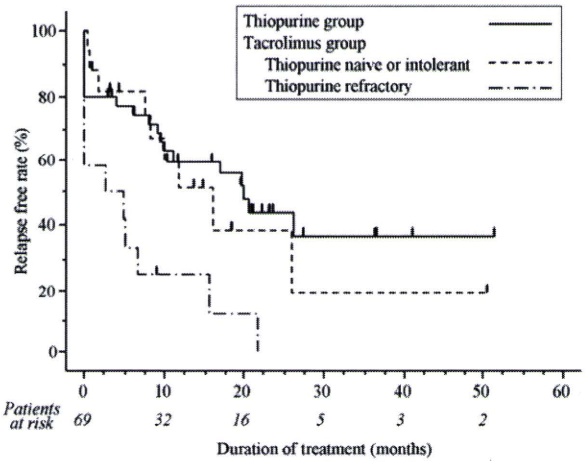

FIGURE 2. Relapse-free time intervals of thiopurine-refractory patients and thiopurine-naive or thiopurine-intolerant patients in the tacrolimus group and in the thiopurine group. The overall cumulative relapse-free survival of thiopurine-refractory patients in the tacrolimus group was significantly lower than that in the other 2 groups [log-rank test; $P=0.0104$ (vs thiopurine-naive or intolerant patients) and $P=0.0008$ (vs thiopurine group)]. There was no statistical difference between the thiopurine-naive or thiopurine-intolerant tacrolimus and thiopurine groups ($P=0.5594$).

necessary in 4 patients (16.7%). One patient (4.2%) contracted bacterial pneumonia. He had received a combination of tacrolimus and AZA, and recovered with antibiotic administration and discontinuation of the tacrolimus and AZA. A temporary rise in serum creatinine levels above 1.3 mg/dL occurred in 4 patients (16.7%). In 3 cases, tacrolimus withdrawal was necessary and serum creatinine levels normalized after discontinuation. In the other case, renal function normalized with dose reduction of tacrolimus.

The thiopurines were discontinued because of side effects in 5 (14.7%) of 34 patients undergoing thiopurine maintenance therapy. Of those, 1 patient (2.9%) contracted bacterial pneumonia as described above, 1 patient (2.9%) developed leukopenia, 1 patient (2.9%) developed pancreatitis, and 2 patients (5.9%) experienced nausea. Herpes progenitalis (2.9%, n = 1) and mild leukopenias (5.9%, n = 2) were also observed.

All of the patients in both groups recovered with conventional therapy. There was no mortality in either of the groups.

TABLE 5. Adverse Events That Developed During Tacrolimus Treatment

Adverse Events	Cases (%)
Tremor	5 (20.8)
Renal function impairment (rise in creatinine above 1.3 mg/dL)*	4 (16.7)
Hot flashes	3 (12.5)
Bacterial pneumonia	1 (4.2)
Hyperkalemia	1 (4.2)
Epigastralgia	1 (4.2)
Headache	1 (4.2)

*In 1 case, tacrolimus withdrawal was not necessary.

DISCUSSION

The findings of this study showed that the effects of tacrolimus as maintenance therapy in thiopurine-naive or thiopurine-intolerant patients with UC are comparable with those of thiopurines. To our knowledge, this is the first study to show that tacrolimus therapy is valuable for maintaining remission in patients with refractory UC in comparison with thiopurine therapy.

First, we investigated the efficacy of thiopurines for maintaining remission in patients with refractory UC enrolled in this study. Our study showed that the proportions of UC patients maintaining steroid-free remission with thiopurines at 1 and 3 years were 59.2% and 36.5%, respectively (Fig. 2). In a prospective, observational cohort study by Chebli et al,[14] the proportion of patients with steroid-dependent UC who received AZA for 3 years and remained in steroid-free remission was 45% and 57.5% on an intention-to-treat basis and per protocol basis, respectively. Fraser et al[15] reviewed the clinical notes of 622 patients with inflammatory bowel disease (272 Crohn's disease, 346 UC, and 4 indeterminate colitis) who were treated with AZA to maintain remission and showed that the relapse-free rate based on a Cox regression analysis was 63% at 60 months. Although the relapse-free rate in the later study seems to be higher than that in thiopurine therapy in an earlier study and in this study, patients who received AZA for less than 3 months were excluded in the study by Fraser et al, whereas all patients who were administered thiopurines were enrolled in other studies. Thus, in our study, the clinical outcome of patients treated with thiopurines was similar to that in earlier reports.[14,15]

Then, we investigated the efficacy of tacrolimus as maintenance therapy for patients with refractory UC in comparison with thiopurines. Our study showed that the proportions of patients intolerant or naive to thiopurines who could maintain steroid-free remission with tacrolimus at 1 and 3 years were 51.1% and 19.2%, respectively (Fig. 2), which was similar to that in patients with thiopurines. In contrast, the proportions of patients who were refractory to thiopurines at 1 and 3 years were 25.0% and 0%, respectively (Fig. 2). Relapse-free survival in this group was significantly lower than that in thiopurine group. These data suggested that administration of tacrolimus with trough levels of 5 to 10 ng/mL as maintenance therapy could be an alternative therapy for UC patients intolerant to thiopurines, but might be less effective in thiopurine-refractory patients with UC.

Some reports recommend tacrolimus trough levels of 5 to 10 ng/mL for long-term administration to avoid rejection in patients with liver, renal, and small bowel transplantation.[16,17] Our earlier report also showed that the same trough level range might be optimal for maintaining remission in patients with refractory UC based on its effect and safety.[9] According to these earlier reports, in this study, we treated UC patients by adjusting the tacrolimus trough levels to 5 to 10 ng/mL. Our data suggested, however, that patients with UC who are refractory to thiopurines should be controlled with higher trough levels of tacrolimus, a combination of thiopurines and tacrolimus, or infliximab.

One limitation of this study concerns the difference of the induction therapy between the tacrolimus and the thiopurine groups. In fact, 82.8% of the patients in the tacrolimus group were treated with tacrolimus, whereas 70% of the patients in the thiopurine group received either CS or cytapheresis (Table 4). Therefore, we could not

exclude the possibility that patients in the thiopurine group had less severe disease than those in the tacrolimus group. To solve this issue, additional studies might be required with enrolling patients who received the same induction therapies.

Finally, we evaluated the adverse effects related to long-term administration of tacrolimus therapy. In this study, tremor was the most frequent side-effect and severe adverse events rarely occurred during tacrolimus maintenance therapy. The frequency of drug withdrawal because of side effects was similar between the tacrolimus and thiopurine groups, indicating that long-term tacrolimus administration with trough levels of 5 to 10 ng/mL could be tolerable in patients with refractory UC.

In conclusion, our study showed that tacrolimus therapy is a viable alternative for maintaining steroid-free remission in UC patients intolerant to thiopurines, although its efficacy and the therapeutic strategy for thiopurine-refractory UC remains to be established.

REFERENCES

1. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet*. 2007;369:1641–1657.
2. Sands BE. Inflammatory bowel disease: past, present, and future. *J Gastroenterol*. 2007;42:16–25.
3. Faubion WA Jr, Loftus EV Jr, Harmsen WS, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology*. 2001;121:255–260.
4. Swartz SL, Dluhy RG. Corticosteroids: clinical pharmacology and therapeutic use. *Drugs*. 1978;16:238–255.
5. Ogata H, Matsui T, Nakamura M, et al. A randomized dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis tacrolimus. *Gut*. 2006;55:1255–1262.
6. Baumgart DC, Pintoffl JP, Sturm A, et al. Tacrolimus is safe and effective in patients with severe steroid-refractory or steroid-dependent inflammatory bowel disease—a long-term follow-up. *Am J Gastroenterol*. 2006;101:1048–1056.
7. Fellermann K, Tanko Z, Herrlinger KR, et al. Response of refractory colitis to intravenous or oral tacrolimus (FK506). *Inflamm Bowel Dis*. 2002;8:317–324.
8. Ng SC, Arebi N, Kamm MA. Medium-term results of oral tacrolimus treatment in refractory inflammatory bowel disease. *Inflamm Bowel Dis*. 2007;13:129–134.
9. Yamamoto S, Nakase H, Mikami S, et al. Long-term effect of tacrolimus therapy in patients with refractory ulcerative colitis. *Aliment Pharmacol Ther*. 2008;28:589–597.
10. Högenauer C, Wenzl HH, Hinterleitner TA, et al. Effect of oral tacrolimus (FK 506) on steroid-refractory moderate/severe ulcerative colitis. *Aliment Pharmacol Ther*. 2003;18:415–423.
11. Ziring DA, Wu SS, Mow WS, et al. Oral tacrolimus for steroid-dependent and steroid-resistant ulcerative colitis in children. *J Pediatr Gastroenterol Nutr*. 2007;45:306–311.
12. Nakase H, Mikami S, Matsuura M, et al. Rescue therapy with tacrolimus for a patient with severe ulcerative colitis refractory to combination leukocytapheresis and high-dose corticosteroid therapy. *Intern Med*. 2007;46:717–720.
13. Lichtiger S, Present DH. Preliminary report: cyclosporin in treatment of severe active ulcerative colitis. *Lancet*. 1990;336:16–19.
14. Chebli LA, Chaves LD, Pimentel FF, et al. Azathioprine maintains long-term steroid-free remission through 3 years in patients with steroid-dependent ulcerative colitis. *Inflamm Bowel Dis*. 2010;16:613–619.
15. Fraser AG, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut*. 2002;50:485–489.
16. Langnas AN. Advances in small-intestine transplantation. *Transplantation*. 2004;15:S75–S78.
17. McMaster P, Mirza DF, Ismail T, et al. Therapeutic drug monitoring of tacrolimus in clinical transplantation. *Ther Drug Monit*. 1995;17:602–605.