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Rapid Induction Therapy with Oral Tacrolimus in Elderly Patients with Refractory Ulcerative Colitis Can Easily Lead to Elevated Tacrolimus Concentrations in Blood: A Report of 5 Cases

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Case series

Patient: —
Final Diagnosis: **Ulcerative colitis**
Symptoms: **Diarrhea • hematochezia**
Medication: **Tacrolimus**
Clinical Procedure: —
Specialty: **Gastroenterology and Hepatology**

Objective: **Unusual setting of medical care**

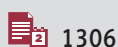
Background: Tacrolimus is reportedly effective for the treatment of refractory ulcerative colitis (UC). At our hospital, there has been an increase in the number of patients, including elderly patients, with refractory UC treated with tacrolimus. Here, we review the data from 5 patients with elderly-onset UC treated with tacrolimus as remission induction therapy.

Case Report: The subjects were 5 patients ≥ 65 years of age with refractory UC who had received oral tacrolimus as remission induction therapy between 2009 and 2014 (3 men and 2 women; median age at onset, 75 years). At the start of the tacrolimus treatment, the median duration of disease was 3 months, and the type of UC was total colitis in 4 cases, and left-sided colitis in 1 case. The drugs used concomitantly at the start of tacrolimus treatment were mesalazine (5 cases) and an immunomodulator drug (1 case). Standard induction therapy (0.05 mg/kg/day) was used in 2 patients and rapid induction therapy (0.1 mg/kg/day) was used in the remaining 3 patients. One week after the start of treatment, the blood trough concentrations of tacrolimus were over the target level of 15 mg/mL in 4 patients. The clinical activity index values on day 0 and day 14 were 10.6 ± 2.1 and 7.6 ± 3.4 , respectively. The ulcerative colitis endoscopic index of severity in the remaining 3 patients, after excluding the 2 patients who required colectomy within 14 days after the start of tacrolimus therapy, was 7.3 ± 1.0 before the start of the tacrolimus treatment, improving to 4.5 ± 0.5 on day 14. Subsequently, 1 of these 3 patients was also judged to need surgery due to symptom exacerbation, while complete remission was maintained in the other 2 patients.

Conclusions: In elderly-onset refractory UC patients, tacrolimus appears to be effective as remission induction therapy. However, since tacrolimus concentrations in the blood can rise easily in elderly patients, frequent monitoring of the drug concentrations and dosage adjustments are necessary.

MeSH Keywords: **Aged • Colitis, Ulcerative • Tacrolimus**

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/903339>



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Background

Tacrolimus is a strong immunomodulator drug; it is a calcineurin inhibitor that suppresses the production of TNF- α and IFN- γ by decreasing the synthesis of the T cell-derived cytokine interleukin-2. In Japan, tacrolimus was approved as a drug for the treatment of refractory ulcerative colitis (UC) in July 2009. Tacrolimus is known as a rapidly acting and reliable immunosuppressive agent, and according to both domestic and international studies, its efficacy rate in patients with refractory UC is about 70% [1–3]. However, the drug has a narrow therapeutic range and shows larger intra- and intersubject variations in its pharmacokinetics, and persistent elevation of the blood tacrolimus levels can trigger renal dysfunction and lead to other serious adverse effects. For these reasons, individualized dosage adjustments by therapeutic drug monitoring are essential in patients receiving tacrolimus. Tacrolimus concentrations in the blood easily rise due to changes in body composition with advancing age [4]. In this study, we examined the efficacy and safety of tacrolimus in elderly patients with refractory UC.

Case Report

Patient characteristics

The subjects were 3 men and 2 women, with a median age at onset of UC of 75 years (range, 69–76 years). The median duration of the disease was 3 months (range, 0–47 months). Tacrolimus was administered as rapid induction therapy (0.1 mg/kg/day) in 3 patients (60%) and as standard induction therapy (0.05 mg/kg/day, according to the dosage instructions in the package insert) in the remaining 2 patients (40%).

In terms of the extent of involvement, 4 patients were classified as having total colitis and 1 as having left-sided colitis. Concomitant mesalazine and a steroid were used in all 5 patients; 1 was steroid-dependent and 4 were steroid-resistant. An immunomodulatory drug was also used concomitantly in 1 patient. In previous treatments, 3 patients had undergone cytopheresis therapy and 1 had received infliximab (Table 1).

Administration and dose adjustment

Blood tacrolimus concentrations were measured in the hospital using a Siemens EMIT® 2000 device. Dose adjustments were made on the days after blood trough levels were measured. Tacrolimus concentrations in the blood were adjusted to obtain a target level of 10–15 ng/mL from the start of tacrolimus administration until the second week, and a target level of 5–10 ng/mL after the second week. At the first blood sampling, 2 patients had a tacrolimus blood trough level >15 ng/mL, and

Table 1. Clinical characteristics.

| | |
|---|------------|
| Sex, male/female | 3/2 |
| Age at onset, years | 75 (69–76) |
| Age at entry, years | 75 (71–80) |
| Duration of disease, months | 3 (0–47) |
| Extent at diagnosis | |
| Total colitis | 4 |
| Left-sided colitis | 1 |
| Initial dose of tacrolimus | |
| Rapid induction therapy (0.1 mg/kg/day) | 3 |
| Standard induction therapy (0.05 mg/kg/day) | 2 |
| Pretreatment | |
| Infliximab | 1 |
| Cytopheresis | 3 |
| Combined treatment | |
| Mesalazine | 5 |
| Azathioprine | 1 |
| Steroid | 5 |
| Steroid dependent/resistant | 1/4 |

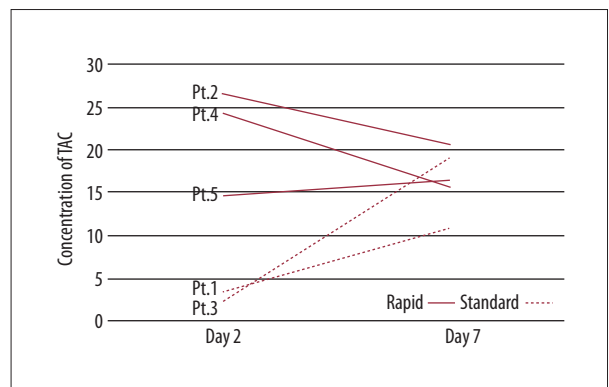


Figure 1. Concentration of tacrolimus. All 3 patients who received rapid induction therapy showed tacrolimus blood trough concentrations >15 ng/mL in the blood samples collected a week after the start of the tacrolimus therapy.

at the blood sampling performed a week later 4 patients had a blood trough level >15 ng/mL. Both of the 2 patients with tacrolimus blood trough levels over 15 ng/mL at the first blood sampling received rapid induction therapy. All 3 patients who received rapid induction therapy showed tacrolimus blood trough concentrations >15 ng/mL in blood samples collected a week after the start of tacrolimus therapy (Figure 1).

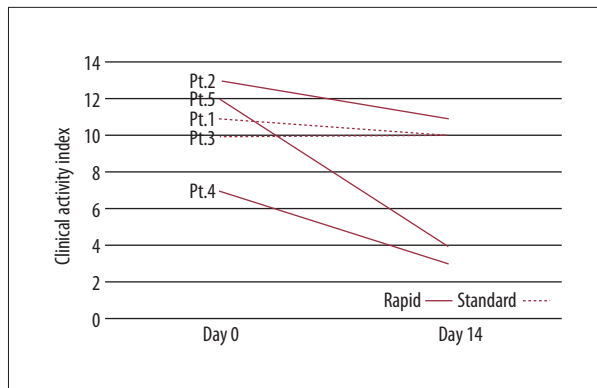


Figure 2. CAI score. The Lichtiger's clinical activity index values (CAI; score 0–21) on day 0 and day 14 were 10.6 ± 2.1 and 7.6 ± 3.4 , respectively, the value at 2 weeks after the start of the tacrolimus treatment (i.e., on day 14) being significantly lower; all of the patients, except for 1 of the 2 patients who received standard induction therapy, showed a decrease in CAI.

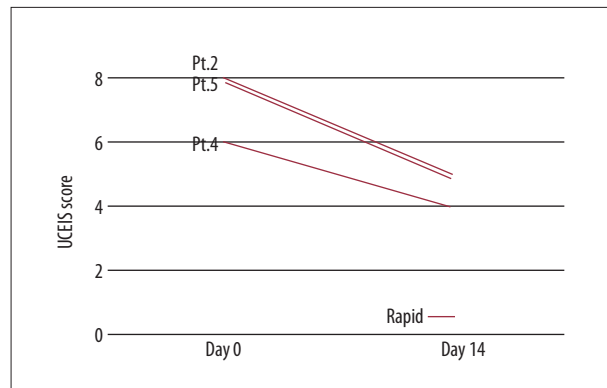


Figure 3. UCEIS score. With the exclusion of 2 patients who required colectomy within 14 days after the start of tacrolimus therapy, the ulcerative colitis endoscopic index of severity (UCEIS; score 0–8) in the remaining 3 patients improved from 7.3 ± 1.0 before the start of treatment to 4.5 ± 0.5 on day 14 after the start of the tacrolimus induction therapy.

Table 2. Clinical characteristics and outcomes.

| Pt. | Sex | Age | Duration of disease (months) | Extent at diagnosis | Steroid dependent/resistance | Pretreatment | Combined treatment (mg/day) | Induction of TAC | Outcome | Serum creatinine (mg/dL) | | Adverse effects | Complication |
|-----|-----|-----|------------------------------|---------------------|------------------------------|--------------|------------------------------|------------------|------------------|--------------------------|--------|---------------------------|---------------|
| | | | | | | | | | | Day 0 | Day 14 | | |
| 1 | M | 80 | 47 | Left | Resistance | CAP, IFX, | 5ASA(4000), PSL(60), AZA(50) | Standard | Surgery (day 11) | 0.56 | 0.35 | – | CMV infection |
| 2 | F | 75 | 0 | Total | Resistance | – | 5ASA(3600), PSL(60) | Rapid | Surgery (day 19) | 0.47 | 0.45 | – | – |
| 3 | M | 69 | 3 | Total | Resistance | CAP | 5ASA(4000), PSL(60) | Standard | Surgery (day 10) | 0.53 | 0.63 | – | – |
| 4 | F | 76 | 1 | Total | Dependent | CAP | 5ASA(4000), PSL(40) | Rapid | Remission | 0.51 | 0.47 | – | – |
| 5 | M | 71 | 1 | Total | Resistance | – | 5ASA(3600), PSL(50) | Rapid | Remission | 0.70 | 0.96 | Elevated serum creatinine | – |

Pt. – patient; 5ASA – mesalazine; AZA – azathioprine; PSL – prednisolone; CAP – cytapheresis; IFX – infliximab; TAC – tacrolimus; CMV – cytomegalovirus.

Clinical response

There were 3 cases (60%) in which the tacrolimus administration could be continued until day 14. The Lichtiger's clinical activity index values (CAI) on day 0 and day 14 were 10.6 ± 2.1 and 7.6 ± 3.4 , respectively, and the value at 2 weeks after the start of the tacrolimus treatment (i.e., on day 14) were significantly lower; all of the patients, except for 1 of the 2 patients who received standard induction therapy, showed a decreased CAI (Figure 2). Tacrolimus administration was discontinued in 2 patients who showed no clinical improvement; both of these patients underwent total colectomy (one on day 10 and the other on day 11). With the exclusion of these 2 patients in whom

the treatment was switched to surgery during the course of treatment, the ulcerative colitis endoscopic index of severity (UCEIS) in the remaining 3 patients improved from 7.3 ± 1.0 before the start of treatment to 4.5 ± 0.5 on day 14 after the start of the tacrolimus induction therapy (Figure 3). However, one of these latter 3 patients developed symptomatic exacerbation at a later date, and underwent total colectomy on day 19 (Table 2). In 2 patients who showed clinical improvement, Patient 4 died due to other causes after 1 month. Patient 5 showed elevated serum creatinine level after 5 months, and then stopped tacrolimus therapy. He has maintained the improved status for 36 months.

Adverse effects

In terms of the complications encountered after the start of tacrolimus administration, 1 patient developed cytomegalovirus (CMV) infection and 1 patient showed mild elevation of serum creatinine level (0.7→1.2 mg/dL, day 140) (Table 2).

Discussion

The incidence of UC has shown an increasing trend in recent years, and associated with this trend, the number of elderly patients with UC is also rising. In the United States, 10–15% of all UC patients are age 60 years or older, of which 65% are 60–69 years old, 25% are 70–79 years old, and 10% are 80–89 years old [5,6]. In Japan, a comparison between 1994 and 2012 shows that the number of UC patients aged 10–29 years has increased by 1.3-fold, whereas the number of UC patients aged 60 years or older has increased by 2.2-fold [7].

In general, elderly patients often have concurrent diseases, as well as decreased organ function reserve. The postoperative length of hospital stay is longer in elderly UC patients [8] and their prognosis after emergency surgery is extremely poor [9,10]. Ikeuchi et al. reported that the perioperative mortality rate following emergency surgery was 2.1% among juvenile patients, and was markedly higher (24.4%; 11/45) among elderly patients over 60 years of age [11]. Therefore, it is especially important to avoid emergency surgery in elderly UC patients. Ogata et al. reported tacrolimus had a 62% efficacy rate in patients with steroid-refractory UC [1]. Furthermore, with the use of rapid induction therapy, a higher remission rate and a higher efficacy rate against recurrent UC can be obtained [12]. In our study, tacrolimus was found to be efficacious in 2 elderly patients with refractory UC (40%) who received rapid induction therapy with oral tacrolimus. Surgery was avoided in these 2 patients, which indicates that tacrolimus is an effective agent for rapid induction therapy in elderly UC patients.

However, the safety of tacrolimus in elderly patients has been questioned. The drug has a narrow therapeutic range and shows

large intra- and intersubject variations in its pharmacokinetics, and persistent elevation of tacrolimus concentrations in the blood can trigger renal dysfunction and lead to other serious adverse effects. Therefore, individualized dosage adjustments by therapeutic drug monitoring are essential in patients receiving treatment with tacrolimus. The incidence of adverse effects increases when the blood trough levels exceed 10 ng/mL [4]; therefore, during the initial stage of tacrolimus administration with a target blood concentration of ≥ 10 ng/mL, caution must be exercised against excessive elevation of tacrolimus concentrations in the blood and the occurrence of adverse effects. In this study, the tacrolimus trough concentrations in the blood on day 7 were over the upper limit of the therapeutic range of 15 ng/mL in 4 of the 5 patients, indicating that the blood tacrolimus concentrations tend to rise easily in elderly patients.

A positive correlation has been reported between blood tacrolimus trough concentrations and serum creatinine levels [4]. In our study, only 1 patient showed a minor elevation of serum creatinine concentration at 3 months after the start of treatment, which resolved immediately upon discontinuation of tacrolimus. As compared to juvenile patients, elderly patients are more likely to experience adverse effects of drugs; therefore, when treating elderly patients with tacrolimus, it is essential to ensure strict monitoring of the blood trough levels and frequent testing of serum creatinine levels [13].

Conclusions

For remission induction therapy in elderly patients with refractory UC, tacrolimus administered by the rapid saturation method can be effective. However, because tacrolimus concentrations in the blood easily rise in elderly patients, very careful dose adjustments with frequent monitoring of blood concentrations is necessary.

Conflicts of interest

The authors declare that they have no conflicts of interest to disclose.

References:

1. Ogata H, Matui T, Nakamura M et al: A randomized dose finding study of oral tacrolimus(FK506)therapy in refractory ulcerative colitis. *Gut*, 2006; 55: 1255–62
2. Schmidt KJ, Herrlinger KR, Emmrich J et al: Short-term efficacy of tacrolimus in steroid-refractory ulcerative colitis – experience in 130 patients. *Aliment Pharmacol Ther*, 2013; 37: 129–36
3. Miyoshi J, Matsuoka K, Inoue N et al: Mucosal healing with oral tacrolimus is associated with favorable medium- and long-term prognosis in steroid-refractory/dependent ulcerative colitis patients. *J Crohns Colitis*, 2013; 7: 609–14
4. Opelz G: Effect of immunosuppressive therapy on graft half-life projections. The collaborative Transplant Study. *Transplant Proc*, 1999; 31: 31–33
5. Hussain SW, Pardi DS: Inflammatory bowel disease in the elderly. *Drugs Aging*, 2010; 27: 617–24
6. Loftus EV Jr, Silverstein MD, Sandborn WJ et al: Ulcerative colitis in Olmsted County, Minnesota, 1940–1993: Incidence, prevalence, and survival. *Gut*, 2000; 46: 336–43
7. Ulcerative colitis, diagnostic criteria for Crohn's disease, treatment plan, Health and Labour, Sciences research grants for research on intractable diseases from the Ministry of Health, Labour and Welfare: "Research on Refractory Inflammatory Bowel Disease" (Research Team led by Watanabe), Annual Report, 2013, 2014

8. Ananthakrishnan AN, McGinley EL, Binion DG: Inflammatory bowel disease in the elderly is associated with worse outcomes: A national study of hospitalizations. *Inflamm Bowel Dis*, 2009; 15: 182–89
9. Ikeuchi H, Uchino M, Matsuoka H et al: Prognosis following emergency surgery for ulcerative colitis in elderly patients. *Surg Today*, 2014; 44: 39–43
10. Almog G, Sachar DB, Bodian CA, Greenstein AJ: Surgery for ulcerative colitis in elderly persons: Changes in indications for surgery and outcome over time. *Arch Surg*, 2001; 136: 1396–400
11. Ikeuchi H, Uchino M: Front-line surgical therapy for ulcerative colitis. *Nihon Shokakibyo Gakkai Zasshi*, 2016; 113: 424–49
12. Zimmerman J, Gavish D, Rachmilewitz D: Early and late onset ulcerative colitis: Distinct clinical features. *J Clin Gastroenterol*, 1985; 7: 492–98
13. Staatz CE, Tett SE: Pharmacokinetic considerations relating to tacrolimus dosing in the elderly. *Drugs Aging*, 2005; 22: 541–57