The Efficacy of Oral Tacrolimus in Patients with Moderate/Severe Ulcerative Colitis not Receiving Concomitant Corticosteroid Therapy

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Abstract

Objective  The calcineurin inhibitor tacrolimus has been shown to be safe and effective as salvage therapy for steroid-refractory ulcerative colitis (UC). Since differences in the onset of action between various agents are thought to influence the achievement and maintenance of disease remission, top-down or accelerated step-up therapy with tacrolimus may be useful. However, the efficacy of tacrolimus in moderate to severe UC patients not receiving concomitant steroids remains unknown.

Methods  Ten patients (11 attacks) with active, moderate to severe UC were treated with oral tacrolimus at a dose of 0.1 mg/kg body weight daily. The dosages were adapted to maintain trough whole-blood levels of 10 to 15 ng/mL to induce remission and 5 to 10 ng/mL to maintain remission. Lichtiger scores, the incidence of adverse effects (serum creatinine and glucose) and long-term outcomes were assessed.

Results  At four weeks after the initiation of tacrolimus therapy, clinical remissions were observed for eight attacks (72.7%) and clinical responses were demonstrated for three attacks. At 12 weeks after the initiation of tacrolimus treatment, clinical remissions were achieved for nine attacks (90%). After a mean follow-up of 10.4 months, clinical remissions were maintained for eight of 11 attacks. During the tacrolimus treatment, the serum creatinine and glucose levels were not significantly elevated.

Conclusion  Oral tacrolimus is a safe and effective therapy for the treatment of moderate to severe UC in patients not receiving concomitant treatment with systemic steroids. Although further 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.

Key words: ulcerative colitis, tacrolimus, top-down, accelerated step-up

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Introduction

Ulcerative colitis (UC) is an idiopathic inflammatory bowel disease (IBD) characterized by a chronic relapsing/intermittent clinical course. Aminosalicylates are typically used as first-line treatments for patients with UC, while steroids are usually considered to be second-line treatments used to induce remission when remission cannot be achieved with aminosalicylates. Because steroids have a rapid onset of action and are highly effective, they are reserved for diseases that fail to respond to primary therapy in patients with severe UC; however, these drugs are associated with considerable systemic adverse effects (1). Nevertheless, approximately 20% of patients with UC have chronically active diseases that require several courses of steroids. As a result, there are many steroid-dependent patients who experience severe complications of steroid treatment necessitating dose
reduction before stable remission can be achieved (2, 3). Since differences in the onset of action of various agents are thought to influence the achievement and maintenance of disease remission, developing a steroid-sparing, well-tolerated treatment regimen is urgently needed.

Calcineurin inhibitors, such as cyclosporine A (CsA) and tacrolimus, inhibit the production of interleukin-2 (IL-2) and T lymphocyte activation (4). Since these agents have a rapid onset of action and are highly effective in patients with refractory UC, they are approved as alternative treatment options for refractory UC under the national health insurance system in Japan (5). An insufficient number of studies have demonstrated the long-term efficacy of tacrolimus in the treatment of patients with refractory UC. Tacrolimus has been primarily used as salvage therapy because its immunosuppressive effects are greater and its variability in absorption and serum levels are lower than those of CsA (6).

Since differences in the onset of action of various agents are thought to influence the achievement and maintenance of disease remission (1), early intervention with tacrolimus may improve the long-term prognosis of UC patients, just as infliximab has done for patients with Crohn’s disease (6). However, no studies have thus far evaluated the efficacy of tacrolimus in the treatment of UC patients not receiving concomitant steroids. We herein evaluated the efficacy and safety of tacrolimus in UC patients who were not concomitantly receiving steroid therapy.

### Materials and Methods

#### Patients

Between November 2009 and May 2012, 10 patients (11 attacks) with active UC who were not receiving corticosteroids at the time of initiation of tacrolimus therapy were consecutively enrolled in this retrospective, single-center study. All patients received oral tacrolimus therapy for remission induction. This study was approved by the Ethical Committee of Osaka Medical College. The patients were informed of the potential risks and benefits of tacrolimus therapy and provided signed informed consent forms before undergoing any procedures. In all cases, the diagnosis was established according to standardized criteria using prior clinical assessments, radiology, endoscopy and histology (7). The disease activity was evaluated using Lichtiger scores (the modified Trulove-Witts severity index), which range from 0 (best) to 21 (worst). A response was defined as a Lichtiger clinical activity score <10 and a decrease ≥3, as previously described (8). Clinical remission was retrospectively defined as a score ≤4 (9). To evaluate mucosal damage and healing during colonic endoscopy, the Mayo endoscopic index was used (10), which consists of a scale ranging from 0 (normal or inactive) to 3 (spontaneous bleeding, ulceration) according to the type of endoscopic damage. Mucosal healing was considered to have occurred when the Mayo index score obtained during endoscopy was 0 to 1 (11, 12).

### Treatment

All patients were hospitalized at the time of initiation of tacrolimus therapy and given oral tacrolimus without a meal at an initial oral dose of 0.1 mg/kg per day twice daily. Blood was collected to determine the tacrolimus whole-blood trough concentration at 24 hours, 48 hours, four days, seven days and every seven days thereafter after providing the initial dose. The dosage was then adapted to achieve a trough level between 10 and 15 ng/mL. The patients were observed clinically and using routine laboratory tests to evaluate disease activity and the occurrence of side effects. The patients were hospitalized until their clinical conditions had stabilized and their tacrolimus levels were within the therapeutic range. Clinical activity scores were obtained daily at seven days, 10 days, 14 days and every seven days thereafter after the initiation of tacrolimus treatment. After clinical remissions were achieved, the tacrolimus whole-blood trough concentrations were maintained at lower levels, between 5 and 10 ng/mL. Thereafter, the patients were regularly seen in our outpatient clinic at least every four weeks. The trough whole-blood levels and biochemical values, including the serum creatinine and fasting blood glucose levels, were measured at each visit.

### Assessment and statistics

The primary endpoint of this study was the induction of remission at four and 12 weeks after the initiation of tacrolimus treatment. The secondary endpoint was safety. Continuous data were statistically analyzed using Student’s t-test. The Wilcoxon test was used to analyze clinical scores (i.e., Lichtiger scores). The results are expressed as the mean ± SD. P values of less than 0.05 were considered to be statistically significant. All calculations were made using the Statview system (SAS Institute, Cary, NC, USA).

### Results

#### Patient characteristics

Between November 2009 and May 2012, 10 patients (11 attacks) with moderate/severe UC who were not currently receiving corticosteroids were given oral tacrolimus for remission induction. The baseline patient characteristics are shown in Table 1. All patients were afflicted with pancolitis. The median duration of UC was seven months (range: 1 to 36 months). The baseline Lichtiger scores ranged from 10 to 21, suggesting that all patients had moderate to severe disease activity at the initiation of tacrolimus therapy. For three patients, this was their first attack. Three patients were steroid-naive and seven patients were steroid-dependent. Steroid dependency was defined as either chronic active UC occurring more than once a year or at least three times every two years regardless of the administration of intensive medical therapy, including corticosteroids (13). However, the total amount of steroids administered prior to tacrolimus
therapy in each patient was sometimes not available because the patients were referred to our hospital from other hospitals without such data. Eight patients had been treated with 5-aminosalicylic acid or salazosulfapyridine, while three patients had received concomitant azathiopurine at a stable dose.

Response to treatment

Tacrolimus was administered for a median of 21 weeks (range: 11 to 60 weeks). The Lichtiger scores significantly decreased beginning at three days after the initiation of tacrolimus treatment (Fig. 1), and the C-reactive protein (CRP) levels were significantly suppressed beginning at four days after the initiation of tacrolimus treatment (Fig. 2) (Table 2). Four weeks after the initiation of therapy, tacrolimus treatment resulted in clinical remission in eight of 11 attacks (72.7%) and a clinical response in three attacks. At 12 weeks after the initiation of tacrolimus therapy, clinical remissions were observed for nine attacks (81.8%). Overall, clinical responses were observed for all attacks at four and 12 weeks after the initiation of tacrolimus therapy (Table 3).

Long-term response

Within a median follow-up period of nine months (range: 4 to 20 months), eight of 10 patients were in complete clinical remission and two patients presented with relapses (Nos. 1, 2 and 3 in Table 3; Nos. 1 and 2 represent the same patient). Oral tacrolimus was re-administered to one of the relapsed patients. Although the second round of tacrolimus treatment resulted in temporary clinical remission, this patient underwent colectomy four months later (Nos. 1 and 2 in Table 3). The remaining nine patients were colectomy-free and treated with azathioprine (n=5) and/or mesalazine (n=9). One of these patients, who had received tacrolimus for 13 weeks (No. 3 in Table 3), relapsed six months after the end of tacrolimus treatment, at which time he received infliximab treatment.

Adverse effects

The mean levels of serum creatinine and glucose were not

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### Table 1. The Patients’ Baseline Characteristics

<table>
<thead>
<tr>
<th>No</th>
<th>Age &amp; gender</th>
<th>Extension</th>
<th>Duration (months)</th>
<th>Clinical Course</th>
<th>Response to corticosteroids</th>
<th>Total given steroid (mg)</th>
<th>Lichtiger score</th>
<th>Endoscopic score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19M</td>
<td>Pancolitis</td>
<td>7</td>
<td>Intermittent</td>
<td>Dependent</td>
<td>1056</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>20M</td>
<td>Pancolitis</td>
<td>14</td>
<td>Intermittent</td>
<td>Dependent</td>
<td>1056</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>45M</td>
<td>Pancolitis</td>
<td>19</td>
<td>Continuous</td>
<td>Naive</td>
<td>0</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>41F</td>
<td>Pancolitis</td>
<td>4</td>
<td>Intermittent</td>
<td>Dependent</td>
<td>NA</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>48F</td>
<td>Pancolitis</td>
<td>1</td>
<td>First attack</td>
<td>Naive</td>
<td>0</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>57F</td>
<td>Pancolitis</td>
<td>36</td>
<td>Intermittent</td>
<td>Dependent</td>
<td>5150</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>53F</td>
<td>Pancolitis</td>
<td>36</td>
<td>Intermittent</td>
<td>Dependent</td>
<td>NA</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>47F</td>
<td>Pancolitis</td>
<td>18</td>
<td>Intermittent</td>
<td>Naive</td>
<td>0</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>21F</td>
<td>Pancolitis</td>
<td>1</td>
<td>First attack</td>
<td>Naive</td>
<td>0</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>58M</td>
<td>Pancolitis</td>
<td>1</td>
<td>First attack</td>
<td>Naive</td>
<td>0</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>35F</td>
<td>Pancolitis</td>
<td>6</td>
<td>Intermittent</td>
<td>Dependent</td>
<td>1645</td>
<td>13</td>
<td>2</td>
</tr>
</tbody>
</table>

NA: non applicable
significantly affected during tacrolimus treatment (Table 2). Two months after the start of tacrolimus treatment, one patient developed a systemic Candida albicans infection, which resolved following intravenous micafungin sodium and tacrolimus dosage reduction. Other documented clinical reactions and laboratory abnormalities thought to be related to tacrolimus included tremors (n=2), nausea (n=2), headaches (n=1) and hypomagnesemia (1.31±0.20 mg/dL, n=9).

**Discussion**

To our knowledge, no reports have yet described the efficacy of tacrolimus in patients with moderate to severe UC not receiving concomitant corticosteroid therapy. The present findings demonstrated the safety and efficacy of oral tacrolimus in active UC patients as an alternative treatment option to steroids and may have relevance to the utility of top-down or accelerated step-up therapy with oral tacrolimus in patients with moderate to severe UC.

Tacrolimus is a macrolide immunosuppressant that is structurally similar to rapamycin and has been found to have potent immunosuppressive properties that are 10- to 100-fold more potent in inhibiting lymphocyte activation than CsA (14-16). Thus far, several uncontrolled (9, 14, 15, 17, 19) and two placebo-controlled studies (13, 18) have demonstrated that tacrolimus can induce remission in both adults (9, 13-15, 17, 18) and children (19). Another calcineurin inhibitor, CsA, is also highly active (60% to 80%) in patients with UC whose disease fails to respond to intravenous corticosteroid therapy (20). However, CsA has not been shown to improve long-term prognoses because it does not appear to be able to prevent relapse or colectomy once administration is stopped (6). Moreover, CsA is known to be associated with many adverse effects, such as infections, renal dysfunction, hypertension and neurological toxicity (6). Although similar adverse events, including tremors, hyperglycemia, nephrotoxicity and infection, are observed in association with tacrolimus therapy, these effects are generally mild and reversible (19-21); thus, tacrolimus can be safely administered on a long-term basis. Yamamoto et al. investigated the efficacy of tacrolimus as maintenance therapy for patients with refractory UC and suggested that the administration of tacrolimus with low trough levels (5 to 10 ng/mL) as maintenance therapy may represent an alternative therapy for UC patients (22). In the present study, three months of tacrolimus treatment resulted in clinical remission in 90% of

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**Table 2. Clinical and Laboratory Values Obtained before and during Tacrolimus Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Day0</th>
<th>Day1</th>
<th>Day2</th>
<th>Day3</th>
<th>Day4</th>
<th>Day5</th>
<th>Week1</th>
<th>Week4</th>
<th>Week12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichtiger score</td>
<td>13.09</td>
<td>12.27</td>
<td>11.55</td>
<td>10.82*</td>
<td>NA</td>
<td>8.64*</td>
<td>7.36*</td>
<td>3.36*</td>
<td>2.80*</td>
</tr>
<tr>
<td>CRP</td>
<td>5.32</td>
<td>4.45</td>
<td>3.90</td>
<td>5.03</td>
<td>0.90*</td>
<td>2.88*</td>
<td>3.28*</td>
<td>0.34*</td>
<td>0.09*</td>
</tr>
<tr>
<td>Serum CRP</td>
<td>±8.97</td>
<td>±7.72</td>
<td>±8.01</td>
<td>±7.75</td>
<td>±2.01</td>
<td>±6.65</td>
<td>±7.18</td>
<td>±0.39</td>
<td>±0.12</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.67</td>
<td>0.66</td>
<td>0.68</td>
<td>0.75</td>
<td>0.81</td>
<td>0.79</td>
<td>0.78</td>
<td>0.60</td>
<td>0.69</td>
</tr>
<tr>
<td>Serum glucose</td>
<td>98.60</td>
<td>101.11</td>
<td>95.38</td>
<td>99.00</td>
<td>101.67</td>
<td>96.80</td>
<td>98.67</td>
<td>87.8</td>
<td>89.83</td>
</tr>
<tr>
<td></td>
<td>±15.62</td>
<td>±15.42</td>
<td>±12.51</td>
<td>±15.48</td>
<td>±12.82</td>
<td>±14.39</td>
<td>±16.68</td>
<td>±10.28</td>
<td>±9.09</td>
</tr>
</tbody>
</table>

*p<0.05 vs. baseline

**Table 3. Duration of Tacrolimus Therapy and Treatment Outcomes**

<table>
<thead>
<tr>
<th>No</th>
<th>Duration of tacrolimus therapy (weeks)</th>
<th>Response (4 and 12 weeks)</th>
<th>Endoscopic score (end of follow-up)</th>
<th>Final outcome (end of follow-up)</th>
<th>Duration of follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>Remission</td>
<td>2</td>
<td>Relapse after 6 months Colectomy</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>Remission</td>
<td>0</td>
<td>Relapse after 4 months</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>Response</td>
<td>1</td>
<td>Low activity</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>Remission</td>
<td>1</td>
<td>Remission</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>Remission</td>
<td>1</td>
<td>Remission</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>Remission</td>
<td>0</td>
<td>Remission</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>Response/Remission</td>
<td>NA</td>
<td>Remission</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>Remission</td>
<td>NA</td>
<td>Remission</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>Remission</td>
<td>0</td>
<td>Remission</td>
<td>9</td>
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<tr>
<td>10</td>
<td>11</td>
<td>Response/Remission</td>
<td>1</td>
<td>Remission</td>
<td>9</td>
</tr>
<tr>
<td>11</td>
<td>28</td>
<td>Remission</td>
<td>0</td>
<td>Remission</td>
<td>7</td>
</tr>
</tbody>
</table>
attacks, and remission was maintained in eight of nine patients during a mean follow-up period of 11.1 ± 4.5 months. Recently, mucosal healing has emerged as a desirable treatment goal for patients with UC because the therapeutic goal of clinical remission appears to be insufficient in maintaining long-term remission and changes the natural history of UC. In addition, the degree of mucosal healing has been reported to be correlated with improved clinical outcomes, including colectomy, in UC patients. Mucosal healing is considered to have occurred when the Mayo index score obtained during endoscopy is 0 to 1 (11, 12). However, the relapse ratio has been reported to significantly differ between scores of 0 and 1 (23). In this study, at least four patients presented with a Mayo endoscopic score=1 after undergoing tacrolimus therapy, although they were in complete clinical remission. Therefore, the effects of long-term administration of tacrolimus in patients with UC remain unknown, and further study is required.

Evaluation of the mean serum creatinine and glucose levels indicated no significant differences during three months of tacrolimus treatment. With respect to infection, one patient developed a systemic Candida albicans infection, which was easily resolved with intravenous micafungin sodium and a reduced tacrolimus dosage. Therefore, we believe that tacrolimus will play a major role in inducing and maintaining remission in UC patients, just as infliximab has done for Crohn’s disease patients.

The current UC treatment algorithm involves a step-up therapeutic strategy that is primarily aimed at inducing and maintaining clinical remission. The first-line therapy for UC is the safe and effective 5-aminosalicylate class of drugs, which are clearly effective for the induction and maintenance of clinical remission in patients with mild to moderate UC. However, among the general UC patient population, 40% to 50% of patients will require treatment with steroids, and approximately 20% of patients will require several courses of steroids to achieve remission (steroid-dependency) (2, 3). In the majority of affected patients, UC follows a clinical course that is either intermittent or chronically continuous. Recently, several reports have shown that top-down therapy with infliximab induces rapid clinical responses, exhibits steroid-sparing effects, enhances patient quality of life, promotes mucosal healing and reduces hospitalization times and surgeries (25-29). These results suggest that some patients may benefit from top-down therapy and have led to a clinical debate about the utility of top-down vs. step-up strategies, since top-down therapy may not be suitable for all patients with UC (24, 25). In CD patients, top-down therapy has been recognized to include the early introduction of biologics and/or immunomodulators in patients with newly diagnosed disease (30). However, in UC patients, “top-down” therapy has not yet been clearly defined. In this study, seven of 11 patients were steroid-dependent. Recently, such patients have been considered candidates for “accelerated step-up therapy,” which while still “step-up,” is dosed using an 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 (31, 32). For many patients, such an accelerated step-up approach may be the best strategy (33). Therefore, in the present study, we evaluated the efficacy of tacrolimus in the treatment of moderate to severe UC patients not receiving concomitant steroids, including five steroid-naïve patients, and found that the administration of oral tacrolimus is highly effective in the treatment of both steroid-dependent and steroid-naïve UC patients. These results suggest that tacrolimus therapy represents a potential alternative to systemic steroids as primary therapy for induction of remission in patients with moderate to severe UC.

In conclusion, the results of this study demonstrate that oral tacrolimus is a safe and effective therapy for the treatment of moderate to severe UC in patients not receiving systemic steroids. Further studies are required to establish the efficacy and safety of top-down therapy using oral tacrolimus in patients with UC.

The authors state that they have no Conflict of Interest (COI).

References


