Chapter 10

Oral Tacrolimus in Patients with Ulcerative Colitis

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Additional information is available at the end of the chapter

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Abstract

Tacrolimus is a macrolide immunosuppressant that is structurally similar to rapamycin and has been found to have potent immunosuppressive properties, showing 10- to 100-fold higher potency for inhibiting lymphocyte activation than cyclosporine A (CsA). Because less variability in absorption and serum levels is observed among patients treated with tacrolimus compared with those who receive oral CsA, tacrolimus has been suggested to be more easily and safely administered to patients with refractory ulcerative colitis (UC) than CsA. However, because oral tacrolimus has a slower onset of action than intravenous CsA and food intake is known to reduce tacrolimus serum trough levels due to its low absorption rate, the proper method for administration of oral tacrolimus has not been determined. Moreover, the long-term effects of oral tacrolimus also remain unclear. In this chapter, key issues regarding the use of oral tacrolimus in patients with UC are reviewed.

Keywords: ulcerative colitis, refractory disease, accelerated step-up, cyclosporine A, top-down therapy

1. Introduction

Tacrolimus, also known as the macrolide immunosuppressant FK506 (formerly FR900506), is a powerful and selective anti-T-lymphocyte agent discovered in 1984. The first letter "T" represents Tsukuba, Japan, where tacrolimus was first identified. Because tacrolimus is a macrolide, the letters "ACROL" are included after the initial T. Finally, the letters "IMUS" represent the immunosuppressive effects of the drug [1]. Tacrolimus was isolated from the fermentation broth of the fungus *Streptomyces tsukubaensis*, which was isolated from a soil sample in Tsukuba, Ibaraki Prefecture, Japan [2].

The molecular structure of tacrolimus is completely different from that of cyclosporine A (CsA). However, their immunosuppressive properties are remarkably similar [2–5]. Initial reports showed that tacrolimus acts as an immunosuppressant by inhibiting interleukin 2 (IL-2) production and blocking the response of mixed lymphocyte culture at concentrations 100 times lower than that of CsA [5]. Early multicenter trials were conducted to evaluate the safety and efficacy of tacrolimus in patients who underwent liver transplantation; these trials showed that the effects of tacrolimus were equivalent to those of CsA-based immunosuppressive regimens [1, 6, 7]. Thus, clinically, tacrolimus was initially developed as a drug for the prevention and/or treatment of graft rejection in organ transplantation patients [8, 9].

Regarding the inflammatory bowel disease (IBD), tacrolimus has been used to treat fistulizing Crohn's disease (CD) and refractory ulcerative colitis (UC) [10]. Because topical administration of tacrolimus can result in high concentrations in the tissue and can effectively regulate the local immune response, topical tacrolimus has also been used to treat refractory distal colitis and extraintestinal UC, such as pyoderma gangrenosum [11–13]. Moreover, tacrolimus has a rapid onset of action and is highly effective in patients with refractory UC; therefore, tacrolimus is approved as an alternative treatment option for refractory UC under the national health insurance system in Japan [14]. The physicochemical properties of tacrolimus result in large variations in oral absorption and metabolism for clearance from the body [9]. Moreover, the therapeutic window of tacrolimus is narrow. Thus, therapeutic drug monitoring is necessary.

2. Clinical pharmacokinetics

Tacrolimus is highly lipophilic and is excreted from the body after undergoing extensive metabolism [9]. Food intake is known to reduce serum level of tacrolimus resulting from its low absorption rate [14]. After absorption, tacrolimus is metabolized by the liver and small intestinal microsomes containing cytochrome P-450 3A4 and 3A5, which are responsible for the biotransformation of tacrolimus [9]. After being metabolized, tacrolimus is mainly excreted in the feces and bile as conjugates. Using ^{14}C-labeled tacrolimus, Iwasaki et al. reported that urinary excretion accounts for less than 3% of the total dose administered and that less than 0.5% of the unaltered drug is detectable in feces and urine in health human subjects [15]. Because ketoconazole, fluconazole, erythromycin, diltiazem, cimetidine, methylprednisolone, and CsA are also metabolized by cytochrome P-450, tacrolimus should be used with caution in patients receiving these drugs [16]. On the other hand, coadministration of rifampicin significantly increases tacrolimus clearance; indeed, rifampicin treatment causes decreased levels of tacrolimus in the blood [17]. Because genetic polymorphisms are known to exist in cytochrome P-450 3A4 and 3A5, the determination of cytochrome P-450 3A genotypes in patients with refractory UC may provide useful information for selecting the optimal dosage of tacrolimus [9]. In patients with UC, Hirai et al. analyzed the association of cytochrome P-450 3A5 genetic polymorphisms with tacrolimus pharmacokinetics and efficacy in Japanese patients with UC. Their results showed that the trough level of tacrolimus is significantly higher in cytochrome P-450 3A5-nonexpressing (*3*3) patients than in cytochrome P-450 3A5-expressing (*1*3 and *1*1) patients and that the short-term remission rate is significantly

different among these patient groups [18]. Additionally, lack of food intake and silencing of cytochrome P-450 3A5 are associated with achievement of optimal trough levels on multivariate analysis. The proton pump inhibitor lansoprazole is also metabolized by cytochrome P-450 3A4 and elevates the blood concentration of tacrolimus. Therefore, when lansoprazole is coadministered with tacrolimus, repeated therapeutic drug monitoring is needed to prevent the incidence of adverse events [19]. Because tacrolimus is also a substrate of P-glycoprotein, polymorphisms in P-glycoprotein may also determine tacrolimus response in patients with UC [20]. Elevated intestinal P-glycoprotein decreases tacrolimus absorption, thereby leading to decreased blood concentrations and decreased efficacy in patients treated with tacrolimus [21].

3. Immunosuppressive effects

Calcineurin inhibitors, such as CsA and tacrolimus, block the production of IL-2 and the activation of T lymphocytes [22]. CsA and tacrolimus belong to the family of immunophilin-binding drugs, and the drug-immunophilin complex inhibits calcineurin, preventing dephosphorylation of nuclear factor of activated T cells (NFAT) and resulting in decreased expression of cytokines, such as IL-2 [5, 8, 23, 24] (**Figure 1**). Although their immunosuppressive properties are similar, tacrolimus has been found to show 10- to 100-fold more potent inhibition of lymphocyte activation than CsA [5]. Additionally, tacrolimus acts on other pathways, including blockade of cytokine receptor expression and cytokine effects on target cells [25]. Interestingly, CsA, but not tacrolimus, suppresses nitric oxidase production, contributing to the side effects of hypertension and nephrotoxicity and enabling long-term use of CsA [26]. On the other hand, tacrolimus is known to be associated with many adverse effects, including hypertension and renal dysfunction [27].

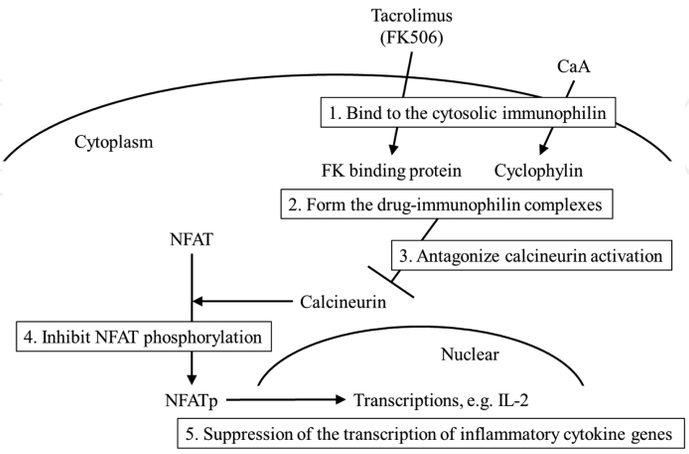

Figure 1. Calcineurin inhibitors in T cells. CsA and tacrolimus bind to immunophilin. The drug-immunophilin complexes inhibit calcineurin, preventing dephosphorylation of NFAT and resulting in decrease expression of cytokines, such as IL-2.

4. Tacrolimus in the treatment of refractory UC

UC is an idiopathic IBD characterized by a chronic relapsing/intermittent clinical course. Aminosalicylates are typically used as first-line treatment for patients with UC, while steroids are usually considered a second-line treatment and are used to induce remission when remission cannot be achieved with aminosalicylates [28]. Because steroids have a rapid onset of action and are highly effective, they are reserved for treatment in patients with severe UC who fail to respond to primary therapy. However, these agents are associated with considerable systemic adverse effects [29]. Nevertheless, approximately 20 % of patients with UC have chronically active disease that requires several courses of steroids [30]. As a result, many patients with refractory UC (e.g., steroid-refractory or steroid-dependent UC) experience severe complications associated with steroid treatment before stable remission can be achieved, and many of these patients ultimately require colectomy [30, 31].

Oral tacrolimus began to be used as an alternative treatment option for refractory UC in July 2009 under the national health insurance system in Japan [14]. Because tacrolimus does not depend on mucosal integrity for absorption, less variability in absorption and serum level is observed among patients treated with tacrolimus compared with those who received oral CsA [32]. Thus, oral tacrolimus has been suggested to be more easily and safely administered to patients with refractory UC than CsA. A study published by Ogata et al. was the first randomized controlled trial to demonstrate the efficacy of oral tacrolimus in refractory UC [33]. Importantly, they also confirmed that tacrolimus showed efficacy in a trough concentration-dependent manner. In their study, patients with refractory UC were randomly assigned to a high trough concentration (10–15 ng/mL) group, low trough concentration (5–10 ng/mL) group, or placebo group. A total of 68.4% of patients in the high trough concentration group improved within 2 weeks after administration of tacrolimus, whereas only 38.1% of patients in the low trough concentration group experienced disease improvement. To date, several uncontrolled and placebo-controlled studies have demonstrated that tacrolimus can induce remission in both adults and children, and these reports suggested that tacrolimus had a dramatic concentration-dependent effect, with the optimal target range appearing to be 10–15 ng/mL with a relatively short period of efficacy [34–38].

Nonetheless, we have still occasionally experienced patients who did not demonstrate improvement even though the appropriate trough level was achieved with oral tacrolimus using standard dosing (an initial dose of 0.025 mg/kg daily is approved under the national health insurance in Japan). We previously examined the short-term efficacy of tacrolimus in refractory UC and found that the clinical response rate at 4 weeks after the initiation of tacrolimus treatment correlated with the mean trough level at 8–21 days after treatment and that the primitive trough level was increased within 5 days after administration, which was important for obtaining the appropriate trough level at 8 days after tacrolimus administration [39]. Even when the starting dose of tacrolimus was set to 0.1 mg/kg/day to obtain early achievement of the appropriate trough level, more than 7 days was required to achieve the target tacrolimus blood concentration because food intake is known to reduce serum levels of tacrolimus by slowing the absorption rate [40]. Therefore, we conducted a prospective,

multicenter, observational study to evaluate the efficacy and safety of rapid induction therapy with oral tacrolimus, starting at 0.1 mg/kg/day without a meal, in patients with steroid-refractory UC [41]. The dose was adjusted to maintain trough levels of 10–15 ng/mL for the first 2 weeks. Beginning at 2 weeks after the initiation of tacrolimus therapy, the tacrolimus trough concentration was gradually maintained at a lower level of 5–10 ng/mL. From this analysis, 0.15–0.16 mg/kg/day oral tacrolimus was needed to achieve the appropriate trough level; the mean trough level reached a peak on day 2, and 93.5% of patients could maintain high trough levels for the first 7 days of treatment. After 2 weeks, 73.1% of patients with refractory UC experienced clinical responses, and 75.4% of patients achieved clinical remission at 4 weeks after tacrolimus initiation.

Regarding the long-term efficacy in patients with refractory UC, Yamamoto et al. investigated the efficacy of tacrolimus as maintenance therapy for patients with refractory UC and reported that the cumulative colectomy-free survival rate was 62% at 65 months. They also reported that the colectomy-free survival rate was significantly higher in patients who responded to tacrolimus within 30 days than in those who did not and suggested that tacrolimus should be administered to achieve a low trough level (5–10 ng/mL) as maintenance therapy in patients with UC [42].

Currently, antitumor necrosis factor alpha (anti-TNFα) antibodies, such as infliximab and adalimumab, are also used as a treatment option for patients with refractory UC [43, 44]. Because there is no need to adjust the drug concentration when treating patients with these biologics and because they can be used for both induction and maintenance of remission in UC, such treatments have been widely used in the case of refractory UC. However, to date, there are very few reports comparing the efficacy of tacrolimus and anti-TNFα antibodies for refractory UC. Recently, Yamamoto et al. retrospectively compared the short-term safety and efficacy of tacrolimus versus anti-TNFα antibodies (infliximab or adalimumab) for moderate-to-severe active UC and reported that the response rate was higher in patients treated with tacrolimus, although no significant difference was observed [45].

Patients with refractory UC who failed second-line therapies with cyclosporine, tacrolimus, or infliximab have limited medical options to achieve remission and avoid colectomy. To date, several studies have evaluated the efficacy of infliximab as rescue therapy in patients who were refractory to tacrolimus and reported that the short-term response rates ranged from 25.0 to 75.0% [46–49]. Administration of infliximab in patients with refractory UC who did not respond to tacrolimus may be useful for induction remission and could help to avoid the need for colectomy. However, it is still unclear which sequential therapeutic strategies (tacrolimus switching to infliximab or infliximab switching to tacrolimus) should be used.

5. Top-down or accelerated step-up therapy with oral tacrolimus

In patients with CD, top-down therapy involves early introduction of biologics and/or immunomodulators in patients with newly diagnosed disease. With regard to UC, top-down therapy may not be suitable for all patients. Recently, studies have examined the use of

"accelerated step-up therapy," which involves a "step-up" aggressive treatment algorithm that preserves the concept of matching severity to treatment potency yet recognizes the potential benefits of the earlier use of biologics and/or immunomodulators [50]. For many patients with UC, such an accelerated step-up approach may be the best strategy [51]. Because differences in the onset of action of various agents are thought to influence the achievement and maintenance of disease remission, early intervention with tacrolimus may improve the long-term prognosis of patients with UC, similar to the effects of infliximab in patients with CD. Therefore, we evaluated the efficacy of oral tacrolimus in patients with moderate-to-severe UC not receiving concomitant steroid therapy. The results showed that early intervention with tacrolimus was highly effective at inducing remission (72.7% at 4 weeks and 90.0% at 12 weeks) and maintenance remission (72.5% at a mean follow-up of 10.4 months) [52]. Although additional studies are required to establish the efficacy and safety of oral tacrolimus therapy in patients with UC, oral tacrolimus may represent a top-down or accelerated step-up treatment option for patients with moderate-to-severe UC (**Figure 2**).

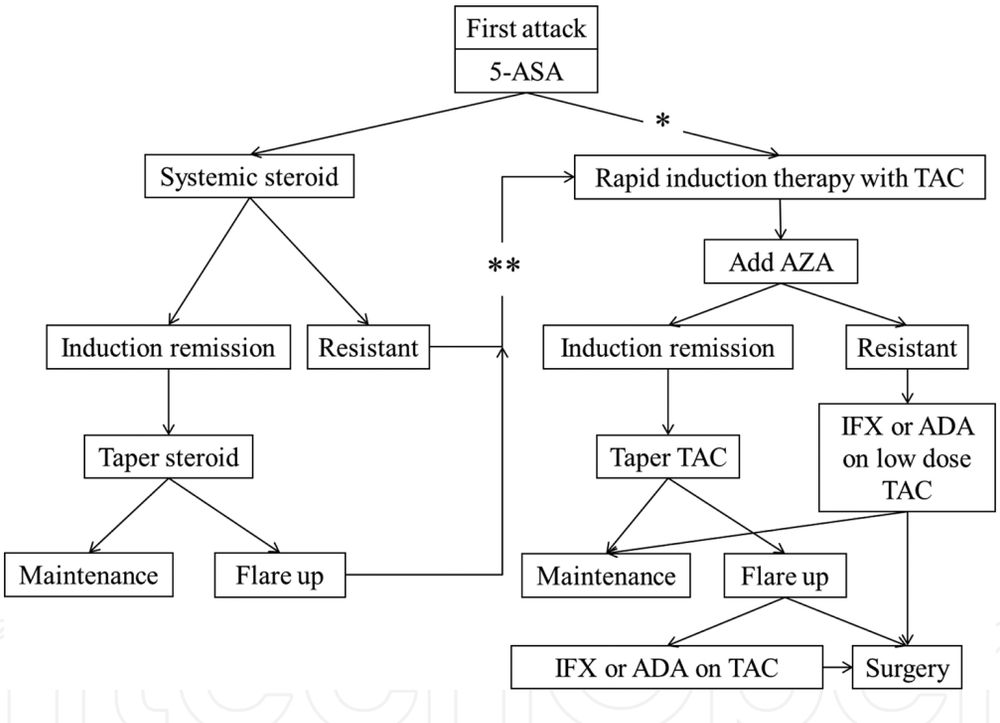

Figure 2. Treatment options for patients with moderate/severe UC. Because prompt intervention with potent medical therapy is crucial in the management of severe UC, top-down therapy with tacrolimus may be useful for avoiding steroid dependency and improving prognosis (*). Recognizing the potential benefits of the earlier use of immunomodulators/biologics and accelerating the introduction of these drugs are defined as "accelerated step-up therapy," thereby avoiding therapies that have minimal efficacy (**).

6. Impact of tacrolimus on cytomegalovirus (CMV) colitis

CMV infection has been reported to be a cause of refractory UC. Because the specific endoscopic features of refractory UC associated with CMV infection have not been clearly descri-

bed, diagnosing CMV infection at an early stage is difficult [53]. Although quantitative real-time polymerase chain reaction (qPCR) for detecting CMV infection in colonic mucosa has been shown to exhibit high sensitivity, the appropriate therapeutic approach for patients with UC having CMV-DNA-positive colonic mucosa remains unclear. In a randomized trial comparing tacrolimus and CsA for prevention of liver allograft rejection, the incidence of CMV infection was found to be significantly lower in patients receiving tacrolimus (15.7 and 25.0% for tacrolimus and CsA, respectively) [7]. Alessiani et al. also reported that tacrolimus treatment in liver transplant recipients resulted in a significantly lower incidence of symptomatic CMV infection compared with that observed after CsA treatment [54]. Shiraki et al. showed the suppressive effects of tacrolimus on CMV replication in vitro [55]. In contrast to tacrolimus, CsA has been reported to enhance the replication of CMV [55]. We used qPCR to identify patients with UC having CMV infection and assessed the outcomes of patients with CMV infections [56]. Our results showed that all CMV-DNA-positive patients who were treated with oral tacrolimus without ganciclovir showed clinical responses and decreased numbers of CMV-DNA copies (**Figure 3**). Because the use of steroids is known to increase the risk of CMV infection, which is associated with disease exacerbation and refractoriness, oral tacrolimus should be used prior to steroid therapy in patients with severe or refractory UC [57].

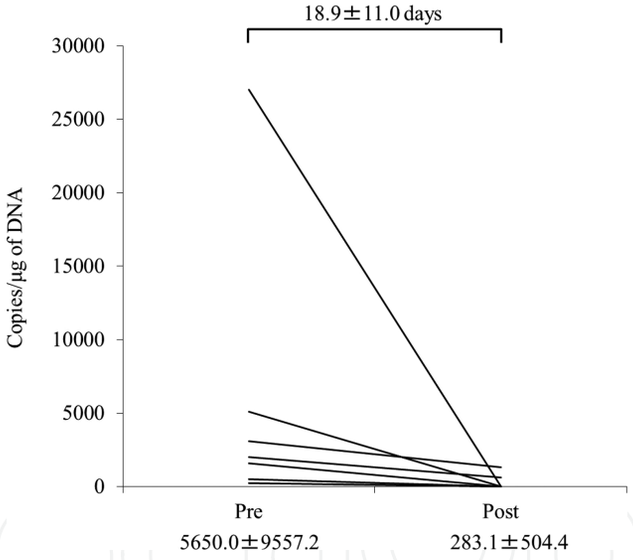

Figure 3. All CMV-DNA-positive patients who were treated with oral tacrolimus showed clinical responses and decreased numbers of CMV-DNA copies without concomitant ganciclovir [56].

7. Adverse effects

Similar to CsA, tacrolimus is known to be associated with many adverse effects, such as infections, renal dysfunction, hypertension, hyperglycemia, and neurological toxicity. However, these effects are generally mild and reversible. Although nephrotoxicity may be a limiting factor for the long-term use of tacrolimus, mean serum creatinine was not significantly elevated following short-term use of tacrolimus. With respect to blood glucose levels, Benson et al.

reported that 62.5% of patients with UC had elevated glucose levels; most of these patients were on corticosteroid therapy at the time [35]. Interestingly, because tacrolimus treatment has strong effects on steroid sparing, the mean fasting blood glucose level was reported to be significantly decreased after the initiation of tacrolimus treatment in patients with refractory UC [41]. During tacrolimus treatment, many patients develop hypomagnesemia (33.3–87.5 %) [33, 35, 41]. Additionally, other adverse effects, such as tremor, nausea, and headache, are often experienced. However, patients rarely have to discontinue tacrolimus therapy due to these adverse effects. Thus, induction therapy with tacrolimus is safe and well tolerated in patients with UC.

8. Conclusions

Tacrolimus is a potent immunosuppressive agent that is useful for inducing remission of refractory UC. Although the long-term efficacy and safety of tacrolimus in patients with UC have not been clearly elucidated, induction therapy with tacrolimus is safe and well tolerated in patients with refractory UC. Because of the requirement for tacrolimus dose adjustment and large variations in the oral absorption and metabolism of tacrolimus, physicians have to know the pharmacokinetics of tacrolimus to obtain maximum efficacy. Rapid induction therapy with oral tacrolimus in the early phase of treatment may provide excellent clinical outcomes and avoid the need for surgery for refractory UC. Therefore, oral tacrolimus may represent a top-down or accelerated step-up treatment option in cases of severe/extensive UC. However, thus far, tacrolimus is used primarily in Japan, and this drug is still not available in some other countries for the treatment of patients with UC because there are only two randomized controlled trials [33, 58] and a small number of studies confirming the efficacy and safety of tacrolimus. Further controlled studies with large numbers of patients are needed.

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