

# Efficacy and Safety of Grapefruit Juice Intake Accompanying Tacrolimus Treatment in Connective Tissue Disease Patients

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## Abstract

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**Objective** It is well known that grapefruit juice (GFJ) elevates the blood tacrolimus (TAC) concentration. We investigated the efficacy and safety of GFJ intake with TAC in cases of connective tissue diseases in which the TAC blood concentration was insufficiently high for clinical improvement, even when 3 mg/day or more of TAC was administered.

**Methods** Seven patients took 200 mL of GFJ every day. The trough levels of the TAC blood concentration were measured before and after GFJ intake and the clinical courses were monitored thereafter.

**Results** First, we surveyed the blood TAC trough levels of 30 recent patients who took 3 mg/day of TAC, and found that 21 patients (70%) did not achieve the minimum target TAC concentration (>5 ng/mL). Seven patients took GFJ due to a lack of efficacy and a relatively low TAC blood concentration. GFJ increased the TAC level from 4.3±2.4 ng/mL to 13.8±6.9 ng/mL (average increase: 3.3-fold). GFJ was also effective in achieving a clinical improvement in most cases without causing any severe adverse events, and it helped to decrease the dosages of glucocorticoid and TAC. In some cases, the blood TAC concentration fluctuated for no apparent reason.

**Conclusion** GFJ intake was effective for the elevation of TAC concentration by approximately three fold and clinical improvement, but special care is required for monitoring its influence on concomitantly used drugs as well as TAC concentration. The addition of GFJ to TAC treatment could be an efficacious treatment option, when the plasma TAC concentration does not reach the minimal target concentration.

**Key words:** blood concentration, connective tissue disease, CYP3A4, grapefruit juice, tacrolimus

(Intern Med 55: 1547-1552, 2016)

(DOI: 10.2169/internalmedicine.55.5553)

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## Introduction

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Tacrolimus (TAC) is an immunosuppressant used for various connective tissue diseases. Warnings have been issued that grapefruit juice (GFJ) intake elevates the TAC blood concentration by inhibiting cytochrome P450 (CYP) 3A4 (1, 2). However, there has been only one reported study with multiple patients regarding the effects of GFJ on the TAC blood concentration (3). This study showed that GFJ intake increased the TAC blood concentration by 2.1-fold in

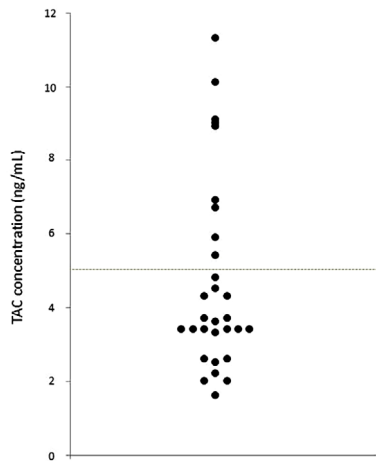
liver transplant patients (3). Since the effects of liver dysfunction or transplant in cases of liver transplantation cannot be ruled out, the effect of GFJ on TAC might differ in connective tissue disease patients. In Japan, up to 3 mg/day of TAC is allowed in the treatment of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), and an increase in TAC dosage is not allowed regardless of TAC blood concentration. From our experience, only some patients who are administered 3 mg/day of TAC reach the target range of TAC blood concentration (5-15 ng/mL by trough level) (4-6). Therefore, we aimed to investigate the efficacy

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Received for publication April 9, 2015; Accepted for publication September 1, 2015

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**Figure 1.** Distribution of TAC blood concentration (trough level) in patients taking 3 mg/day of TAC. TAC blood concentrations were surveyed in 30 connective tissue disease patients who took 3 mg/day of TAC (once daily after dinner). The minimum target TAC concentration (5 ng/mL) is shown by a dotted line.

and safety of combined treatment with GFJ and TAC in seven patients with connective tissue diseases whose TAC blood concentrations were not high enough to achieve clinical improvement.

## Materials and Methods

Patients were recruited from Kyoto University Hospital between January 2010 and March 2013. All of the patients took TAC at a single daily dose after dinner and TAC blood trough levels were measured after 12 hours (C12) by a chemiluminescent enzyme immunoassay (CLIA) (ARCHITECT™i1000; Abbot, Abbot Park, USA). Seven connective tissue disease patients whose TAC (Prograf®; Astellas Pharma, Tokyo, Japan) blood concentration was not high enough to induce clinical improvement, even when administered 3 mg/day or more of TAC, were selected for this study. The patients consumed ~200 mL of fresh GFJ once daily because a study on patients taking the calcium-channel antagonist felodipine showed that the effectiveness of GFJ intake for an increase in felodipine blood concentration persisted for more than 24 hours (7); the TAC blood trough levels and clinical courses were followed thereafter. This study was conducted in accordance with the Declaration of Helsinki and its amendments and was approved by the Kyoto University Hospital Ethics Committee. All data are expressed as the mean±standard deviation (SD) values as appropriate. Student's *t*-test was used for the statistical analyses. *p* values of <0.05 were considered to indicate statistical significance.

## Results

First, we determined the proportion of patients with a rec-

ommended target blood trough level (>5 ng/mL) who took 3 mg/day of TAC. We randomly selected 30 recent patients who took 3 mg/day of TAC, and their TAC trough levels were measured (Fig. 1). Surprisingly, we found that the TAC blood concentration (C12) reached the target level in only nine patients (30%). The median trough level (C12) was 3.65 ng/mL. After informed consent had been obtained, seven connective tissue disease patients whose TAC blood concentration was not high enough to achieve clinical improvement started to consume GFJ (200 mL daily). These patients included those with SLE (four cases), dermatomyositis (DM) (one case), mixed connective tissue disease (MCTD) (one case) and Sjögren's syndrome (SS) (one case) (Table).

Patient #1 was a 23-year-old woman who presented with continuous hair loss and elevated anti-dsDNA antibody (Ab) titer. When she was 21 years old, she developed fever and arthralgia, and was diagnosed with SLE by satisfying the 1997 revised American College of Rheumatology (ACR) classification criteria (8), including malar rash, non-erosive arthritis, leukopenia and positivity for antinuclear antibodies (ANAs) 160x (speckled) and anti-dsDNA Ab (16 U/mL). She showed hypocomplementemia (C3 28.1 mg/dL, C4 4.5 mg/dL, CH50 13 U/mL). She was treated with an initial dose of 20 mg of daily prednisolone (PSL) for her fever, arthritis and face rash. When the PSL was tapered to 18 mg/day, TAC was added because her face rash slightly worsened. When the PSL was decreased to 15 mg/day, massive hair loss occurred and she started wearing a wig. Her laboratory data were almost normal except for a low level of C3 (59.7 mg/dL). Since an increase of TAC (5 mg/day) was not effective for her hair loss, even within the effective concentration range (6.4 ng/mL), we attempted to elevate the TAC concentration by administering GFJ in the expectation of a clinical improvement. GFJ increased the TAC trough (C12) level from 6.4 to 23.7 ng/mL (3.7-fold) and improved her hair loss. By monitoring the TAC concentration, a physician adjusted the TAC dose, but the TAC blood concentration fluctuated during the course. As shown in Table and Fig. 2, after 10 months, the TAC dose could be decreased from 5 to 3 mg/day, and PSL was also decreased to 10 mg/day without flare of the disease, although complement remained slightly low (C3 58.2 mg/dL, C4 12.8 mg/dL, CH50 42 U/mL). There were no significant side effects, except for transient fatigue, nasal discharge, headache, skin eruption and arthralgia two weeks after the initiation of GFJ, which we assume were due to viral infection rather than side effects of TAC.

Patient #2 was a 38-year-old woman who presented with increased urinary protein levels. She had been diagnosed with SLE based on malar rash, non-erosive arthritis, renal disorders, elevated anti-dsDNA Ab and positivity for ANA 640x (homogeneous, speckled) at the age of 20. Treatment started with 30 mg/day of PSL, which induced a remission, but after self-withdrawal of PSL at age 34, SLE flared. Urinary protein increased (6.6 g/day), urinary occult blood was

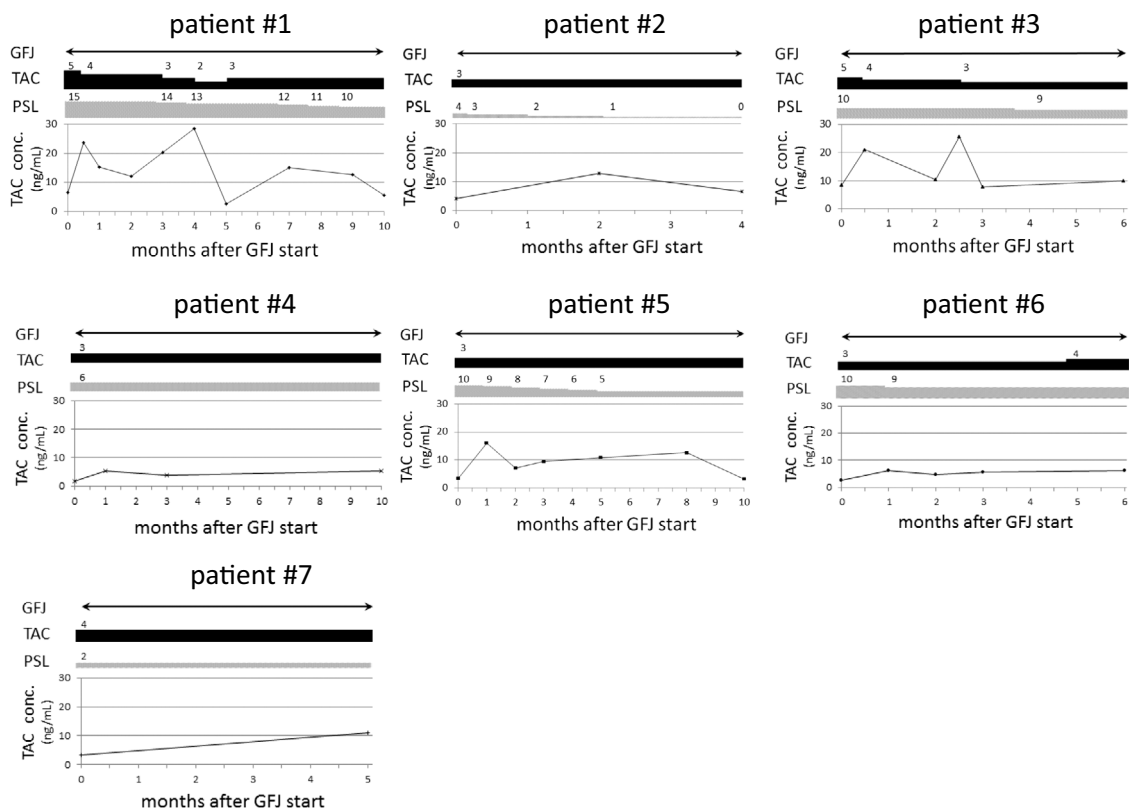
**Table.** Summary of the 7 Cases before and after GFJ Intake.

Pt.	Dx.	Age (y.o.) /Sex	Main target	Other medications*	Observation period (months)	TAC conc. (ng/mL) before/after GFJ (fold increase)	PSL dose before/after GFJ (mg/day)	TAC dose before/after GFJ (mg/day)	Effects
1	SLE	23/F	hair loss	omeprazole	10	6.4/23.7 (3.7)	15/10	5/3	hair loss improved
2	SLE	38/F	nephritis	omeprazole	4	4.1/12.8 (3.1)	4/0	3/3	proteinuria decreased
3	MCTD	27/F	nephritis	omeprazole	6	8.5/21 (2.5)	10/9	5/3	complement level increased
4	DM	43/F	myositis	none	10	1.7/5.5 (3.2)	6/6	3/3	CK decreased
5	SLE	22/F	thrombocytopenia	none	10	3.3/15.9 (4.8)	10/5	3/3	platelet count increased
6	SS	35/F	face annular erythema	omeprazole	6	2.7/6.2 (2.3)	10/9	3/4	rash improved
7	SLE	21/F	nephritis	none	5	3.4/11.2 (3.3)	2/2	4/4	no change
Mean±SD		29.7±8.9			7.3±2.6	4.3±2.4 /13.8±6.9 (3.3±0.8) <sup>†</sup>	8.1±4.1 /5.9±3.5	3.7±1.0 /3.3±0.5	

\* Other medications that can affect TAC concentration or that can be affected by GFJ intake are shown.

<sup>†</sup> p=0.0025 according to Student's *t* test (TAC conc. before vs. after GFJ).

Ab: antibody, CK: creatine kinase, Conc.: concentration, DM: dermatomyositis, Dx.: diagnosis, F: female, GFJ: grapefruit juice, MCTD: mixed connective tissue disease, PSL: prednisolone, Pt.: patient, SS: Sjögren's syndrome, SLE: systemic lupus erythematosus, TAC: tacrolimus, y.o.: years old



**Figure 2.** Time course of tacrolimus blood concentration. Tacrolimus (TAC) blood trough concentrations (Conc) are plotted during grapefruit juice (GFJ) intake in seven patients. TAC and prednisolone (PSL) dosages (mg/day) are also shown in the upper part of each panel.

positive (2+) with massive pathogenic casts, anti-dsDNA Ab was elevated (142 U/mL) and complement was very low (C3 33.6 mg/dL, C4 2.4 mg/dL, CH50 <7.0 U/mL). Renal biopsy revealed lupus nephritis Class IV-S (A/C) + V by the International Society of Nephrology/Renal Pathology Soci-

ety Classification (9), and she was treated with 60 mg/day of PSL and six courses of intravenous cyclophosphamide, which again induced a remission. At the age of 38, when she was taking 4 mg of PSL and 3 mg of TAC daily, proteinuria developed again (203-337 mg/gCre). Urine occult

blood remained negative and sediment was normal. Complement and anti-DNA Ab were also normal. We considered her condition as a minor flare. In addition, she started to drink GFJ because her blood TAC concentration was below the target range, although there was the other treatment option of adding angiotensin II receptor blockers (ARBs), which may decrease proteinuria and delay the progression of chronic nephropathies (10). GFJ increased the TAC blood trough (C12) level from 4.1 to 12.8 ng/mL (3.1-fold) and was effective in decreasing proteinuria, which may be the effect of TAC to stabilize the podocyte cytoskeleton through the inhibition of calcineurin expression (11). After 12 months, she could stop taking PSL and has been in remission for about a year. During the course, there were no severe adverse events.

Patient #3 was a 27-year-old woman with MCTD. When she was 20 years old, she developed fever, Raynaud's phenomenon, malar rash, myositis, myocarditis, pleuritis, fingertip ulceration, proteinuria and hair loss. Her laboratory results showed positivity for anti-U1 ribonucleoprotein (RNP) Ab and anti-dsDNA Ab, elevated creatine kinase (CK) (3,476 IU/L) and low complement (C3 44 mg/dL, C4 3.0 mg/dL, CH50 <5 U/mL). She was treated with a high-dose corticosteroid and all of the disease activity markers normalized. After the corticosteroid was tapered to 10 mg/day, complement decreased and proteinuria sometimes occurred (up to ++) without occult blood. TAC was added and the dose was increased to 5 mg/day, upon which the proteinuria improved but the complement remained low (C3 64.2 mg/dL, C4 10.5 mg/dL, CH50 22 U/mL). We attempted to elevate the TAC concentration by administering GFJ in the expectation of a further clinical improvement and decreasing the corticosteroid dose. After the administration of GFJ, the TAC trough (C12) level elevated from 8.5 to 21 ng/mL (2.5-fold), and complement increased (C3 96.8 mg/dL, C4 15.9 mg/dL, CH50 34 U/mL). During the course, the TAC blood concentration fluctuated even though a physician attempted to adjust TAC by dose monitoring TAC concentration. The patient's PSL dose was decreased from 10 to 9 mg/day, and her TAC dose was decreased from 5 to 3 mg/day. There were no adverse events caused by the GFJ.

Patient #4 was a 43-year-old woman with DM. When she was 38 years old, she was diagnosed with DM based on symptoms of arthritis, Gottron's papules, scabrous fingers (so-called mechanic's hand), elevated CK level (2,201 IU/L), interstitial pneumonia and positivity for anti-Jo-1 Ab. She was started on treatment with 60 mg/day of PSL, and the dose was tapered gradually. When minor flares of the disease occurred at ~6 mg/day of PSL, methotrexate (MTX) and TAC were added with some increase of PSL (up to 10 mg/day). TAC was added because the MTX dose could not be increased due to concerns about liver dysfunction. At age 43, when she was taking 6 mg/day of PSL and 3 mg/day of TAC with MTX, a minor flare occurred again with elevated CK (246 IU/L) and the reappearance of mechanic's hand. Since the TAC blood concentration was too low, GFJ was

administered and TAC trough level (C12) elevated from 1.7 to 5.5 ng/mL (3.2-fold). CK decreased to normal, and her mechanic's hand disappeared gradually. There were no adverse events caused by the GFJ.

Patient #5 was a 22-year-old woman with SLE. When she was 19 years old, she was diagnosed with SLE based on thrombocytopenia (18,000/ $\mu$ L), photosensitivity, malar rash, panniculitis and a high titer of ANA. Initially, she was successfully treated with 60 mg/day of PSL, but the thrombocytopenia was often exacerbated by tapering the corticosteroid. At age 21, TAC was added to increase the platelet count and was partially effective, but PSL could not be reduced to below 10 mg/day due to the possibility of thrombocytopenia recurrence. Since the TAC concentration was low, GFJ was added at age 22, and the TAC trough level (C12) elevated from 3.3 to 15.9 ng/mL (4.8-fold), which was effective for maintaining the platelet count and decreasing the PSL dose (from 10 to 5 mg/day). There were no adverse events caused by the GFJ.

Patient #6 was a 35-year-old woman with SS. When she was 32 years old, she had fever, annular erythema on her face and body, and bilateral parotid swelling, and she was positive for anti-SS-A/Ro Ab and anti-SS-B/La Ab. She was successfully treated with PSL at 25 mg/day, but her erythema relapsed several times after the reduction of PSL to 7-9 mg/day. When she was 34 years old, mizoribine (150 mg/day) was applied, but it was not effective, and TAC was started. Since her TAC dosage remained low at 3 mg/day, she started taking GFJ at the age of 35. The TAC trough (C12) level elevated from 2.7 to 6.2 ng/mL (2.3-fold), which was at least effective for suppressing the relapse. PSL could be reduced to 9 mg/day from 10 mg/day. She wanted to maintain this dosage because of her upcoming marriage. There were no adverse events caused by GFJ.

Patient #7 was a 21-year-old woman with SLE. At age 17, she showed malar rash, arthralgia, nephritis [Class IV-G (A)], leukocytopenia, hypocomplementemia and positivity for ANA 640x (speckled), anti-DNA Ab and anti-Sm Ab. She was initially treated with 55 mg/day of PSL alone, but TAC was added when PSL was reduced to 40 mg/day due to a poor response of urine protein (++) and occult blood (++) . Subsequently, nephritis and other activity markers normalized and PSL was tapered smoothly to 2 mg/day, when complement became lower and anti-DNA Ab elevated. She started to drink GFJ, which elevated the TAC trough level (C12) from 3.4 to 11.2 ng/mL (3.3-fold), and disease activity subsided. There were no severe adverse events caused by the GFJ.

The clinical courses and demographic information of patients #1 to #7 are summarized in Fig. 2 and Table. Overall, after GFJ intake, the patients' mean blood TAC concentration (C12) increased from  $4.3 \pm 2.4$  ng/mL to  $13.8 \pm 6.9$  ng/mL (a  $3.3 \pm 0.8$ -fold increase). In some cases (Pt. #1, 2, 3 and 5), the TAC concentration fluctuated for unknown reasons (Fig. 2). GFJ intake was effective at achieving clinical improvement in most cases, which resulted in reduction of

the dosages of glucocorticoid and TAC (Table and Fig. 2). Two of the seven patients were able to decrease the dose of TAC, four patients (#2, 4, 5 and 7) stayed at the same dose, whereas patient #6 required a greater dose of TAC. The administration of GFJ did not have significant effects on patients' WBC counts ( $p=0.49$ ), Hb levels ( $p=0.094$ ), platelet counts ( $p=0.44$ ), serum creatinine levels ( $p=0.74$ ), alanine aminotransferase levels ( $p=0.51$ ), serum potassium levels ( $p=0.70$ ) or blood sugar levels ( $p=0.39$ ) (data not shown). There were no significant side effects.

## Discussion

This is the first study to describe the efficacy and safety of GFJ intake with TAC for treating connective tissue diseases. Although a report from China has described an increase in TAC bioavailability due to GFJ in liver transplant patients (3), the results could not be applied directly to cases of connective tissue diseases because there might have been some effects from the liver transplant. We also showed that an increase in the TAC blood concentration resulted in a clinical improvement and decreases in PSL and TAC dosages. This is a great benefit for patients, clinically and economically.

The increase in TAC concentration in our cases (~3.3-fold) was comparable to but a little greater than that described in a previous report (mean 2.1-fold) (3). This might have been because the previous reported study involved liver transplant recipients, or the pre-GFJ intake TAC concentrations were higher (mean: 9.0 ng/mL) than those of patients with collagen vascular disease (mean: 4.3 ng/mL).

In some cases, the TAC concentration fluctuated for unknown reasons. There are many other drugs that are metabolized by CYP3A4 (e.g., calcium channel blockers, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and minor tranquilizers) (2), and the concomitant use of such drugs can affect TAC concentration, but none of our patients was taking such drugs, except omeprazole, which we confirmed to have no effect on the TAC blood concentration. There is an additional case report on liver transplant patients that shows that GFJ intake increased the TAC blood concentration by 10-fold (12), but this may have been an exceptional case and the GFJ intake was maintained for only three days.

Dietary contents (e.g., a fat-rich diet) or diarrhea might impair the absorption of TAC (13), which could have affected our patients' TAC concentrations. Furanocoumarin is the main effector of CYP3A4 inhibition in GFJ, and its concentration varies among different breeds of grapefruit, parts of the fruit, and the season and environment in which the crop was grown (2, 14). Some of our patients drank different kinds of GFJ products and skipped a GFJ dose from time to time, which might have influenced the fluctuations in TAC concentration, but 200 mL of GFJ usually contains a sufficient amount of furanocoumarin to inhibit CYP3A4 in the gut completely (2).

Fortunately, no severe side effects, including nephrotoxicity and hyperglycemia, occurred, but in general, GFJ intake can affect the blood concentrations of calcium channel blockers (e.g., nisoldipine, nifedipine and amlodipine), HMG-CoA reductase inhibitors (e.g., simvastatin, atorvastatin and pravastatin) and minor tranquilizers (e.g., triazolam) (2). Therefore, careful monitoring of the side effects of GFJ on other drugs is important during GFJ consumption.

We added GFJ intake to TAC treatment in case the TAC blood concentration was not high enough, and obtained some clinical efficacy. Although the package insert of TAC describes the minimal TAC target trough level as 5 ng/mL and TAC dose dependence in terms of efficacy has been suggested in some diseases and organ transplantation, the response to TAC varies from patient to patient and further investigation of the relationship between efficacy and the TAC blood concentration should be performed. In addition, we have to be careful that the blood TAC trough level does not exceed 20 ng/mL, which is indicated in the package insert of the drug for safety reasons.

We should also consider the maintenance therapy after remission induction. Mizoribin may be an option in Japan because it costs one-third of the price of TAC. In addition, we should recognize the potential risk of flare by the incidental cessation of GFJ. From an economic point of view, GFJ provides a great cost benefit. It may reduce the costs for TAC by elevating the TAC blood concentration. Taking the findings together, when the TAC blood concentration is not high enough to induce remission and it is considered that the risk of adding GFJ is not so high, we propose that TAC with GFJ may be a good option for a period of remission induction. For maintenance therapy, other medications including TAC without GFJ should be considered. Our data (patients #1 and #3) also suggested that the clinical efficacy of TAC is dose-dependent, as reported previously (5, 6). Therefore, when the clinical efficacy is not enough with TAC treatment, it may be worth trying to increase the dose of TAC even when the TAC trough level is in the target range ( $>5$  ng/mL). However, we included only seven patients here, which is a limitation of our study.

In summary, the GFJ intake induced an approximately three fold increase in the TAC blood concentration in patients with connective tissue disease, which resulted in a clinical improvement in most cases without causing any adverse events. Moreover, the administration of GFJ can reduce the dosages of glucocorticoids and/or TAC. GFJ could be a useful treatment option for patients who exhibit a low blood TAC concentration. However, special attention should be paid to the adverse effects of GFJ consumption on TAC and other concomitant medications.

### Author's disclosure of potential Conflicts of Interest (COI).

Takao Fujii: Employment, Mitsubishi Tanabe Pharma, Bristol-Myers, Chugai Pharmaceutical and Eisai; Research Funding, Astellas Pharma. Motomu Hashimoto: Employment, Mitsubishi Tanabe Pharma, Bristol-Myers, Chugai Pharmaceutical and Eisai;

Research Funding, Astellas Pharma. Koichiro Ohmura: Research Funding, Astellas Pharma. Naoichiro Yukawa: Research Funding, Astellas Pharma. Hajime Yoshifuji: Research Funding, Astellas Pharma. Tsuneyo Mimori: Research Funding, Astellas Pharma.

## References

1. Lampen A, Christians A, Gonschior AK, et al. Metabolism of the macrolide immunosuppressant, tacrolimus, by the pig gut mucosa in the Ussing chamber. *Br J Pharmacol* **117**: 1730-1734, 1996.
2. Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interactions. *Br J Clin Pharmacol* **46**: 101-110, 1998.
3. Liu C, Shang YF, Zhang XF, et al. Co-administration of grapefruit juice increases bioavailability of tacrolimus in liver transplant patients: a prospective study. *Eur J Clin Pharmacol* **65**: 881-885, 2009.
4. Wilkes MR, Sereika SM, Fertig N, et al. Treatment of antisynthetase-associated interstitial lung disease with tacrolimus. *Arthritis Rheum* **52**: 2439-2446, 2005.
5. Gerich ME, Pardi DS, Bruining DH, et al. Tacrolimus salvage in anti-tumor necrosis factor antibody treatment-refractory Crohn's disease. *Inflamm Bowel Dis* **19**: 1107-1111, 2013.
6. Chen YP, Wang W, Wang ZK, Wei DN, Zhang J. The clinical efficacy and safety of tacrolimus in patients with myasthenia gravis. *Zhonghua Nei Ke Za Zhi* **52**: 567-569, 2013 (in Chinese, Abstract in English).
7. Lundahl J, Regårdh CG, Edgar B, Johnsson G. Relationship between time of intake of grapefruit juice and its effect on pharmacokinetics and pharmacodynamics of felodipine in healthy subjects. *Eur J Clin Pharmacol* **49**: 61-67, 1995.
8. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* **40**: 1725, 1997.
9. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* **15**: 241-250, 2004.
10. Tylicki L, Lizakowski S, Rutkowski B. Renin-angiotensin-aldosterone system blockade for nephroprotection: current evidence and future directions. *J Nephrol* **25**: 900-910, 2012.
11. Zhang Q, Shi SF, Zhu L, et al. Tacrolimus improves the proteinuria remission in patients with refractory IgA nephropathy. *Am J Nephrol* **35**: 312-320, 2012.
12. Fukatsu S, Fukudo M, Masuda S, et al. Delayed effect of grapefruit juice on pharmacokinetics and pharmacodynamics of tacrolimus in a living-donor liver transplant recipient. *Drug Metab Pharmacokinet* **21**: 122-125, 2006.
13. Bekersky I, Dressler D, Mekki QA. Effect of low- and high-fat meals on tacrolimus absorption following 5 mg single oral doses to healthy human subjects. *J Clin Pharmacol* **41**: 176-182, 2001.
14. De Castro WV, Mertens-Talcott S, Rubner A, Butterweck V, Derendorf H. Variation of flavonoids and furanocoumarins in grapefruit juices: a potential source of variability in grapefruit juice-drug interaction studies. *J Agric Food Chem* **54**: 249-255, 2006.