate after 4, 8, 12, and 24 weeks of tacrolimus treatment in patients with AKI was lower than that in patients without AKI. Six patients (6.5%) had chronic kidney disease (CKD) after tacrolimus treatment completion, and all patients with CKD developed AKI during treatment. The median duration of treatment with no improvement in AKI was significantly longer in patients with CKD than in those without CKD (p = 0.016). ***Conclusion:*** We revealed the risk factors for tacrolimus-induced nephrotoxicity. Renal impairment occurrence adversely affected the tacrolimus treatment outcome; therefore, it is important to carefully administer tacrolimus to prevent renal impairment.
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Introduction

Ulcerative colitis (UC) is an idiopathic inflammatory bowel disease characterized by a chronic relapsing/intermittent clinical course. Corticosteroids are prescribed for UC that does not improve the following administration of 5-aminosalicylate. Furthermore, tacrolimus (TAC) is a treatment option for refractory UC that is steroid-resistant or dependent [1, 2]. Calcineurin inhibitors, such as TAC and cyclosporine A, block T-lymphocyte proliferation through the downregulation of interleukin-2 [3–5]. Ogata et al. [6] reported that TAC had a high remission-

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Correspondence to:
Kazuki Kakimoto, kazuki.kakimoto@ompu.ac.jp

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inducing effect in a randomized, placebo-controlled, double-blind trial for refractory UC. TAC is often administered to hospitalized patients, especially those with severe UC, due to the drug's superior performance in severe UC [7–9]. However, nephrotoxicity is known to be a critical side effect of TAC [10–12]. There are two types of TAC-related renal toxicities: acute nephropathy and chronic nephropathy [13, 14]. The acute type is dose-dependent and reversible; it is caused by renal vasoconstriction (due to released vasoactive substances), which may eventually lead to acute kidney injury (AKI). Chronic nephrotoxicity is associated with the development of structural damage, including arteriolopathy and tubulointerstitial fibrosis, which may lead to chronic kidney disease (CKD). Most TAC-induced renal impairment in UC results in AKI, and renal impairment improves with TAC dose reduction or discontinuation [15, 16]. However, if TAC is tapered or discontinued, the outcome of TAC therapy may be adversely affected because the target trough value cannot be maintained. Therefore, TAC-induced nephrotoxicity is an important clinical issue; however, no studies have examined the risk factors involved in the development of renal impairment.

In this study, we investigated the risk factors involved in the development of TAC-induced AKI and CKD in patients with UC. In addition, we examined whether renal impairment adversely affected the outcomes of TAC treatment.

Patients and Methods

Patients

Between January 2011 and May 2019, 93 patients with moderate/severe UC who were administered TAC therapy at Osaka Medical and Pharmaceutical University Hospital were consecutively enrolled in this retrospective, single-center study. This study was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University.

In all cases, the diagnosis was established according to standardized criteria using prior clinical assessments, radiology, endoscopy, and histology. All patients were administered oral TAC for remission induction at an initial oral dose of 0.1 mg/kg per day: twice daily. TAC whole blood trough concentration was measured once every 2–3 days after starting on the initial dose. The dosage was adapted to achieve a high trough level of 10–15 ng/mL. The high trough dose administration continued for 2 weeks, followed by a low trough dose administration of 5–10 ng/mL for 3 months. Three months after TAC administration, the dose was gradually reduced and then discontinued. In patients who could not taper or discontinue TAC due to worsening UC, the treatment was continued. Disease activity was evaluated using the Lichtiger index [17, 18]. Clinical remission was defined as a score of ≤3. Severe disease activity was defined as score of ≥12, and moderate disease activity was defined as score from 8 to 11.

Table 1. Baseline demographics and clinical characteristics

Patients, *n*	93
Male/female, *n*	56/37
Age, median (IQR), years	45 (25–60)
Duration of disease, median (IQR), months	36 (7–113)
UC location; left side/extensive, *n*	12/81
Concomitant medication	
Aminosalicylates, *n* (%)	84 (90.3)
Azathioprine, *n* (%)	20 (21.5)
Corticosteroids, *n* (%)	53 (57.0)
Previous medications before TAC, *n* (%)	13 (14.0)
TNF antagonist; IFX, ADA, GLM	9 (9.7), 3 (3.2), 1 (1.1)
Past history of treatment failure with biologics, *n* (%)	
TNF antagonist; IFX, ADA	1 (1.1), 1 (1.1)
Lichtiger index, median (IQR)	12 (11–14)
Disease severity, *n* (%): moderate, severe	33 (35.5), 60 (64.5)
Mayo subscore for endoscopy, median (IQR)	3 (2.3–3)
Fasting during the high trough phase, *n* (%)	85 (91.4)
WBC, median (IQR), /μL	7,850 (6,220–13,800)
Hb, median (IQR), g/dL	12.0 (10.6–13.8)
Albumin, median (IQR), g/dL	3.1 (2.6–3.8)
CRP, median (IQR), mg/L	2.0 (0.4–6.5)
Creatinine, median (IQR), mg/dL	0.7 (0.6–0.8)
Creatinine clearance, median (IQR), mL/min	103.9 (90.3–118.1)

UC, ulcerative colitis; IFX, infliximab; ADA, adalimumab; GLM, golimumab; WBC, white blood cell; CRP, C-reactive protein; IQR, interquartile range.

Definitions of Renal Impairment and Assessment

AKI was defined as an increased serum creatinine level ≥1.5 times the level prior to TAC administration (or an increase in serum creatinine levels by ≥0.3 mg/dL), based on the Kidney Disease Improving Global Outcomes (KDIGO) criteria [19]. Based on AKI onset, those who developed AKI during the high trough dose administration period were defined as the "high trough group," and those who developed AKI during the low trough dose administration period after the high trough period were defined as the "low trough group."

CKD was defined by the Kidney Disease Outcomes Quality Initiative clinical practice guidelines for chronic kidney disease as one or both of the following persisting for at least 3 months after the completion of TAC treatment [20]: (1) findings suggestive of renal impairment (abnormal urine analysis, abnormal imaging, abnormal blood, pathological findings, etc.), (2) glomerular filtration rate (GFR) <60 mL/min/1.73 m^2. We investigated the risk factors involved in the development of TAC-induced AKI and CKD in patients with UC. Moreover, we investigated whether nephrotoxicity adversely affected the outcome of TAC treatment.

Statistical Analysis

Quantitative data were summarized using median and interquartile range (IQR), and categorical variables were described using frequency and percentage. We used the Fisher exact test for categorical variables and the Mann-Whitney U test for continuous variables in terms of a comparison of demographic variables between the AKI and non-AKI groups. We also used the Wilcoxon signed-rank test and Kruskal-Wallis test to compare differences in

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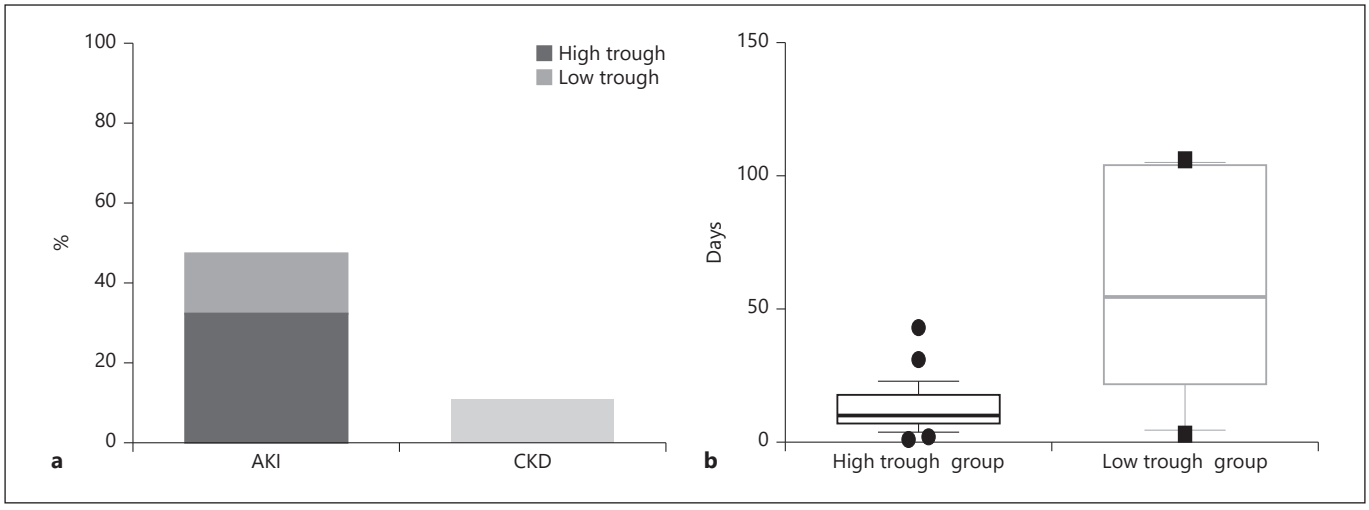

Fig. 1. a Incidence of AKI and CKD. **b** The median duration of TAC treatment in the high trough group and low trough group. AKI, acute kidney injury; CKD, chronic kidney disease.

the duration of TAC treatment. Predictive factors for the development of AKI were examined by multiple logistic regression. In multivariate analysis, variables with a p value <0.05 in the prior univariate analyses were proposed for entry into the model. In addition, age was included as a confounding factor because renal functional reserve decreases with age [21]. Odds ratios with 95% confidence interval (CI) were calculated for selected variables. Statistical significance was set at $p < 0.05$ (two-sided test). All statistical analyses were performed using JMP®, Version 15.2.1, SAS Institute Inc., Cary, NC, 1989–2021, USA.

Results

Patient Characteristics

Between January 2011 and May 2019, 93 patients with moderate/severe UC were administered oral TAC for remission induction. The baseline demographics and clinical characteristics of the patients are presented in Table 1. The median age was 45 years, and 60.2% of the patients were male. The median (IQR) duration of UC was 36 months (7–113 months). In total, 87.1% of patients with UC had extensive disease. Fifty-three patients (57.0%) were on corticosteroids at the start of TAC treatment, and 20 (21.5%) were taking azathioprine as concomitant medication. Thirteen patients (14.0%) had been treated with anti-TNF-α agents (infliximab [IFX]: $n = 9$ [9.7%]; adalimumab [ADA]: $n = 3$ [3.2%]; golimumab: $n = 1$ [1.1%]) and switched to TAC. The median IQR of C-reactive protein (CRP) and Lichtiger's CAI was 2.0 (0.4–6.5) and 12 [11–14], respectively. Sixty patients (64.5%) had severe disease activity at the initiation of TAC treatment. The median IQR for creatinine and creatinine clearance was 0.7 mg/dL (0.6–0.8 mg/dL) and 103.9 mL/min (90.3–118.1 mL/min), respectively.

TAC-Induced AKI

The median TAC treatment duration was 160 days [117–241 days]. AKI occurred in 44 patients (47.3%) during the treatment period (Fig. 1a). Eight of them (18.2%) had creatinine levels below the upper limit of normal (1.07 mg/dL). In total, 34 (36.6%) developed AKI during the high trough phase, and median TAC treatment duration prior to onset of AKI was 10 days (7–17.3 days) (Fig. 1b). Ten patients (10.8%) developed AKI in the low trough phase, and the median TAC treatment duration was 54.5 days (26–97.8 days). Median trough levels at the onset of AKI were 16 ng/mL (13.7–18.1 ng/mL) in the high trough group and 8.1 ng/mL (7.2–9.3 ng/mL) in the low trough group (Fig. 2a). In the high trough group, 17 patients (38.6%) developed AKI when the trough value exceeded the original target value of 15 ng/mL (Fig. 2b). Adverse events other than renal impairment included tremor (14.0%, $n = 13$), nausea (6.5%, $n = 6$), headache (5.4%, $n = 5$), epigastralgia (2.2%, $n = 2$), and sepsis (1.1%, $n = 1$).

The Risk Factors for AKI

To investigate the risk factors associated with the development of AKI, we compared the baseline demographics and clinical characteristics between the AKI and non-AKI groups (Table 2). A comparison of total TAC doses in the AKI and non-AKI groups for the first and

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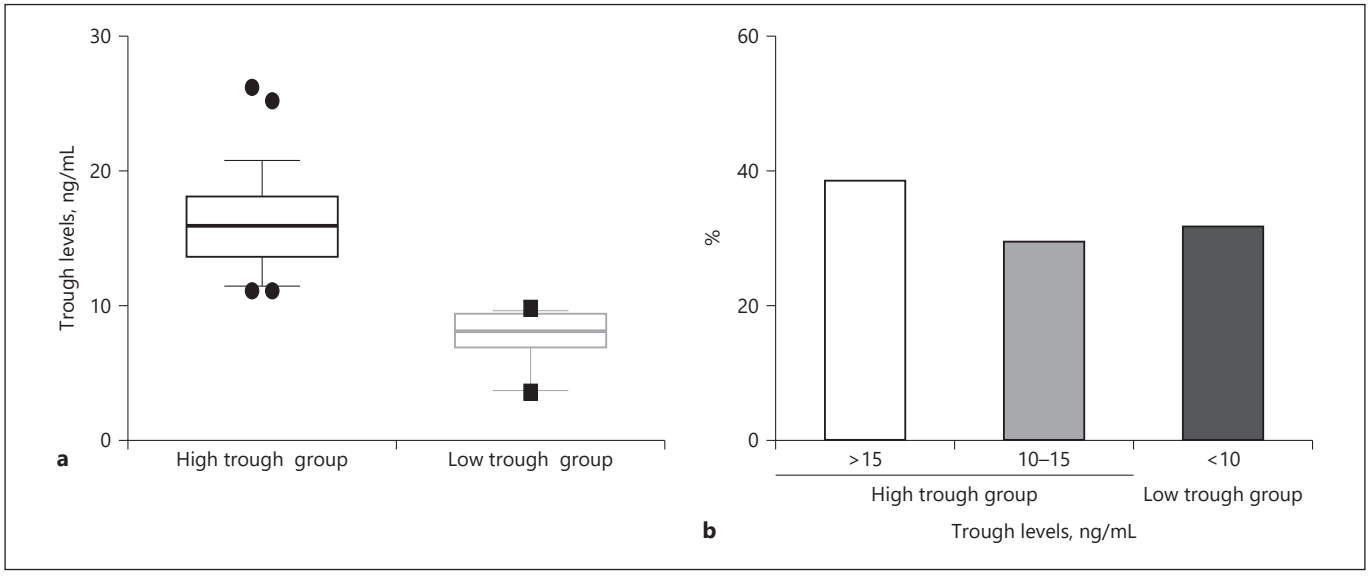

Fig. 2. a Median trough levels at onset of AKI in the high and low trough group. **b** Proportion of patients with UC who developed AKI divided by trough value. AKI, acute kidney injury; UC, ulcerative colitis.

second weeks after TAC initiation showed no significant difference (1W: AKI+: 46 [38–53.3], AKI−: 46 [36–57]; p = 0.80, 2W: AKI+: 80 [63.8–112], AKI−: 95.5 [67.8–127.3]; p = 0.14). Conversely, the median CRP prior to TAC treatment was significantly higher in the AKI group than in the non-AKI group (2.8 mg/L [0.7–10.6 mg/L] vs. 0.8 mg/L [0.3–4.3 mg/L]; p = 0.018). Also, significantly more male patients developed AKI (male/female: AKI+ 33/11 vs. AKI− 23/26; p = 0.006). When we examined whether heavier weight and higher total TAC doses in males than in females were the cause of more cases of AKI in males, we found no significant difference in total TAC doses between males and females in the first and second weeks after TAC initiation (1W: males: 46 [38.8–54.5], females: 48 [35–57]; p = 0.98, 2W: males: 84 [67–116], females: 84 [62.5–119.5]; p = 0.71).

In most cases, 85 (91.4%), TAC treatment was initiated under fasting conditions, and fasting continued during the high trough phase. When we examined whether fasting affected the occurrence of renal impairment, there was no significant difference in the number of patients who fasted in the AKI group compared with the non-AKI group (AKI+: 42 [95.5], AKI−: 43 [87.8]; p = 0.186). Furthermore, there was no significant difference in the number of days to reach the therapeutic goal of high trough TAC levels (10–15 ng/mL) between the AKI and non-AKI groups (3 days [2–4.25 days] vs. 4 days [3–5 days]; p = 0.577). Multivariate logistic regression analysis of male sex, CRP levels, and age showed that only male sex was significantly associated with AKI (p = 0.002, AOR = 4.38, 95% CI [1.69–11.3]) (Table 3).

AKI and the Clinical Outcome of UC

We next examined whether the occurrence of TAC-induced renal impairment would affect the clinical outcome of UC. Following TAC treatment, the clinical remission rates after 4, 8, 12, and 24 weeks of TAC treatment were 62.3%, 65.6%, 67.7%, and 62.4%, respectively. The clinical remission rate with TAC treatment in patients with AKI was significantly lower than that in patients without AKI at all time points (Week 4: 50% [22/44] vs. 73.5% [36/49]; p = 0.02, Week 8: 52.3% [23/44] vs. 77.6% [38/49]; p = 0.01, Week 12: 54.6% [24/44] vs. 79.6% [39/49]; p = 0.01, Week 24: 47.8% [21/44] vs. 75.5% [37/49]; p = 0.006) (Fig. 3). In many cases, the TAC dose was reduced once the patient developed AKI, and TAC treatment was then restarted after AKI improved. However, in 4 patients, TAC treatment was completely discontinued due to highly elevated creatinine levels. Of these 4 patients, only 1 (25%) achieved clinical remission with TAC.

TAC-Induced CKD

Six patients (6.5%) developed CKD following completion of TAC treatment (Fig. 1a), and all patients with CKD developed AKI during TAC treatment. In the 44 patients who developed AKI, we compared the baseline demographics and clinical characteristics of patients with and without CKD and found no significant difference in the

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Table 2. Baseline demographic variables associated with AKI

	AKI (–)	AKI (+)	*p* value
Patients, *n* (%)	49 (52.7%)	44 (47.3%)	
Male/female, *n*	23/26	33/11	0.006
Age, median (IQR), years	41 (23–58.5)	47.5 (29.5–62.8)	0.239
Duration of disease, median (IQR), months	41.5 (9–130.5)	26 (7–57)	0.276
UC location; left side/extensive, *n*	41/8	40/4	0.299
Medications for UC taken at baseline, *n* (%)			
Aminosalicylates	44 (89.8)	40 (90.9)	0.856
Azathioprine	9 (18.4)	11 (25.0)	0.437
Corticosteroids	29 (59.2)	24 (54.5)	0.652
Previous medications before TAC, *n* (%)			
TNF antagonist	9 (9.7)	4 (9.1)	0.198
Past history of treatment failure with biologics, *n* (%)			
TNF antagonist	2 (4.1)	0 (0)	0.175
Lichtiger index, median (IQR)	12 (10–14)	13 (11–14)	0.135
Disease severity, *n* (%): moderate, severe	17 (34.7), 32 (65.3)	16 (36.4), 28 (63.6)	0.867
Mayo subscore for endoscopy, median (IQR)	3 (2–3)	3 (3–3)	0.710
Fasting during the high trough phase, *n* (%)	43 (87.8)	42 (95.5)	0.186
WBC, median (IQR), /μL	7,670 (6,220–11,760)	7,960 (6,110–10,960)	0.829
Hb, median (IQR), g/dL	12.0 (10.7–13.6)	11.6 (10.4–14.1)	0.917
Albumin, median (IQR), g/dL	3.2 (2.5–3.8)	2.9 (2.6–3.7)	0.436
CRP, median (IQR), mg/L	0.8 (0.3–4.3)	2.8 (0.7–10.6)	0.018
Creatinine, median (IQR), mg/dL	0.72 (0.55–0.80)	0.72 (0.63–0.82)	0.236
Creatinine clearance, median (IQR), mL/min	103.9 (88.5–117.2)	105.1 (90.9–122.7)	0.836

AKI, acute kidney injury; UC, ulcerative colitis; WBC, white blood cell; Hb, hemoglobin; CRP, C-reactive protein; IQR, interquartile range.

Table 3. Multivariate analysis of predictive factors for AKI

Variables	Odds ratio	95% CI		*p* value
		lower	upper	
Age (years)	1.768	0.349	8.958	0.491
Male gender	4.379	1.694	11.321	0.002
CRP (mg/L)	8.503	0.777	93.004	0.080

AKI, acute kidney injury; CRP, C-reactive protein; CI, confidence interval.

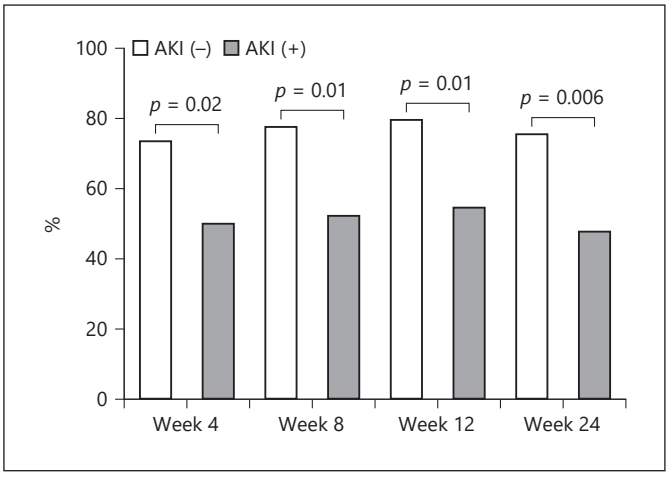

Fig. 3. Clinical remission rate with TAC treatment in patients with or without AKI. AKI, acute kidney injury.

variables (Table 3). The median total TAC treatment duration was not significantly different between patients without AKI, without CKD with AKI, and with CKD with AKI (156 days [109.5–207 days], 163 days [130–240.3 days], and 191.5 days [73.3–332.3 days], respectively; $p = 0.964$) (Fig. 4a). However, there were several cases of patients with AKI who continued to receive TAC for a long period of time despite no improvement in AKI, as their creatinine levels did not increase further. The median TAC treatment duration without improvement in AKI was significantly longer in patients with onset of CKD than in those without onset of CKD (51.5 days [47–204.5 days] and 29 days [9–55 days],

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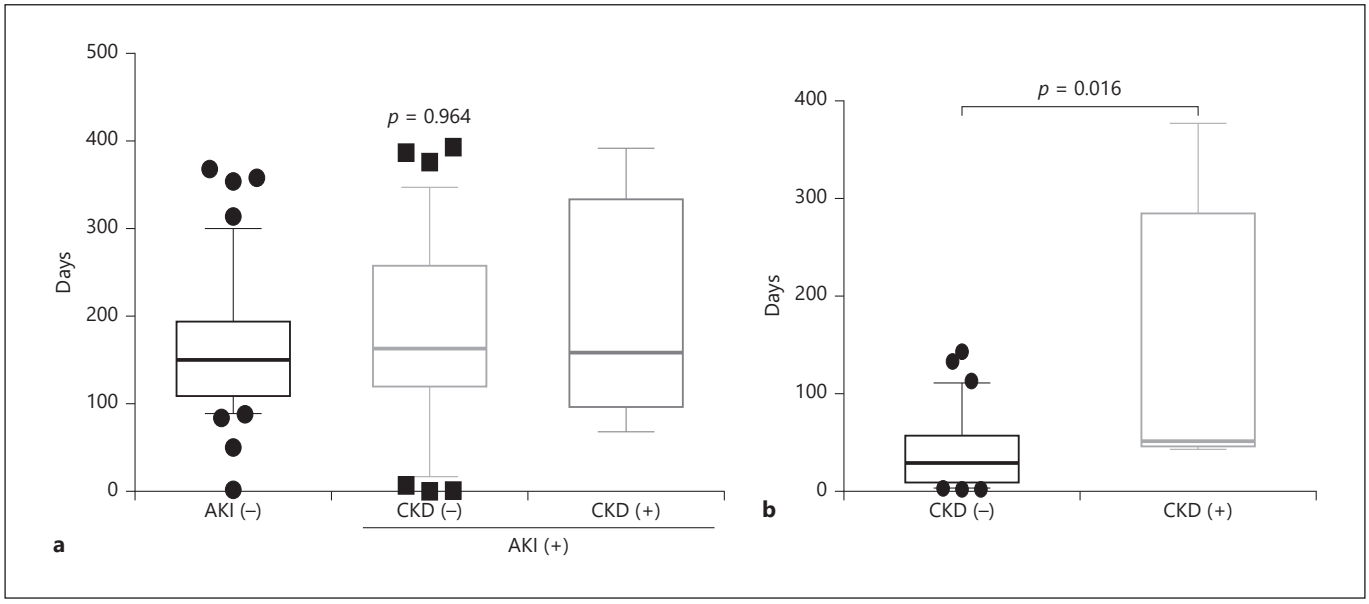

Fig. 4. a Median total TAC treatment duration among patients without AKI, without CKD with AKI, and with CKD with AKI ($p = 0.964$). **b** The median TAC treatment duration without improvement of AKI in CKD patients and non-CKD patients ($p = 0.016$). AKI, acute kidney injury; CKD, chronic kidney disease.

respectively; $p = 0.016$) (Fig. 4b). This suggests that long-term continuous treatment with TAC in the presence of AKI may lead to the development of CKD. Renal impairment in both AKI and CKD was not severe, no electrolyte abnormalities or uremia was noted, and no patients required treatment for renal impairment. Renal function normalized in two of the 6 patients with CKD during the long-term course, but 4 patients continued to have high serum creatinine levels and GFR below 60 mL/min/1.73 m^2.

Discussion

There have been reported cases of TAC-induced nephrotoxicity in patients with UC, and this is the first report to examine risk factors for TAC-induced nephrotoxicity in patients with UC. This study revealed that TAC treatment can result in AKI onset in patients with UC. Furthermore, the remission rate with TAC treatment in patients with AKI was significantly lower than that in patients without AKI, indicating that the presence (or absence) of renal impairment significantly affected the outcome of TAC treatment in patients with UC. TAC is often reduced or discontinued in patients with renal impairment, and the resulting decrease in TAC trough values may reduce the efficacy of TAC by failing to maintain the appropriate trough value range. Although TAC treatment has been reported to be effective for severe UC, surgery is often the only option when TAC treatment is ineffective. Therefore, it is important to carefully administer TAC in order to prevent renal impairment.

Of the 44 patients who developed AKI, 17 patients (38.6%) had a TAC trough level of >15 ng/mL at the time of onset. Originally, the target trough value for the high trough phase was 10–15 ng/mL, but it may temporarily exceed 15 ng/mL during the process of adjusting the TAC dose. Therefore, to prevent TAC-induced AKI, the TAC dose should be reduced to maintain the trough value below 15 ng/mL, rather than continuing with the same TAC dose when the trough value exceeds 15 ng/mL. We examined the baseline demographics and clinical characteristics associated with the development of AKI, and interestingly, in multivariate analysis, the male sex was an independent risk factor for the development of AKI. It is generally known that there are gender differences in renal diseases such as IgA nephropathy and membranous nephropathy, and CKD has been reported to progress more rapidly in males than in females [22–24]. One of the reasons why women present with milder kidney disease is thought to be the influence of female hormones. Estrogen influences the renin-angiotensin-aldosterone system, inhibiting angiotensin-converting enzyme activity and decreasing renal angiotensin II, which is thought to be nephroprotective [25–27]. The finding that males are more prone to TAC renal impair-

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ment than females in this study is theoretically consistent with previous reports. However, this is the first report to our knowledge showing that drug-induced nephrotoxicity is more likely to occur in males, than in females. Although future studies with a larger number of patients are needed, it is suggested that more attention should be paid to renal impairment in males treated with TAC. In this study, however, there was no association between kidney function at the start of TAC treatment and the occurrence of TAC-induced nephrotoxicity. Since most of the patients had normal renal function prior to the TAC treatment, it is still unclear whether UC patients with low renal function are more susceptible to renal impairment from TAC.

It is thought that calcineurin inhibitors cause AKI owing to an imbalance between vasoconstrictors such as endothelin and thromboxane, activation of the renin-angiotensin system, and vasodilators such as prostaglandin E2, prostacyclin, and nitric oxide – resulting in vasoconstriction of afferent arterioles [10]. These changes are dependent on the dose of calcineurin inhibitors and are considered reversible. Although the detailed mechanisms for the development of CKD have not been clarified, it is thought that interstitial fibrosis and tubular atrophy with microvascular vitrification are observed in the kidney, leading to irreversible renal dysfunction [13, 14]. In this study, 6 patients (6.5%) developed CKD due to TAC. Among patients with AKI, there was no significant difference in the total TAC treatment duration between patients with and without CKD. Interestingly, however, the TAC treatment duration in the presence of AKI was significantly longer in patients with CKD than in those without CKD. In patients with AKI, if there is no further increase in creatinine level, TAC may be continued for a long period of time, despite no resolution in AKI. Long-term administration of TAC without improvement of AKI may have caused chronic renal damage and led to the development of CKD. Therefore, TAC dose should be reduced, or the treatment should be discontinued in patients with AKI until AKI resolves, even if there is no further worsening of creatinine levels.

This study had several limitations. First, this was a retrospective cohort study, and the TAC treatment duration was not constant. The basic treatment strategy was to continue TAC for at least 3 months, after which it was tapered off and then discontinued. However, patients whose UC worsened when TAC was tapered had to continue TAC treatment for a longer period of time. This is reflective of TAC treatment in daily clinical practice. Second, the incidence of renal impairment in this study cannot be compared with previous reports because the diagnostic criteria for renal impairment due to TAC treatment differ among previous reports. The definition of renal impairment in previous reports is often an increase in creatinine level above the reference value (e.g., 1.3 or higher), and the timing of renal impairment may be determined at a single point, such as when TAC is discontinued [6, 15, 16]. However, in the present study, renal impairment was defined separately as AKI and CKD, and all occurrences of renal impairment during TAC treatment were accounted accordingly. In addition, since AKI is defined as an increase in creatinine levels compared to levels prior to TAC administration, some patients with low creatinine levels before TAC administration met the definition of AKI but fell below the reference value for creatinine levels. This may have resulted in a high incidence of AKI. However, this is the first report to examine the occurrence of nephrotoxicity in detail. Third, abnormal urine analysis, such as proteinuria, is included in the definition of CKD, but only some patients in the present study had urinalysis performed. Therefore, it is possible that the diagnosis of CKD should be made in patients with proteinuria even if their GFR is above 60, and this diagnosis may have been missed in some cases.

Conclusion

We found that TAC caused a high incidence of renal impairment in UC patients and that male sex was a risk factor for AKI onset. Furthermore, long-term administration of TAC without improvement in AKI may lead to the development of CKD. Renal impairment occurrence adversely affected the TAC treatment outcome, suggesting that it is important to carefully administer TAC to prevent renal impairment.

Statement of Ethics

This study was performed according to the principles of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University (No. 1105-02). Informed consent was replaced by the obligation of information to the participants and the right of participants to opt out due to the study's retrospective nature.

Conflict of Interest Statement

Shiro Nakamura reports receiving speaking fees from AbbVie GK, EA Pharma Co., Ltd., Mitsubishi Tanabe Pharma Corporation., Mochida Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Janssen Pharmaceutical K.K. Dr. Shinya Fukunishi is an Associate Editor of *Digestion*.

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Author Contributions

Satoshi Nakata collected data and wrote the initial draft of the manuscript. Kazuki Kakimoto designed the study, interpreted the data, and drafted the manuscript. Keijiro Numa, Naohiko Kinoshita, Yuka Kawasaki, Yoshihiro Tatsumi, Hideki Tawa, Ryoji Koshiba, Yuki Hirata, Kazuhiro Ota, Naokuni Sakiyama, Yuichi Kojima, Hiroki Nishikawa, Takuya Inoue, Toshihisa Takeuchi, Shinya Fukunishi, Takako Miyazaki, Shiro Nakamura, and Kazuhide Higuchi have contributed to data collection and interpretation and have critically reviewed the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

The data are not publicly available because there is no appropriate site for uploading at present. The data underlying this article will be shared on reasonable request to the corresponding author.

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