Original Article

Long-lasting renal dysfunction following tacrolimus induction therapy in ulcerative colitis patients

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Although tacrolimus (TAC) has remarkable effects in ulcerative colitis (UC) patients when given as remission induction therapy, some can develop renal dysfunction during TAC administration, resulting in withdrawal, though related details remain poorly understood. This study was conducted to determine the impact of oral TAC on renal function for remission induction therapy in UC patients. Fifty-five patients (10 elderly, 45 non-elderly) with UC and treated with oral TAC at our hospital were retrospectively evaluated. Renal function was assessed using estimated glomerular filtration rate (eGFR). Although a high clinical response to TAC was seen in both elderly and non-elderly, a decline in eGFR was noted in nearly all patients regardless of age, with a maximum change of –34.4% from the baseline value at week 11. Furthermore, eGFR decline recovered quickly after TAC discontinuation, though did not return to the baseline at two years following cessation. The rate of eGFR change at week 12 was significantly associated with patient age ($\beta = -0.3242$, $p = 0.0103$) and peak serum trough level during TAC treatment ($\beta = 0.3563$, $p = 0.0051$). Furthermore, the rate of decline in eGFR was significantly greater during treatment with TAC in the elderly as compared to non-elderly, with a large difference in eGFR decline rate between those groups also noted at two years after withdrawal of treatment. Careful attention to renal function when administering oral TAC for UC is important and changes in eGFR should be monitored closely in elderly patients even after treatment cessation.

***Key Words*: ulcerative colitis, tacrolimus, renal dysfunction, nephrotoxicity, elderly**

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by abdominal discomfort as well as such complications as rectal bleeding, abdominal pain, and body weight loss.[1,2] Drugs including 5-aminosalicylates (5-ASA), corticosteroids, immunomodulators, and biologics are generally given for UC, with the main goals treatment induction and maintenance of remission, which are determined by clinical, endoscopic, and histological findings.[3–5]

Tacrolimus (TAC), one of the available calcineurin inhibitors, is an immunosuppressive drug that inhibits T lymphocyte activation and proliferation.[6,7] Although it has long been administered for prevention of rejection after allogeneic organ transplantation,[8] more recently this drug has been used as an alternative medication for steroid-dependent or -refractory patients with moderate to severe UC activity, and several studies have evaluated its therapeutic effects in UC cases.[9] In the first reported randomized double-blind controlled trial, Ogata *et al.*[10] found that oral TAC therapy for steroid-refractory UC was highly effective for shortening the acute phase and rapidly inducing mucosal healing, and guidelines used in several different regions of the world now recommend administration of TAC for steroid-dependent or -refractory UC.[11,12]

On the other hand, adverse events related to TAC, such as nephrotoxicity, neurotoxicity, hypertension, and infections, have been reported to occur in a blood trough level-dependent manner.[13] Of those, nephrotoxicity is one of the most serious adverse events encountered in cases of TAC treatment for various diseases, such as rheumatoid arthritis (RA) and post-transplantation, with some patients forced to discontinue use due to renal dysfunction.[14] In general, the cause is known as drug-induced kidney injury (DKI), which is defined as onset of new kidney injury or worsening of an existing kidney injury caused by drug administration. DKI can be categorized based on the mechanism of pathogenesis, as follows: (1) direct toxic kidney injury; (2) acute interstitial nephritis (AIN); (3) indirect toxicity, such as decrease in renal blood flow; and (4) obstruction of the urinary tract.[15] Of those, TAC-induced nephrotoxicity can result from both direct and indirect toxicity.[16] Previous studies have also shown that TAC can induce vasoconstriction of afferent arterioles to reduce glomerular blood flow, resulting in renal ischemia, which can finally lead to reversible renal failure.[17] Moreover, such renal ischemia caused by long-term administration may also induce irreversible tubulointerstitial damage and glomerulosclerosis, leading to chronic nephrotoxicity. Thus, TAC-induced nephrotoxicity has been established in other diseases, though remains poorly understood in regard to UC cases, with only a few related reports presented.[7,9]

With focus on renal dysfunction as a major adverse event, the present retrospective study was conducted to determine the impact of oral TAC on renal function when given for remission induction therapy in UC patients.

Methods

Patients. This retrospective study investigated patients treated from April 2009 to March 2019 at Shimane University Hospital. It was performed in accordance with the Declaration of Helsinki and the protocol was approved by the ethics committee of Shimane University Faculty of Medicine. Fifty-five patients

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with moderate to severe active UC were included. Steroid-dependent UC was defined when steroid administration could not be reduced to below the equivalent of prednisolone (PSL) at 10 mg/day within three months of starting steroids without recurrent active disease or when relapse occurred within three months of stopping steroids. Steroid-refractory UC was defined as active disease despite PSL up to 0.75 mg/kg/day over a period of four weeks. Patients with a history of colorectal surgery, acute infectious enterocolitis, or regular intake of aspirin and/or other nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from this study. The diagnosis of UC was based on established standard criteria related to symptoms, and standard radiographic and endoscopic results.[2] The extent of colonic involvement was determined from results of a total colonoscopy examination.

The medical records of all 55 patients were retrospectively reviewed, with demographic factors, age, gender, duration of disease, clinical activity, extent type of UC, and concomitant medications taken at the start of TAC noted. At the time of drug initiation, TAC was administered at a dose of 0.1 or 0.05 mg/kg/day, which was then adjusted to achieve a high target trough level of 10–15 ng/ml. The attending physicians advised their patients to stay well hydrated while receiving TAC. Two weeks after starting treatment, the dosage was again adjusted to produce a low target trough level of 5–10 ng/ml. After 12 weeks of administration, TAC was withdrawn or continued depending on clinical response. All patients were evaluated using the Lichtiger index, as previously reported. Clinical remission was defined as Lichtiger index ≤3.[18]

Renal function. Renal function changes during and after TAC treatment were confirmed by determining estimated glomerular-filtration rate (eGFR), calculated using the modification in renal disease (MDRD) equation, as follows: GFR (ml/min/1.73 m^2) = 175 × $(sCr)^{-1.154}$ × $(age)^{-0.203}$ × 0.742 (if female) × 0.808 (if Japanese). Acute kidney injury (AKI) and chronic kidney disease (CKD) definitions were based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, and eGFR was determined using the CKD-EPI equation.[19,20] The rate of change in eGFR was defined as the ratio of eGFR at that time point as compared to the baseline (start of TAC administration).

Statistical analysis. Statistical analysis was performed using the SPSS statistical package, ver. 22.0 (SPSS, Chicago, IL). Normality of distribution was verified using the Shapiro-Wilk test. Parametric numerical results are presented as the mean ± SD, and nonparametric data as the median and interquartile range (IQR). The Mann–Whitney *U* test was used to examine differences between nonparametric data. Univariate and multivariate linear regression analyses were performed to identify factors associated with rate of eGFR change, with the confounders age, eGFR at baseline, maximum trough level, and days of administration. Variables showing $p<0.05$ in univariate regression analysis were entered into multiple regression analysis. All *p* values shown are two-sided and $p<0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics. The baseline characteristics of the enrolled patients are presented in Table 1. They were comprised of 41 males and 14 females, with a median age at start of TAC therapy 39 (range 24.0–52.5) years and duration of disease 38 (16.5–117.0) months. As for disease extent, 81.8% (45/55) of the patients had extensive colitis and 18.2% (10/55) left-sided colitis. Furthermore, 15 (27.3%) were PSL-resistant and 33 (60.0%) were PSL-dependent, while the other 7 (12.7%) were naïve to PSL. At the start of TAC therapy, patients previously treated with 5-ASA, a thioprine (azathioprine or 6-mercaptopurine), a biologic [anti-tumor necrosis factor (TNF)-α antibody], or PSL numbered 44 (80%), 16 (29.1%), 7 (12.7%), and 35 (63.6%), respectively. The median dose of PSL was 15.0 (4.5–30.0) mg. In addition, other concomitant medications given to the patients included rabeprazole ($n = 12$), esomeprazole ($n = 10$), lansoprazole ($n = 1$), vonoprazan ($n = 2$), and amlodipine ($n = 2$).

Clinical response. The clinical course of the 55 patients who received TAC induction therapy over 12 weeks was also investigated using the Lichtiger index. The mean Lichtiger index score was 10 (8–14) at the time of initiation. Within three months after starting TAC administration, two patients (3.6%) required switching to systemic steroid or anti-TNF treatment for exacerbation of the disease (Fig. 1), while four discontinued TAC due to side-effects related to renal dysfunction at the discretion of their physician. At week 12, the mean Lichtiger index score was decreased to 2 (1–4). Among all 55 patients, 37 (67.3%) achieved clinical remission (Lichtiger index ≤3) at week 12 and the median duration of TAC administration was 118 days (97–173). Furthermore, the median time from start of TAC treatment required to reach the target blood trough concentration (10–15 ng/ml) was six days (4–8.5), with a maximum trough level of 18.2 (15.2–22.7) ng/ml noted during treatment on day 19 (10.5–39.5). All patients reached a high trough level within 15 days. Overall, the median target trough concentration in blood at one, two, and 12 weeks after the start of TAC was 12.3 (10.1–14.9), 10.2 (8.0–13.2), and 8.1 (6.8–10.1) ng/ml, respectively.

Renal function. At the start of treatment with TAC, median serum creatinine (sCre) and eGFR levels were 0.7 (0.59–0.82) mg/dl and 93.0 (83.0–109.2) ml/min/1.73 m^2, respectively (Table 1). CKD stage G1 (eGFR: ≥90) was noted in 69.1% (39/55) of the patients and stage G2 (eGFR: 60–89) in 30.9% (16/55), whereas there were none with stage G3 or higher (eGFR: <60). Thus, there were no cases of impaired renal function with an eGFR value less than 60 before starting TAC administration. While a decreased change in eGFR rate was observed from one week after beginning administration, no development of AKI within two weeks of beginning treatment was noted (Fig. 2A). A gradual reduction in eGFR rate was seen until the end of treatment with TAC, with the average change after one, two, four and 12 weeks found to be −7%, −8.4%, −12.9%, and −20.3%, respectively, after starting administration. Nearly all of the patients had a significant decrease in eGFR as compared with their pre- and post-treatment TAC values, with the maximum decrease of 34.4 ± 17.3% seen at week 11 (Fig. 2B). Four patients discontinued administration of TAC due to renal impairment within three months at the discretion of their physician. An improved eGFR rate was promptly observed after cessation of TAC (−8.9% at four weeks, −5.1% at 12 weeks after ending treatment), though none showed recovery to the baseline eGFR at either 52 or 104 weeks following termination (eGFR change: −9.2% and −11.2%, respectively) (Fig. 2C). Multivariate linear regression analysis showed that the rate of change in eGFR at week 12 was significantly correlated with age ($\beta = -0.3242$, $p = 0.0103$) as well as maximum serum trough level during treatment ($\beta = 0.3563$, $p = 0.0051$), whereas pre-treatment eGFR, duration of treatment, and number of days to high trough level did not have an association with eGFR change rate during treatment with TAC (Table 2). Those results indicated that age contributes to development of renal dysfunction in patients who have received treatment with oral TAC. During TAC administration, observed adverse events other than decreased kidney function were hypomagnesemia ($n = 35$), myalgia ($n = 2$), headache ($n = 1$), tremors ($n = 1$), nausea ($n = 1$), and hyperkalemia ($n = 1$). Of those, hypomagnesemia was most often observed and treated with magnesium supplementation. As for magnesium level, the lowest noted was 1.5 (1.4–1.8) mg/dl in a patient undergoing treatment with TAC. On the other hand, there was no correlation between magnesium level and maximum rate of change in eGFR shown by Spearman's correlation test ($p = 0.1847$). Moreover, concomitant

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Table 1. Baseline characteristics of eligible patients

Total number of patients, *n*	55
Age (year), median (IQR)	39 (24.0–52.5)
Duration of disease (month), median (IQR)	38 (16.5–117.0)
Gender	
Male, *n* (%)	41 (74.5)
Female, *n* (%)	14 (25.5)
Medical history	
Hypertension, *n* (%)	0 (0)
Diabetes mellitus, *n* (%)	2 (3.6)
Disease extent	
Proctitis, *n* (%)	0 (0)
Left-sided colitis, *n* (%)	10 (18.2)
Extensive coitis, *n* (%)	45 (81.8)
Response to steroid therapy	
Refractory, *n* (%)	15 (27.3)
Dependent, *n* (%)	33 (60.0)
Naïve, *n* (%)	7 (12.7)
Medications	
Yes, *n* (%)	51 (92.7)
5-Aminosalicylates, *n* (%)	44 (80.0)
Thioprines (azathioprine or mercaptopurine), *n* (%)	16 (29.1)
Biologics, *n* (%)	7 (12.7)
Predonisolone, *n* (%)	35 (63.6)
Dose of predonisolone (mg), median (IQR)	15.0 (4.5–30.0)
Other concomitanct medications	
Yes, *n* (%)	27 (49.1)
Proton pump inhibitors	23 (41.8)
Potassium-competitive acid blocker	2 (3.6)
Calcium channel blocker	2 (3.6)
Lichtiger score, median (IQR)	10 (8–14)
Blood examination results	
C-reactive protein (mg/dl), median (IQR)	2.0 (0.5–4.0)
Serum albumin (g/dl), median (IQR)	3.0 (2.8–3.9)
White blood cell count (/μl), median (IQR)	8,430 (6,273–10,205)
Hemoglobin (g/dl), median (IQR)	12.0 (10.0–12.9)
Platelet count ($\times 10^3$/μl), median (IQR)	332 (264–432)
Renal function	
BUN (mg/dl), median (IQR)	11.1 (7.9–14.0)
Cre (mg/dl), median (IQR)	0.70 (0.59–0.82)
eGFR (ml/min/1.73 m^2), median (IQR)	93.0 (83.0–109.2)
Na (mEq/L), median (IQR)	140 (138–141)
K (mEq/L), median (IQR)	4.1 (3.8–4.4)
Cl (mEq/L), median (IQR)	104 (102–107)
Ca (mg/dl), median (IQR)	8.7 (8.3–9.0)
Mg (mg/dl), median (IQR)	2.1 (2.0–2.3)
CKD stage	
G1, *n* (%)	38 (69.1)
G2, *n* (%)	17 (30.9)
G3 and above, *n* (%)	0 (0)

administration of other medications, such as a proton pump inhibitor (PPI) or calcium channel blocker (Ca-blocker), did not have a significant effect on the peak rate of change in eGFR, determined with a Mann–Whitney *U* test ($p = 0.2141$).

Renal dysfunction in elderly patients with UC. Next, we conducted a retrospective analysis of patients divided into elderly (≥60 years old) and non-elderly (<60 years old) groups to clarify the relationship between age and renal function in regard to TAC treatment. Of the 55 patients with UC analyzed, 10 were elderly and 45 were non-elderly, with a median age of 67 (60.5–68) and 32 (23.0–45.0) years, respectively (Table 3). The duration of disease was significantly longer in the elderly group [35 (11–79) vs 142 (64.3–264) months]. In addition, white blood cell [9,115 (7,160–11,760) vs 6,350 (5,835–6,800)/μl] and platelet [372

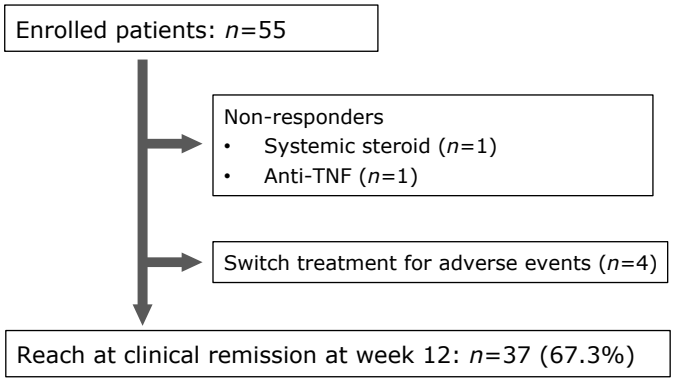

Fig. 1. Flowchart of treatment outcomes in UC patients treated with oral tacrolimus (TAC) ($n = 55$). Clinical remission was defined as Lichtiger index ≤3. TNF, tumor necrosis factor.

(271.3–476.8) vs 261 (210.8–292.5) $\times 10^3/\mu l$] counts in the elderly group were significantly greater, while other clinical characteristics did not differ significantly between them. As for clinical response to TAC treatment, eight of 10 (80%) patients in the elderly group reached clinical remission within 12 weeks, whereas only 29 of 45 (64.4%) in the non-elderly group responded to treatment. These results suggest that elderly show better response to treatment with TAC.

There was no change in sCre between the elderly and non-elderly groups [0.64 (0.54–0.7) vs 0.71 (0.6–0.82) mg/dl], while there was a significant difference for eGFR [83.3 (71.8–87) vs 94.6 (86.5–111) ml/min/1.73 m^2]. In addition, the rate of change in eGFR was significantly greater during TAC administration in the elderly patients (−12.3% vs −5.8%, −19.5% vs −5.9%, −26.1% vs −9.9%, and −33.4% vs −17.2% at 1, 2, 4, and 12 weeks, respectively, after TAC treatment) (Fig. 3A). On the other hand, there was no significant difference for median target trough concentration during the course of treatment between the groups [week two: 12.9 (9.8–15.3) vs 12.7 (11.5–13.9), week 12: 8.1 (7.0–10.2) vs 6.9 (5.8–8.4)]. All of the patients showed recovery of eGFR rate after cessation of TAC, though improvement in that rate to the baseline at 24 (−18.5% vs −7.6%), 52 (−22.4% vs −6%), and 104 (−20.7% vs −11.4%) weeks after the end of treatment was worse in the elderly group (Fig. 3B). Furthermore, 50% (5/10) of the elderly patients showed progression from CKD stage G1 or G2 to G3a/b by the end of treatment, which remained persistent without improvement even after two years (Fig 3C). In contrast, 86.7% (39/45) of those in the non-elderly group were in CKD stage G1 or 2 at the completion of TAC, and 94.2% remained at the same stage two years later, with only 5.8% in CKD stage G3a/b.

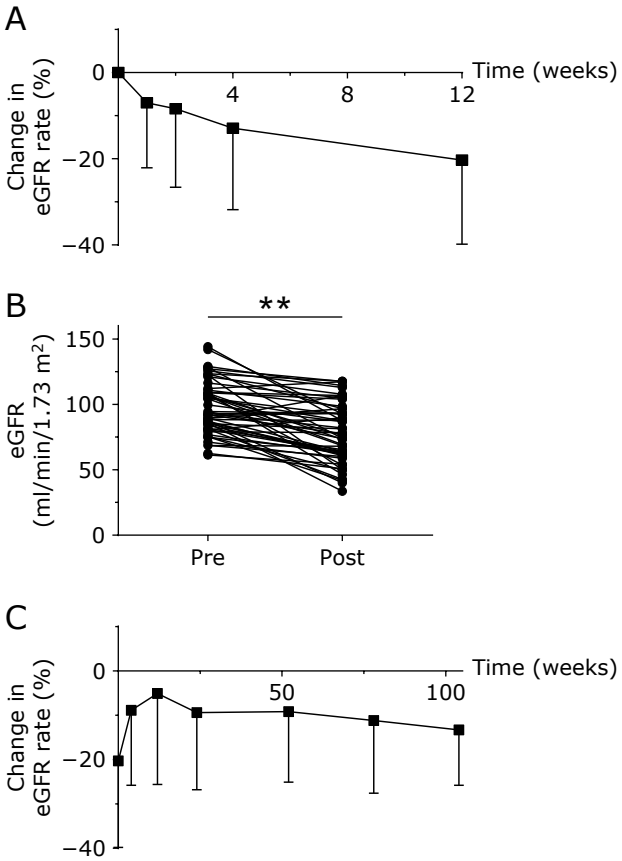

Fig. 2. Rates of eGFR change after (A) beginning administration and (C) discontinuation of tacrolimus (TAC). On the horizontal axis, one week after the (A) start and (C) discontinuation of treatment are shown. The vertical axis represents the rate of change in eGFR, which was defined as the ratio of eGFR at that time to that seen at the baseline (start of TAC administration). (B) eGFR before and after TAC treatment. Pre, pre-treatment; Post, post-treatment.

Discussion

The present study of the influence TAC induction therapy on renal damage in UC patients indicated that TAC treatment induced a decline in eGFR in most of the treated patients examined, particularly those who were elderly, which remained for a long period after cessation. There are the first known long-term monitoring results presented that show an association of TAC-induced renal dysfunction with patient age.

In 2006, Ogata *et al.*[10] conducted the first randomized, double-blind, controlled trial of oral TAC in patients with steroid-refractory UC. They reported a clinical response rate at two weeks after treatment of 68.4% in the high trough group (10–15

Table 2. Univariate and multivariate linear regression models testing for rate of change in eGFR

	Univariate		Multivariate		
	β	p value	β	95% CI	p value
Age	–0.3565	0.0075	–0.3242	–0.6693, –0.1224	0.0054
eGFR at baseline	–0.1333	0.3319			
Maximam trough level	0.38	0.0046	0.3563	0.1734, 2.4191	0.0245
Number of days to high trough level	–0.0037	0.8653			
Days of administration	–0.0013	0.9926			
R^2					0.249

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Table 3. Comparison between characteristics of non-elderly and elderly patients with UC

	Non-elderly	Elderly	*p* value
Total number of patients, *n*	45	10	
Age, years, median (IQR)	32 (23–45)	67 (60.5–68)	<0.001**
Duration of disease, months, median (IQR)	35 (11–79)	142 (64.3–264)	0.005**
Gender			
Male/Female, *n* (%)	34/11 (75.6/24.4)	7/3 (70/30)	0.715
Disease extent			
Proctitis/Left-sided colitis/Extensive colitis, *n* (%)	0/8/37 (0/16.7/82.2)	0/2/8 (0/20/80)	0.869
Response to steroid therapy			
Refractory/Dependent/Naïve, *n* (%)	14/26/5 (31.1/57.8/11.1)	1/7/2 (10/70/20)	0.359
Medications			
Yes, *n* (%)	41 (91.1)	10 (100)	0.983
5-Aminosalicylates, *n* (%)	35 (77.8)	9 (90)	0.382
Thioprines (azathioprine or mercaptopurine), *n* (%)	12 (26.7)	4 (40)	0.401
Biologics, *n* (%)	5 (11.1)	2 (20)	0.446
Predonisolone, *n* (%)	30 (66.7)	5 (50)	0.321
Dose of predonisolone (mg), median (IQR)	15 (5–30)	8 (2–25)	0.745
Lichtiger score, median (IQR)	11 (8.0–14.0)	10.0 (8.0–11.8)	0.272
Blood examination results			
C-reactive protein (mg/dl), median (IQR)	1.6 (0.5–4.2)	1.1 (0.6–3.3)	0.612
Serum albumin (g/dl), median (IQR)	3.2 (2.9–4.0)	3.1 (2.8–3.2)	0.186
White blood cell count (/μl), median (IQR)	9,115 (7,160–11,760)	6,350 (5,835–6,800)	0.013*
Hemoglobin (g/dl), median (IQR)	11.8 (9.3–13.3)	11.4 (11.0–11.9)	0.799
Platelet count (×10^3/μl), median (IQR)	372 (271.3–476.8)	261 (210.8–292.5)	0.015*
Renal function			
BUN (mg/dl), median (IQR)	10.1 (7.5–14.1)	12.0 (10.6–13.6)	0.271
Cre (mg/dl), median (IQR)	0.71 (0.60–0.82)	0.64 (0.54–0.70)	0.107
eGFR (ml/min/1.73 m^2), median (IQR)	94.6 (86.5–111.0)	83.3 (71.8–87.0)	0.044*
Na (mEq/L), median (IQR)	139 (138–141)	140 (139–141)	0.558
K (mEq/L), median (IQR)	4.1 (3.8–4.5)	3.9 (3.4–4.2)	0.129
Cl (mEq/L), median (IQR)	104 (102–106)	107 (104–108)	0.16
Ca (mg/dl), median (IQR)	8.7 (8.4–9.15)	8.4 (8.3–8.5)	0.172
Mg (mg/dl), median (IQR)	2.1 (2.0–2.3)	2.1 (2.1–2.2)	0.942
CKD stage			
G1/G2/G3 and above, *n* (%)	30/15/0 (33.3/66.7/0)	2/8/0 (20/80/0)	0.007**

BUN, blood urea nitrogen; Cre, creatinine. *p<0.05, **p<0.01.

ng/ml) and 38.1% in the low trough group (5–10 ng/ml). In other retrospective analyses, short-term response rates in patients given TAC also generally ranged from 50–70%, with remission rates of 40–60%.[9] In the present study, 67.3% of UC patients treated with TAC reached clinical remission within 12 weeks, slightly superior to those previous reports. Together, these data clearly indicate that treatment with oral TAC can provide remarkable short-time therapeutic effects in patients with UC.

In this retrospective study of moderate to severe UC patients treated with oral TAC, renal dysfunction associated with that treatment was definitely found. First, while eGFR values were within normal limits before treatment, a declining trend was shown early after beginning TAC regardless of age and then continued throughout the administration period, with the lowest values as compared to the baseline shown at 11 weeks. Second, though not previously reported for other diseases, renal function in the present UC patients for up to two years after TAC discontinuation was analyzed. Those findings showed that eGFR improved quickly after cessation of TAC, however, recovery to pre-treatment levels was not attained even after two years. These results indicate that TAC-induced nephrotoxicity may be sustained in patients with UC for a prolonged period after discontinuation of treatment.

As noted in previous studies of other diseases, TAC-induced nephrotoxicity is dependent on serum trough concentration and occurs more frequently at concentrations above 10 ng/ml.[21,22] For UC patients undergoing TAC therapy, the target trough concentration for induction of early clinical remission is also recommended to be 10–15 ng/ml for the first two weeks and then 5–10 ng/ml for up to 12 weeks. In the present patients, the trough level was 12.3 in the first and then 10.2 ng/ml in the second week, which may have been related to the earlier decline in eGFR during treatment. Furthermore, multivariate analysis demonstrated a significant correlation between rate of decrease in eGFR and maximum trough concentration during treatment. Thus, we concluded that TAC treatment for UC causes a trough-dependent decrease in eGFR, the same as seen with that given for other diseases. Certain drugs metabolized by CYP3A5 (PPIs, Ca-blockers, etc.) are also known to impact the blood concentration of TAC. Although some patients were taking those drugs while receiving TAC treatment, their effect on renal function was considered to be largely insignificant because an appropriate concentration was maintained, confirmed by routine blood trough measurements, as noted above.

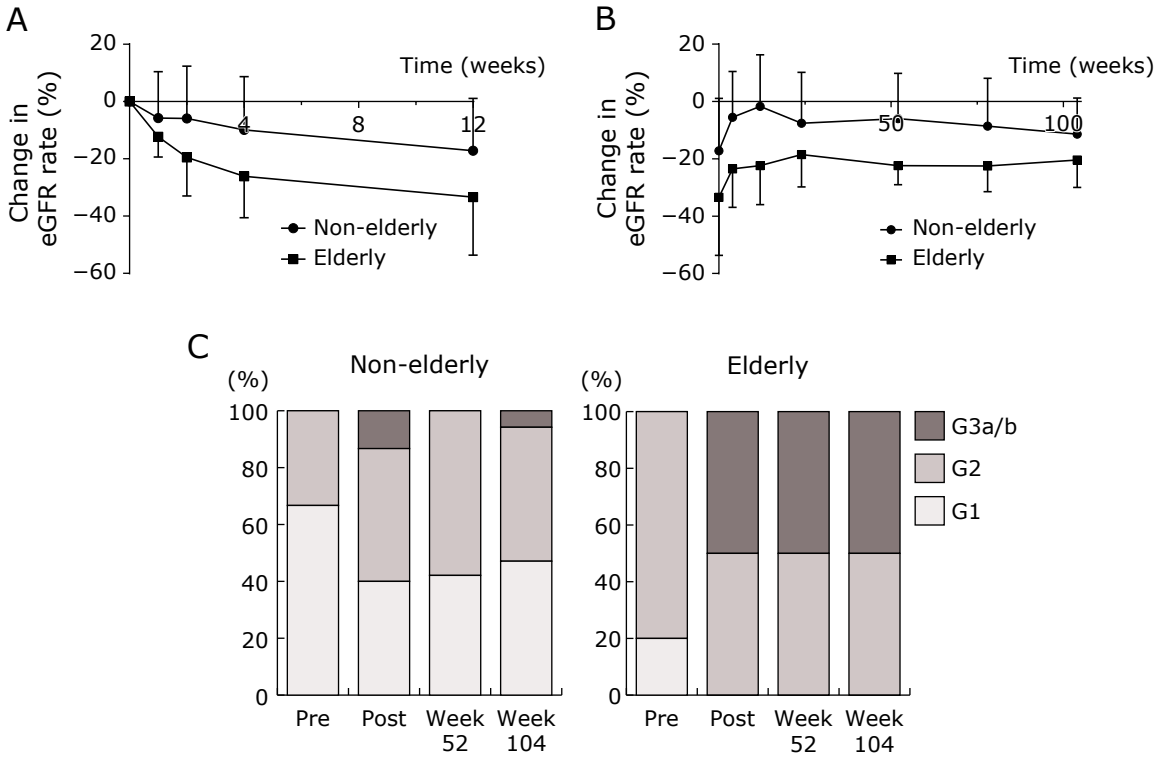

Fig. 3. Rates of eGFR change after (A) initiation and (B) cessation of treatment in elderly (black squares) and non-elderly (black circles) patients treated with oral tacrolimus (TAC). On the horizontal axis, one week after the (A) start and (B) discontinuation of treatment are shown. The vertical axis represents the rate of change in eGFR. (C) Chronic kidney stage (CKD) at baseline (Pre), time of withdrawal of TAC (Post), and 52 and 102 weeks after cessation in non-elderly (left) and elderly (right). CKD stages were based on eGFR value (ml/min/1.73 m^2), as follows: G1 (≥90), G2 (60 to 89), G3a (45 to 59), G3b (30 to 44).

According to post-marketing surveillance of the safety of TAC in patients with RA, one of the risk factors for renal impairment is age over 65.[13] The present multivariate analysis results as well showed a correlation of rate of decline in eGFR with patient age, thus we also conducted analysis after dividing the UC cohort into elderly and non-elderly patients. The efficacy of TAC in elderly patients with UC has only been presented in a few case series reports. Our results showed that 80% of those in the elderly group reached clinical remission within 12 weeks after starting TAC treatment, whereas the rate for induction of clinical remission was 64.4% in the non-elderly group. Furthermore, the elderly group also demonstrated a higher short-term therapeutic response to TAC treatment.

As for renal function, the rate of decline in eGFR was significantly greater in the elderly as compared to non-elderly group from the first week of TAC administration until the end of treatment, whereas there was no difference in serum trough concentration during treatment between then. Furthermore, even after TAC was stopped, recovery of eGFR in the elderly was significantly worse as compared with the non-elderly patients. Elderly individuals generally have a lower metabolic capacity and significantly greater risk for developing kidney damage as compared to non-elderly, which may have influenced the present results.[23] Nevertheless, our findings suggest that renal function should be carefully followed for a long period after completion of TAC therapy in elderly patients.

In conclusion, the present study provides evidence that oral TAC treatment has beneficial effects as remission induction therapy for moderate to severe UC in both non-elderly and elderly patients. Notably, a TAC-induced decline in eGFR was observed in most cases, though especially in the elderly group for an extended period after cessation. Therefore, careful monitoring of renal function is crucial to better elucidate the balance between benefits and risks of TAC treatment. In addition, oral TAC should be cautiously administered in elderly patients and may be better to avoid because of effects on renal function.

Author Contributions

NC and NO contributed to drafting of the manuscript. KK, NI, and SI contributed to the study concept and design. KK, SK, EO, TY, and HS contributed to acquisition of data. AO, YM, KS, and HT contributed to analysis and interpretation of data.

Abbreviations

5-ASA	5-aminosalicylate
CKD	chronic kidney disease
eGFR	estimated glomerular-filtration rate
TAC	tacrolimus
UC	ulcerative colitis

Conflicts of Interest

SI reports receipt of personal fees from Takeda Pharmaceutical Co., Ltd. and AbbVie GK, and receiving grants for commissioned/joint research from Zeria Pharmaceutical Co., Astellas Pharma Inc., EA Pharma Co., Ltd., Janssen Pharmaceutical K.K., JIMRO Co., Ltd., Takeda Pharmaceutical Co., Ltd., AbbVie GK, and Nippon Kayaku Co., Ltd. No other authors have personal or financial conflicts to declare.

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References

1 Podolsky DK. Inflammatory bowel disease. *N Engl J Med* 2002; **347**: 417–429.
2 Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. *Lancet* 2017; **389**: 1756–1770.
3 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**: 1324–1338.
4 Sonoyama H, Kawashima K, Ishihara S, *et al*. Capabilities of fecal calprotectin and blood biomarkers as surrogate endoscopic markers according to ulcerative colitis disease type. *J Clin Biochem Nutr* 2019; **64**: 265–270.
5 Dorrington AM, Selinger CP, Parkes GC, Smith M, Pollok RC, Raine T. The historical role and contemporary use of corticosteroids in inflammatory bowel disease. *J Crohns Colitis* 2020; **14**: 1316–1329.
6 Fellermann K, Ludwig D, Stahl M, David-Walek T, Stange EF. Steroid-unresponsive acute attacks of inflammatory bowel disease: immunomodulation by tacrolimus (FK506). *Am J Gastroenterol* 1998; **93**: 1860–1866.
7 Naganuma M, Fujii T, Watanabe M. The use of traditional and newer calcineurin inhibitors in inflammatory bowel disease. *J Gastroenterol* 2011; **46**: 129–137.
8 Starzl TE, Todo S, Fung J, Demetris AJ, Venkataramman R, Jain A. FK 506 for liver, kidney, and pancreas transplantation. *Lancet* 1989; **2**: 1000–1004.
9 Wu B, Tong J, Ran Z. Tacrolimus therapy in steroid-refractory ulcerative colitis: a review. *Inflamm Bowel Dis* 2020; **26**: 24–32.
10 Ogata H, Matsui T, Nakamura M, *et al*. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006; **55**: 1255–1262.
11 Harbord M, Eliakim R, Bettenworth D, *et al*. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *J Crohns Colitis* 2017; **11**: 769–784.
12 Komaki Y, Komaki F, Ido A, Sakuraba A. Efficacy and safety of tacrolimus therapy for active ulcerative colitis; a systematic review and meta-analysis. *J Crohns Colitis* 2016; **10**: 484–494.
13 Takeuchi T, Kawai S, Yamamoto K, Harigai M, Ishida K, Miyasaka N. Post-marketing surveillance of the safety and effectiveness of tacrolimus in 3,267 Japanese patients with rheumatoid arthritis. *Mod Rheumatol* 2014; **24**: 8–16.
14 Schwarz A, Haller H, Schmitt R, *et al*. Biopsy-diagnosed renal disease in patients after transplantation of other organs and tissues. *Am J Transplant* 2010; **10**: 2017–2025.
15 Usui J, Yamagata K, Imai E, *et al*. Clinical practice guideline for drug-induced kidney injury in Japan 2016: digest version. *Clin Exp Nephrol* 2016; **20**: 827–831.
16 Issa N, Kukla A, Ibrahim HN. Calcineurin inhibitor nephrotoxicity: a review and perspective of the evidence. *Am J Nephrol* 2013; **37**: 602–612.
17 Lanese DM, Conger JD. Effects of endothelin receptor antagonist on cyclosporine-induced vasoconstriction in isolated rat renal arterioles. *J Clin Invest* 1993; **91**: 2144–2149.
18 Lichtiger S, Present DH, Kornbluth A, *et al.* Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994; **330**: 1841–1845.
19 Levey AS, Eckardt KU, Tsukamoto Y, *et al*. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005; **67**: 2089–2100.
20 Section 2: AKI Definition. *Kidney Int Suppl (2011)* 2012; **2**: 19–36.
21 Böttiger Y, Brattström C, Tydén G, Säwe J, Groth CG. Tacrolimus whole blood concentrations correlate closely to side-effects in renal transplant recipients. *Br J Clin Pharmacol* 1999; **48**: 445–448.
22 Furst DE, Saag K, Fleischmann MR, *et al*. Efficacy of tacrolimus in rheumatoid arthritis patients who have been treated unsuccessfully with methotrexate: a six-month, double-blind, randomized, dose-ranging study. *Arthritis Rheum* 2002; **46**: 2020–2028.
23 Sturm A, Maaser C, Mendall M, *et al*. European Crohn's and Colitis Organisation topical Review on IBD in the elderly. *J Crohns Colitis* 2017; **11**: 263–273.