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Mucosal healing with oral tacrolimus is associated with favorable medium- and long-term prognosis in steroid-refractory/dependent ulcerative colitis patients

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Abstract

Background: Oral administration of tacrolimus is an effective remission induction therapy for steroid-refractory/dependent ulcerative colitis (UC).
Aim: This study aimed to evaluate the short- as well as medium- and long-term effectiveness of tacrolimus therapy.
Methods: The medical records of 51 patients treated with tacrolimus for UC at our hospital between July 2009 and December 2011 were reviewed retrospectively. Clinical remission and improvement were defined as a Lichtiger score of 4 or less and as a Lichtiger score of ≤ 10 and a reduction in the score of ≥ 3 compared with the baseline score, respectively. Endoscopic findings were evaluated based on the endoscopic activity index and Mayo endoscopic score.
Results: The clinical effectiveness combining clinical remission and improvement was observed in 62.7% of the patients at 3 months. Thirty-six patients underwent colonoscopy at 3 months, and 12 (33.3%) and 10 patients (27.8%) showed Mayo endoscopic scores of 0 and 1, respectively. On Kaplan–Meier analysis, the overall percentage of event-free survivors, who did not require colectomy nor switching to other induction therapy such as infliximab, was 73.0% at 6 months, 49.9% at 1 year, and 37.8% at 2 years. Patients with a Mayo endoscopic score of 0–1 at 3 months showed significantly better medium- and long-term prognosis than those with a score of 2–3 ($p < 0.01$). All adverse events, including infections in 2 patients, were reversible.

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Conclusions: Tacrolimus therapy was effective for inducing clinical and endoscopic remission of steroid-refractory/dependent UC. Endoscopic improvement was associated with favorable medium- and long-term prognosis.

1. Introduction

Ulcerative colitis (UC) is a form of chronic inflammatory bowel disease and is characterized by periods of remission and episodes of relapse. The pathogenesis of UC remains unclear and, therefore, radical therapy has not yet been established. 5-Aminosalicylates (5-ASA), immunomodulators (IMs) and corticosteroids have been employed as therapeutic options for UC for decades. Although steroids are an effective induction therapy, approximately 20% of patients fail to show improvement with steroid treatment.[1,2] Lichtiger et al.[3] reported the effectiveness of intravenous cyclosporine A (CSA), which inhibits calcineurin activity, for steroid-refractory UC in 1994. Several studies also reported that oral tacrolimus, another calcineurin inhibitor, could be an effective induction therapy for steroid-refractory or steroid-dependent UC.[4–7] Ogata et al.[8,9] clearly showed the short-term efficacy of oral tacrolimus for steroid-refractory UC in randomized prospective studies in 2006 and 2011. Recently, a German group reported a large retrospective analysis of patients treated with tacrolimus showing the short-term efficacy and safety of tacrolimus therapy in steroid-refractory UC patients.[10] Interestingly, the same group suggested the possibility that ABCB1 single-nucleotide polymorphisms may be a predictive factor for short-term efficacy of tacrolimus.[11] Thus far, this is the only report of a factor to predict the efficacy of tacrolimus.

Some retrospective studies also showed the medium- and long-term effectiveness of oral tacrolimus therapy in adults and children.[12–17] Yamamoto et al.[18] reported the potential of administering tacrolimus as a maintenance therapy. However, in those studies, the number of subjects was limited, and endoscopic improvement was not assessed.

In this study, we retrospectively evaluated the clinical and endoscopic effectiveness of oral tacrolimus therapy and the medium- and long-term prognosis of UC patients after induction therapy with oral tacrolimus. To our knowledge, this is the first report that assesses the endoscopic improvement and its impact on the medium- and long-term prognosis after tacrolimus therapy. The data obtained from our experience and detailed endoscopic analysis of a large patient population treated with tacrolimus would offer valuable information for the treatment of intractable UC patients.

2. Methods

2.1. Patients and treatment protocol

Oral tacrolimus has been approved for the treatment of steroid-refractory UC and steroid-dependent UC since July 2009 in Japan. Between July 2009 and December 2011, 51 patients with UC were treated with tacrolimus at Keio University Hospital. We reviewed their medical records retrospectively.

The clinical disease activity of the patients was assessed by trained physicians and scored according to the Lichtiger clinical activity index.[3] The Lichtiger index is composed of the following items: the number of daily bowel movements, entity of abdominal pain and tenderness, use of antidiarrhoics, blood in stools, general well-being, fecal incontinence and nocturnal diarrhea. In this scoring system, a higher score indicates more severe disease (score range 0–21).

We assessed the patients with colonoscopy at 3 months after the introduction of tacrolimus. We employed the endoscopic activity index (EAI)[19] and Mayo endoscopic score to evaluate endoscopic severity. The EAI is scored using the following six items: ulcer size, ulcer depth, redness, bleeding, edema, and mucus exudates. A score of zero to two or three is given to each item and a higher score indicates more severe endoscopic activity (score range 0–16).[19] In the Mayo endoscopic score, normal or inactive disease is scored as 0 and mild, moderate or severe disease is assigned a score of 1, 2 and 3, respectively.[20] We used EAI to demonstrate the change of endoscopic severity before and after the therapy, because EAI has been reported to be able to detect improvement after therapeutic intervention more quantitatively than other endoscopic indices.[19]

At our hospital, when starting oral tacrolimus, all patients were hospitalized and the initial dose of tacrolimus was 5 mg/body/day in two divided doses. We adjusted the trough level of tacrolimus in the whole blood based on the report by Ogata et al.[8], with a range of 10–15 ng/ml for the initial 2 weeks and subsequently a range of 5–10 ng/ml.

2.2. Definition and evaluation of effectiveness

Clinical response was assessed using the Lichtiger index. "Clinical remission" was defined as a score of 4 or less. "Improvement" was defined as a score of ≤ 10 and a reduction in the score of ≥ 3 compared with the baseline score before tacrolimus administration. All other cases were defined as "No response". We evaluated the clinical effectiveness at 3 months. Mucosal healing was defined as a Mayo endoscopic score of 0 or 1.

We defined patients who did not need colectomy or whose medication was not switched from tacrolimus to other induction therapy including infliximab (IFX) as "event-free survivors".

2.3. Statistical analysis

The evaluation of changes in EAI was carried out by Wilcoxon signed-rank test. In the analysis of predictive factors for