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Short-Term and Long-Term Outcomes of Infliximab and Tacrolimus Treatment for Moderate to Severe Ulcerative Colitis: Retrospective Observational Study

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Background/Aims: While some studies have shown that IFX and TAC exhibit similar efficacy against UC in the short-term, it is unclear which drug produces better long-term outcomes. In this study, we compared the long-term efficacy of IFX and TAC in patients with moderate to severe UC. Methods: This retrospective study was conducted from 2009 to 2017. It included patients with no history of IFX or TAC treatment. We analyzed the clinical response and remission rates at 12 and 52 weeks, and colectomy-free and relapse-free survival were evaluated until the end of the study. Results: At 12 weeks, 94.4% and 77.8% of the patients in the IFX group (n = 18) had demonstrated clinical responses and clinical remission, respectively, whereas 72.7% of the patients in the TAC group (n = 11) exhibited clinical responses and clinical remission. The clinical response, clinical remission, and colectomy-free rates did not differ significantly between the groups. At 52 weeks, clinical responses and clinical remission had been achieved in 76.5% and 70.6% of the patients both in the IFX group, respectively. In the TAC group, clinical responses and clinical remission were achieved in 50.0% of patients. Relapse-free and colectomy-free survival were estimated significantly better in IFX group evaluated by Kaplan-Meier curves. Conclusion: This study indicates that IFX and TAC produce similar short-term outcomes in UC patients, but IFX produces better long-term outcomes than TAC especially with avoidance of colectomy. Our data suggest that IFX therapy may be prioritized over TAC for the treatment of moderate to severe UC.

INTRODUCTION

Ulcerative colitis (UC) is a common form of inflammatory bowel disease that is characterized by a remitting and relapsing course. To induce remission, most patients with mild UC are initially treated with 5-aminosalicylates (5-ASA) with or without corticosteroids. However, as approximately 30% of cases of UC are steroid-resistant or steroid-dependent,[9] patients with moderate to severe UC often need to be treated with anti-tumor necrosis factor-α (anti-TNF-α) agents or calcineurin inhibitors.

In Japan, three anti-TNF-α agents, infliximab (IFX), adalimumab (ADA), and golimumab (GLM), are approved for use for the treatment of UC. In clinical trials (ACT1 and ACT2), IFX was shown to be superior to a placebo at achieving and maintaining clinical remission.[23, 24] In addition, ADA and GLM were demonstrated to be superior to a placebo at achieving and maintaining clinical remission (ULTRA1, ULTRA2, ULTRA3,[2, 22, 25] and PURSUIT[1, 6]). Calcineurin inhibitors, such as cyclosporin A (CyA) and tacrolimus (TAC), are immunosuppressive agents, which can be used to induce remission in moderate to severe UC. CyA was demonstrated to be an effective remission-inducing therapy for steroid-refractory UC in a clinical trial.[12] The latter study suggested that CyA is effective against UC, but the outcome evaluation was conducted on day 14; thus, only the very short-term effects of CyA were assessed. There have been no large studies examining the long-term efficacy of CyA. In addition, some randomized controlled trials have suggested that TAC is effective against steroid-refractory UC in the short-term.[17, 18] TAC is about 100 times more potent than CyA[10] and easily absorbed;[4] therefore, it is considered that TAC is more effective against steroid-refractory UC than CyA. Furthermore, UC is a chronic disease with the risk of repeating aggravation and remission, therefore, it is important to select appropriate remission induction therapy with the envision of long lasting remission maintenance therapy. As no previous large studies have demonstrated that TAC is effective against UC in the long-term, it remains unclear whether TAC is an effective long-term therapy for UC.

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While some studies have shown that IFX and TAC have similar short-term (8-12 weeks) effects against UC, it is unclear which of these treatments produces better long-term outcomes.[3, 15, 32] In the clinical setting, IFX and TAC are used to induce remission in patients with steroid-resistant or -dependent UC, as well as steroid-naïve patients with suspected or definitively diagnosed cytomegalovirus (CMV) reactivation, which is refractory to steroid therapy.[29] In this study, we retrospectively investigated the ability of IFX and TAC to induce remission in UC as well as the outcomes of following maintenance therapies for UC by analyzing the short-term and long-term outcomes of these treatments.

PATIENTS AND METHODS

1. Study design and endpoints

This was a retrospective single-center study conducted from January 2009 to December 2017 at Kobe University Hospital. We examined the short-term and long-term outcomes of patients with moderate to severe UC and compared the outcomes of the IFX-treated patients with those of the TAC-treated patients. First, we compared the clinical response and remission rates seen at 12 weeks after the start of IFX or TAC treatment. Secondly, we compared the clinical response and remission rates observed at 52 weeks after the start of IFX or TAC treatment for the patients who exhibited clinical responses at 12 weeks. The definition of clinical response and remission are stated below in the "clinical outcomes" section. Thirdly, colectomy-free survival and relapse-free survival were evaluated until the end of this study. This study was approved by the ethics committee at Kobe University School of Medicine and was registered at the Kobe University Hospital Clinical and Translational Research Center.

2. Patients

All of the patients had been definitively diagnosed with UC based on assessments of their clinical features and endoscopic and histological evaluations. The eligible patients for this study were defined as follows: i) having moderate to severe UC, as defined by a Mayo score of > 6 points; ii) having steroid-refractory UC, steroid-dependent UC, or steroid-naïve UC with possible or definitive CMV reactivation; and[27] iii) never having received anti-TNF-α agent or TAC treatment. Steroid-refractory UC was defined as UC that exhibited an insufficient clinical response to > 30 mg/day of oral or intravenous prednisolone (PSL) over one week. Steroid-dependent UC was defined as stated in the European Crohn's and Colitis Organisation (ECCO) guidelines; i.e., UC that relapsed if the PSL dose was reduced to < 10 mg/day or if it occurred within 3 months of PSL therapy being stopped.[13] CMV reactivation was diagnosed based on the endoscopic detection of punched-out ulcers and positive findings during histopathological and/or immunohistochemical examinations, antigenemia assays, and/or the polymerase chain reaction (PCR).[21] Reactivation was suspected if punched-out ulcers were detected, and negative results were obtained in the abovementioned tests. The extent of the disease was determined according to the Montreal classification. [28]

3. Treatment and strategy

IFX was administered as an intravenous infusion at a dose of 5 mg/kg in weeks 0, 2, and 6 to induce remission. After a clinical response was confirmed, maintenance treatment with 5 mg/kg IFX was administered every 6-8 weeks.

TAC was administered orally at an initial dose of 0.05 or 0.1 mg/kg/day. The dosage was adjusted to reach a whole-blood trough level of 10-15 ng/ml (a high trough level), and a high trough level was maintained for 2 weeks. Subsequently, the trough level was adjusted to 5-10 ng/ml (a low trough level), and TAC was continued for up to 3 months for the purpose of remission induction. Thiopurine was administered before TAC ended, and maintenance therapy was performed using thiopurine. But, if the patients wished to continue TAC or the serious side effects of thiopurine was recognized, maintenance therapy was performed using low concentration TAC.

The optimal dose of thiopurine was adjusted to maintain a white blood cell (WBC) count of between 3,000 and 5,000/μl[31] or an increase in the mean corpuscular volume (ΔMCV) of between 3 and 11 fl.[16]

4. Clinical outcomes

Disease activity and clinical responses were evaluated at the baseline and at 12 and 52 weeks using the partial Mayo score (pMS).[11] The severity of any endoscopic findings was evaluated at the baseline and 52 weeks using the Mayo endoscopic score. A clinical response was defined as a reduction in the pMS of at least 3 points. Clinical remission was defined as a pMS of ≤ 2 points, with no individual subscore exceeding 1 point. Relapse was defined as when an alternative induction therapy was required. Relapse-free and colectomy-free survival were defined as the time intervals between the administration of IFX or TAC and relapse or colectomy, respectively. If a patient did not experience any events, the follow-up period was censored at the end of the study or at the date of the last hospital visit.

5. Statistical analyses

The student-t test was used to compare continuous variables, and Pearson's Chi-square test was used to compare categorical variables. Colectomy-free and relapse-free survival were estimated using Kaplan-Meier curves, and comparisons between two groups were performed using the log-rank test. P-values of < 0.05 were considered statistically significant. All statistical analyses were conducted using JMP® 12.2.0 (SAS Institute Inc., Cary, NC, USA).

RESULTS

1. Patients' baseline characteristics

The patients' baseline characteristics are shown in Table I. Of the 29 patients, 18 and 11 patients were initially treated by IFX or TAC, respectively. Except for the proportion of concomitant use of thiopurine, no significant differences in the baseline characteristics of the two groups were found.

2. Short-term outcomes at 12 weeks.

The clinical outcomes of all eligible patients at 12 weeks are shown in Figure 1 and Table II. Of the 18 patients in the IFX group, clinical responses and clinical remission were seen in 17 (94.4%) and 14 (77.8%) patients, respectively. Of the 11 patients in the TAC group, 8 (72.7%) patients exhibited clinical responses and clinical remission. None of the patients in either group needed to undergo colectomy at 12 weeks. At 12 weeks, there were no significant differences in the clinical response rate, clinical remission rate between the two groups.

For those who classified to no responders, one patient who showed no response to initial IFX therapy, clinical remission was achieved by changing their living environment after the cessation of IFX treatment. Of the 3 patients who did not showed any response to initial TAC treatment, 2 underwent colectomy, and one was switched to IFX and achieved clinical remission.

3. Patients' clinical courses during maintenance therapy from 12 weeks to 52 weeks

Of the 17 patients who exhibited clinical responses to IFX therapy at 12 weeks, 4 patients subsequently showed the sign of loss of response to IFX. However, all these 4 patients could maintain clinical response, and 3 of the 4 patients achieved clinical remission by shortening the IFX infusion interval from 8 to 6 weeks. Four patients relapsed before 52 weeks, and one patient was switched to TAC and achieved clinical remission. This patient was subsequently treated with thiopurine monotherapy. One patient was treated with 5-ASA enema with discontinuation of IFX, but mild disease activity remained. One patient switched to ADA and achieved clinical remission. The remaining patient was treated with ganciclovir and cytapheresis (CAP) due to suspected concomitant CMV colitis, and clinical remission was achieved.

Of the 8 patients in the TAC group who exhibited clinical responses at 12 weeks, the response was maintained with TAC monotherapy of a low trough concentration in 4 patients, and with thiopurine therapy in 4 patients. However, agranulocytosis due to the administration of azathioprine (AZA) was seen in one patient, and her treatment was switched to GLM before 52 weeks to keep maintain remission. This patient was subsequently found to have a polymorphism in her NUDT15 gene (homozygote: T/T), which is known to cause defective thiopurine metabolism. [7, 26, 33] Of the 4 patients who relapsed before 52 weeks, 2 patients were switched to IFX, which resulted in achieved clinical remission. However, one of these patients subsequently stopped responding to IFX, and so colectomy was performed. One patient was treated with GLM, which resulted in clinical remission, and the remaining patient underwent colectomy.

Accordingly, the long-term clinical outcomes at 52 weeks are shown and summarized in Figure 1 and Table III. Of the 17 patients who exhibited clinical responses at 12 weeks in the IFX group, 13 (76.5%) exhibited clinical responses, and 12 (70.6%) achieved clinical remission. Of the 8 patients who exhibited clinical responses at 12 weeks in the TAC group, 4 (50%) exhibited clinical responses, and all of them achieved clinical remission.

4. Relapse-free and colectomy-free survival

Based on Kaplan-Meier survival analysis, the relapse-free survival rates at 6 months, 12 months, and 36 months were estimated to be 94%, 78%, and 78% in the IFX group and 55%, 36%, and 24% in the TAC group, respectively (Figure 2). The risk of relapse was significantly higher in the TAC group ($p = 0.001$). Overall, colectomy was performed in total 5 (45%) patients in the TAC group and no patients in the IFX group during this study. In the TAC group, the colectomy-free survival rates at 6 months, 12 months, and 36 months were estimated to be 91%, 82%, and 65%, respectively ($p = 0.006$, Figure 3).

Table I. Patients' baseline clinical characteristics

	Infliximab group (n=18)		Tacrolimus group (n=11)		P-value
Age at induction therapy (median (range)) (years)	47	(13-80)	51	(22-70)	0.5698
Age at diagnosis of UC (median (range)) (years)	42	(11-80)	45	(19-70)	0.4578
Follow-up period (mediam (range)) (weeks)	191	(54-379)	118	(57-416)	0.6187
Disease duration prior to the induction therapy (median (range)) (weeks)	220	(10-1009)	54	(29-1077)	0.6544
Gender					0.8121
Male	9	(50%)	6	(55%)	
Female	9	(50%)	5	(45%)	
Hospitalization	17	(94%)	10	(91%)	0.7154
Disease extent					0.9764
Extensive	13	(72%)	8	(73%)	
Left-sided	5	(28%)	3	(27%)	
Response to corticosteroids					
Refractory	9	(44%)	5	(45%)	0.9577
Dependent	6	(33%)	5	(45%)	0.5139
Naïve	4	(22%)	1	(9%)	0.3637
Concomitant therapy					
5-aminosalicylates	12	(67%)	10	(91%)	0.1388
Pentasa ® (average dose(mg))	8	(4000)	7	(3750)	
Asacol ® (average dose(mg))	4	(3600)	2	(3600)	
Salazosulfapyridine (average dose(mg))	0	(0)	1	(2)	
Corticosteroids	6	(33%)	6	(55%)	0.2604
average dose (mg)	31.4		24.0		
Cytapheresis	4	(22%)	3	(27%)	0.7578
Thiopurine	8	(44%)	0	(0%)	0.0094
azathioprine (average dose(mg))	6	(54.2)	0	(0)	
6-mercaptopurine (average dose(mg))	2	(30.0)	0	(0)	
Clinical disease activity				(0%)	0.5139
Moderate	12	(67%)	6	(33%)	
Severe	6	(55%)	5	(45%)	
Endoscopic Mayo score (median (range))	3	(2-3)	3	(2-3)	0.3489
Mayo score (median (range))	10	(7-12)	9	(8-12)	0.6951
Partial Mayo score (median (range))	7	(4-9)	7	(6-9)	0.4088
Laboratory examination data (mean±SD)				(0%)	
C-reactive protein (mg/dL)	2.0	(0-18.12)	1.3	(0-7.67)	0.0618
Hemoglobin (g/dL)	11.3	(7-13.8)	11.0	(6.3-14)	0.6736
Albumin (g/dL)	2.9	(1.1-4.4)	3.2	(2.3-4.3)	0.4234
Frequency of CMV reactivation	3	(17%)	4	(36%)	0.2291
Punched-out ulcer	5	(28%)	4	(36%)	0.6277

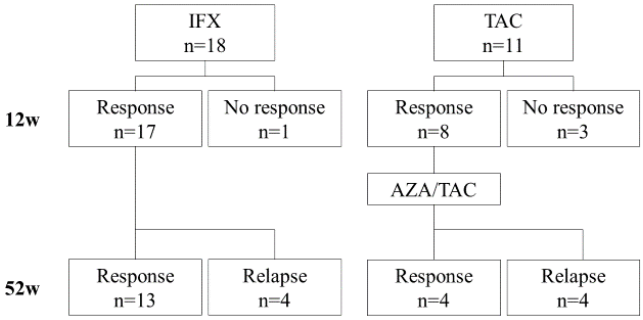

Figure 1. Clinical courses of 30 patients

Table II. Efficacy of infliximab and tacrolimus at 12 weeks

	IFX	(n=18)	TAC	(n=11)	P-value
Response (including remission)	17	(94.4%)	8	(72.7%)	0.100
Clinical remission	14	(77.8%)	8	(72.7%)	0.758
No response	1	(5.6%)	3	(27.3%)	0.100
Colectomy	0	(0%)	0	(0%)	

Table III. Efficacy of infliximab and tacrolimus at 52 weeks

	IFX	(n=17)	TAC	(n=8)	P-value
Response (including remission)	13	(76.5%)	4	(50%)	0.186
Clinical remission	12	(70.6%)	4	(50%)	0.317
Relapse until 52 weeks	4	(23.5%)	4	(50%)	0.186
Colectomy	0	(0%)	2	(25%)	0.032

5. Adverse Event

In the IFX group, mild infusion reaction was observed in one patient in maintenance phase, and she eventually discontinued IFX with disease relapse. In the TAC group, renal dysfunction was observed in 9 patients (81%). Seven patients could complete TAC treatment without dose reduction. Two patients required rapid dose reduction during the low-trough phase, but not high-trough phase. Other serious adverse events to cause the cessation of the treatment by TAC and IFX were not observed during the observational period.

DISCUSSION

UC can expose patients to a risk of emergency colectomy or life-threatening crises in the short-term and to a risk of colectomy due to chronic active inflammation or colorectal cancer in the long-term. For these reasons, the treatment strategy for UC should be based on a desire to achieve long-term remission.

In previous retrospective studies, IFX and TAC exhibited similar short-term efficacy against moderate to severe UC.[15, 30, 32] In agreement with this, IFX and TAC produced similar clinical response and clinical remission rates at 12 weeks in the current study.

As for long-term outcomes, Endo et al. reported that their IFX group exhibited a significantly higher relapse-free survival rate at 18 months than their TAC group (83% vs. 37%, $p < 0.001$).[3] Thus, the clinical remission rate was significantly higher in the IFX group than in the TAC group ($p < 0.001$), which is similar to our result of estimation by Kaplan-Meier analysis. The general treatment strategy after IFX-based induction therapy is to continue administering IFX with or without thiopurines, and the efficacy of this approach has been validated in the ACT1 and ACT2 trials and an associated study.[23, 24] On the other hand, our results and those of previous studies indicate that the maintenance therapy for TAC-treated UC patients requires further optimization to improve its outcomes.

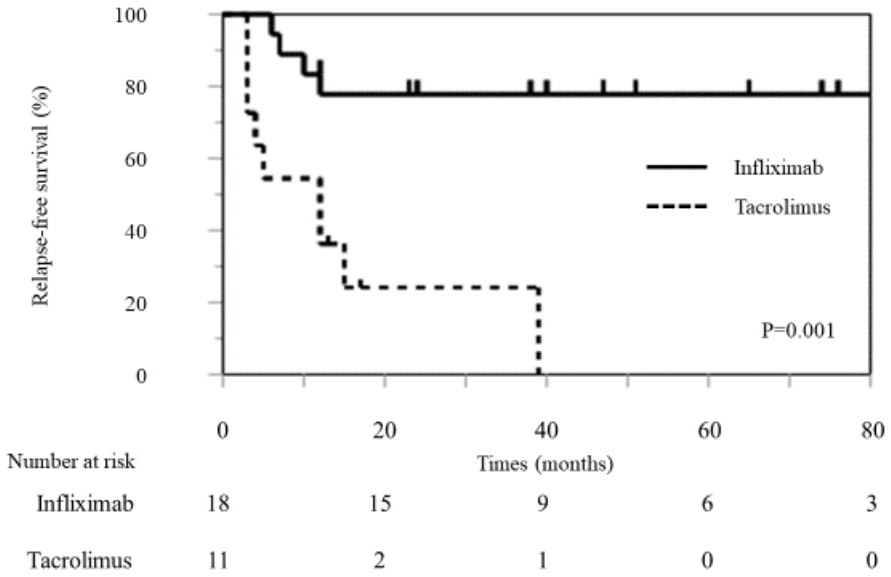

Figure 2. Kaplan-Meier curves of the relapse-free rate: The relapse-free survival rates at 6 months, 12 months, and 36 months were estimated to be 94%, 78%, and 78% in the IFX group and 55%, 36%, and 24% in the TAC group, respectively. The risk of relapse was significantly higher in the TAC group (p = 0.001).

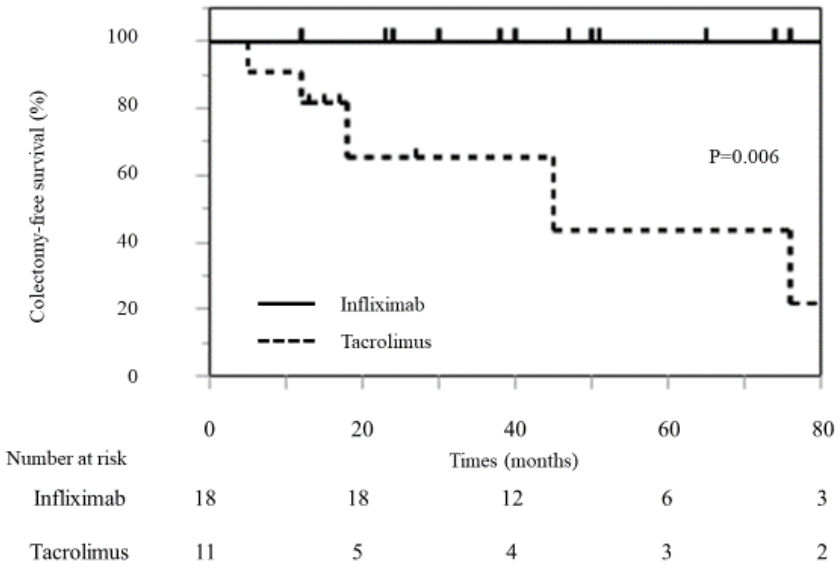

Figure 3. Kaplan-Meier curves of the colectomy-free rate: In the TAC group, the colectomy-free survival rates at 6 months, 12 months, and 36 months were estimated to be 91%, 82%, and 65%, respectively. The risk of colectomy was significantly higher in the TAC group (p = 0.006).

These findings suggest that IFX might be a better choice for maintenance therapy; however, there are some cases in which the administration of IFX should be avoided. For example, IFX is contraindicated for patients with concomitant tuberculosis (TB) infections. [8] Screening for TB is performed using chest X-rays, tuberculin skin tests, or the interferon-gamma release assay (IGRA). In recent years, the IGRA has been favored as a screening test for latent TB infections, but it takes a few days to obtain the results. Furthermore, when the IGRA produces a positive result it is necessary to treat the latent TB infection before anti-TNF-α agents can be used. Therefore, TAC could be indicated for patients in whom a concomitant TB infection cannot be completely ruled out. One important issue regarding the treatment of UC with TAC is that there is no established strategy for maintenance therapy after the induction of remission with TAC. In Japan, it is recommended that TAC should not be used to treat UC for more than 3 months, mainly due to its renal toxicity. Indeed, renal dysfunction was observed at high rate of the patients in the TAC group. Although only 2 patients needed dose reduction due to renal dysfunction in this study, it

obviously should limit the indication of TAC to whom with renal disease. The general approach to maintenance therapy after the induction of remission with TAC is to use thiopurines and/or 5-ASA. However, the optimization of thiopurine dose for maintenance therapy sometimes faces difficulties. The thiopurine dose can be adjusted based on the patient's WBC count[31] and MCV monitoring,[16] but WBC counts are influenced by various factors, especially inflammation or steroid treatment, while the MCV is influenced by anemia. The level of 6-thioguanine nucleotide (6-TGN) is also useful for adjusting the thiopurine dose;[19] however, it does not always correlated with the effects of thiopurine treatment.[5] Moreover, the measurement of 6-TGN levels is not always feasible, for example, it is not covered by the national health insurance system in Japan. It is now widely recognized that thiopurine-induced leukopenia is closely associated with NUDT15 R139C polymorphisms, usually detected in Asian populations, and can make the selection of thiopurine therapy more difficult.[7, 26, 33] Interestingly, Minami et al. reported the efficacy of an alternative rescue therapy involving IFX in cases in which UC relapsed.[15] After initial treatment with TAC, the treatment could be switched to IFX based on the primary physician's decision, and IFX could also be used to maintain remission. In this study, about half of the enrolled patients (10/22) in the TAC group were subsequently switched to IFX, and 6 of 10 patients (60%) achieved clinical remission. Therefore, IFX-based rescue therapy may a good option in cases relapse occurs after remission induction using TAC.

Our study included 10 (IFX: 6, TAC: 4) cases of suspected or definitively diagnosed CMV reactivation. Six patients initially received IFX, and 4 initially received TAC. All 6 patients in the IFX group and 3 out of 4 patients in the TAC group achieved clinical remission. The efficacy of IFX treatment is disputed for concomitant CMV infection, but Pillet et al. reported that it is not associated with a higher risk of CMV reactivation.[20] The relationship between TAC treatment and CMV reactivation is unclear, but Minami et al. reported that CMV infections were associated with worse outcomes after CyA treatment for UC. [14] No firm conclusions can be drawn due to the small number of cases included in this study; however, the findings of previous studies suggest that in cases involving concomitant CMV reactivation IFX may be better selected to induce remission rather than TAC.

This study had several limitations. This was a single-center study with a very small sample size. It was also a retrospective observational study; therefore, the current data should be carefully interpreted. The frequency of concomitant thiopurine therapy differed significantly between the treatment groups in the present study (none of the patients in the TAC group received concomitant thiopurine therapy). In the UC-SUCCESS study, it was shown that combining thiopurines with IFX was more effective at achieving steroid-free remission in UC than IFX monotherapy.[20] On the other hand, thiopurines are generally used for bridging therapy during the transition from remission induction to maintenance therapy in UC patients treated with TAC. As the use of thiopurines with IFX improves the chance of remission being induced, selection bias might have been inevitable. However, we cannot exclude the possibility that this difference in the patients' background characteristics affected the long-term outcomes of the IFX and TAC groups. Nevertheless, together with the findings of previous studies, our findings indicate that there is no definitive established strategy for maintenance therapy after TAC treatment. There will always be some patients in whom TAC treatment is beneficial for inducing remission. To determine the optimal strategy for improving the long-term outcomes of UC, further studies, such as a study involving a direct comparison between sequential TAC and IFX (or anti-TNF-α) therapy and thiopurine monotherapy following the induction of remission with TAC, are warranted.

CONCLUSION

IFX and TAC produced similar short-term outcomes in UC patients, but IFX produced better long-term outcomes than TAC in terms of colectomy avoidance. This suggests that IFX therapy may be the first-choice treatment for moderate to severe UC, whereas improvement of long-term remission maintenance strategy after initial TAC treatment should be helpful for patients in whom IFX is contraindicated.

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