Comparative Effectiveness of Tacrolimus and Infliximab in Hospitalized Patients With Ulcerative Colitis

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INTRODUCTION: **Cyclosporine or infliximab (IFX) have been used to avoid surgery in patients with severe refractory ulcerative colitis (UC). Tacrolimus (Tac) is occasionally used as an alternative to cyclosporine; however, the comparative efficacy of Tac and IFX has not been reported. We aimed to compare the effectiveness of Tac and IFX in hospitalized patients with UC.**

METHODS: **In a propensity score–matched cohort derived from a large nationwide database, 4-year effectiveness was compared between patients initiated on Tac and those initiated on IFX. The primary outcome was the colectomy rate during the index hospitalization. We also analyzed the cumulative medication discontinuation, UC-related rehospitalization, and colectomy rates after discharge.**

RESULTS: **Among 29,239 hospitalized patients, 4,565 were extracted for eligibility, of whom 2,170 were treated with Tac and the remaining 2,395 with IFX. After propensity score matching, 1,787 patients were selected for each group. During the index hospitalization, excluding patients who switched to another molecular-targeted agent, the colectomy rate was higher in the Tac group than in the IFX group (7.8% vs 4.2%, $P < 0.01$). Among patients discharged without colectomy, the cumulative medication discontinuation (28.4% vs 17.1%, $P < 0.01$) and rehospitalization (22.4% vs 15.4%, $P < 0.01$) rates were higher in the Tac group than in the IFX group; however, there was no difference in the cumulative colectomy rate (3.3% vs 2.7%).**

DISCUSSION: **Although Tac and IFX were effective for avoiding surgery in hospitalized patients with UC, IFX was more effective than Tac. IFX also had higher long-term effectiveness. Future prospective studies comparing the efficacy of Tac and IFX are warranted.**

KEYWORDS: tacrolimus; infliximab; ulcerative colitis; colectomy; comparative effectiveness

Clinical and Translational Gastroenterology 2024;15:e00642. https://doi.org/10.14309/ctg.0000000000000642

INTRODUCTION

Ulcerative colitis (UC), categorized as an inflammatory bowel disease together with Crohn's disease (CD), is characterized by repeated relapses and remissions (1). In UC, immune-mediated inflammation causes diffuse and continuous damage to the mucosa from the rectum to the colon, often leading to erosions and ulcers (2). UC onset typically occurs in young adulthood and persists throughout life (3,4); however, the number of patients with UC with elderly onset is increasing (5). The treatment for patients with UC is based on the disease severity. Most patients with UC have mild-to-moderate disease severity, and these patients are mainly treated on an outpatient basis (1–3). By contrast, patients with moderate-to-severe disease and those with acute severe UC (ASUC) based on specific criteria (vital signs and laboratory findings) often require systemic therapy and may require hospitalization or surgery to manage their colitis.

For patients with moderate-to-severe disease, corticosteroids are the standard remission induction therapy, but not used as remission maintenance therapy. Corticosteroids are also used for the primary treatment of ASUC, for which high-dose intravenous corticosteroid therapy is recommended (3). However, approximately 20% of patients do not respond to steroid therapy (6,7). Refractory cases that are resistant to steroid therapy may require surgery. In these cases, cyclosporine A (CsA) or infliximab (IFX)

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Received June 2, 2023; accepted September 15, 2023; published online September 27, 2023

may be used to avoid surgery (3). CsA is a calcineurin inhibitor blocking cytokines mediated by T cells and has efficacy in steroid-resistant patients with ASUC demonstrated over 20 years (8). IFX is a biologic agent that blocks downstream proinflammatory pathways by binding to tumor necrosis factor (TNF)-α and showed efficacy in ASUC (9,10). Two randomized controlled trials (11,12), investigated whether CsA or IFX should be used to treat ASUC and found no difference in short-term efficacy between the 2 agents. A meta-analysis of the randomized controlled trials also reported no difference in short-term response between them (13).

Tacrolimus (Tac), another calcineurin inhibitor developed in Japan, has been proven to be effective and safe for the management of moderate-to-severe steroid-refractory UC (14). In Japan, where CsA is not available, Tac is used as an alternative for CsA. Indeed, along with IFX, Tac is recommended for the treatment of severe UC in Japanese guidelines (2). However, Tac is not currently recommended in the Western guidelines (13). In addition, data on the comparative efficacy of Tac vs IFX are limited to several retrospective studies with small sample sizes (15,16). We sought to examine short-term and long-term outcomes of patients hospitalized for UC and treated with Tac or IFX using a large nationwide database in Japan.

MATERIALS AND METHODS

Diagnosis procedure combination database

The diagnosis procedure combination (DPC) is an inpatient medical billing system introduced in 2003 for acute care hospitals in Japan. This system was used by 1,757 hospitals in 2020, covering approximately 83% of acute care beds in Japan. Every patient is assigned an identification number, which contains a code linked to the facility. Now, we can also track the process of outpatient care. Thus, the course of both outpatient care and inpatient care at the same facility can be followed in chronological order. In this analysis, we first extracted the index hospitalization data in which Tac or IFX was administered for the first time for the treatment of UC. Then, both outpatient and rehospitalization data linked to the index hospitalization data were obtained. If a patient is transferred from one facility to another, he/she is assigned another identification number that contains a different facility code. Therefore, the same patient cannot be tracked across multiple institutions using this database.

This system provides the following information: diagnosis according to the *International Classification of Diseases and Related Health Problems, 10th Revision* (17), date of admission, admission route, date of discharge, discharge destination, discharge outcome, date of last discharge, diagnostic information (diagnosis leading to admission, diagnosis requiring the most medical resources, and comorbidities), patient profile (sex, date of birth, body height, body weight, and smoking index), surgical information (date of surgery, surgical procedure), and medications used (18–21). The DPC database has already been used and verified in many clinical studies (20). We have also reported several studies using the DPC database (22,23).

The study protocol was reviewed and approved by the Ethics Committee of Tohoku University Graduate School of Medicine (2021-1-815). Considering the anonymity of data, informed consent was waived.

Selection of eligible cases

Among patients discharged from hospitals using the DPC system between April 2016 and March 2020, those whose most resource-requiring diseases included confirmed UC were extracted. Of these patients, we intended to select those who were initiated on Tac or IFX for UC for the first time during their hospitalization (index hospitalization). For this purpose, patients with a history of Tac or anti-TNF agents (IFX, adalimumab [ADA], or golimumab [GLM]) use within 6 months before admission were excluded. Those with comorbidities that might require the use of Tac or IFX (myasthenia gravis, lupus nephritis, rheumatoid arthritis, pyoderma gangrenosum, psoriasis, ankylosing spondylitis, Behçet disease, Kawasaki disease, or CD) and those with a hospital stay of 3 days or less were also excluded. We collected the following relevant data: sex, age, body mass index (BMI), smoking history, Charlson comorbidity index (24), date of admission, emergency hospital admission or not, academic hospital admission or not, date of discharge, drugs used (Tac, IFX, ADA, GLM, corticosteroid, azathioprine [AZA], 6-mercaptopurine [6-MP]), and date of colectomy. Emergency admission referred to cases in which a patient was admitted directly after an ambulance visit or directly after an outpatient visit.

During the observation period, several new molecular-targeted agents were approved for the management of UC: tofacitinib in May 2018, vedolizumab in July 2018, and ustekinumab in March 2020. However, these molecular-targeted agents are mainly indicated for moderate disease in an outpatient setting. Therefore, we excluded cases not requiring hospitalization or those treated with these new agents.

Statistical analysis

Propensity score (PS) matching was performed based on the PS of each patient to compare the outcomes between the Tac and IFX groups. We estimated the PS by logistic regression analysis with patient profile (sex, age, BMI, smoking history, and Charlson comorbidity index), admission and discharge information (emergency hospital admission or not, academic hospital admission or not), and concomitant medications (corticosteroids, AZA or 6-MP) as covariates. Age (younger than 60 years or 60 years or older) and BMI (<18.5 or ≥ 18.5 kg/m^2) were classified into 2 categories. The 1:1 nearest neighbor method was used for PS matching. Caliper width was set to 0.2 times the SD of the logit-transformed PS estimate. The discriminability of the model was evaluated by c-statistic. Furthermore, standardized differences were calculated, and baseline characteristics between the 2 groups were judged to be balanced when the standardized difference was less than 0.1.

The rates of discontinuation (from Tac to IFX or another anti-TNF agent and from IFX to Tac or another anti-TNF agent) and colectomy during index hospitalization were compared using the χ^2 test. Among patients who remained on their initial agent (Tac or IFX) and were discharged without colectomy, the cumulative discontinuation rate of Tac or IFX, cumulative UC-related rehospitalization rate, and cumulative colectomy rate after discharge were calculated using the Kaplan-Meier method, and the differences between the 2 groups were compared using the log-rank test. Unlike IFX, Tac is mainly used for remission induction and is often bridged to thiopurines (AZA or 6-MP). Thus, bridging to thiopurines was not included in the discontinuation outcome, and only switching to another molecular-targeted agent with induction effect was considered as an outcome. The primary

outcome was the colectomy rate during index hospitalization; secondary outcomes included discontinuation rate of Tac or IFX during index hospitalization and cumulative discontinuation rate of Tac or IFX, cumulative rehospitalization rate, and cumulative colectomy rate after discharge. Discontinuation of Tac only due to switching to thiopurine (not the switch to another molecular-targeted agent) is not considered a medication discontinuation.

All statistical analyses were performed using JMP Pro16 (SAS Institute, Tokyo, Japan) software. $P < 0.05$ indicated a statistically significant difference.

RESULTS

Patient characteristics

From April 2016 to March 2020, there were 20,534,238 inpatient admissions at hospitals participating in the DPC system. Overall, 29,239 patients had "UC" as the most resource-requiring diagnosis, of which 6,671 patients were treated with Tac or IFX during hospitalization (3,005 patients with Tac and 3,666 patients with IFX). We excluded 1,402 patients with a history of prior administration of Tac or anti-TNF agents (IFX, ADA, or GLM), 113 patients with comorbidities that might require the use of Tac or IFX, 11 patients who underwent colectomy before Tac or IFX use, and 580 patients with a hospital stay of 3 days or less. Consequently, 4,565 patients were included in the final analysis, of whom 2,170 were assigned to the Tac group and the remaining 2,395 to the IFX group (Figure 1).

The patient characteristics are summarized in Table 1. The proportion of older patients (60 years or older) was lower in the Tac group (18.5%) than in the IFX group (25.4%, $P < 0.01$). The proportion of underweight patients (BMI <18.5 kg/m^2) was higher in the Tac group (31.9%) than in the IFX group (26.8%, $P < 0.01$). The rate of emergency admission was lower in the Tac

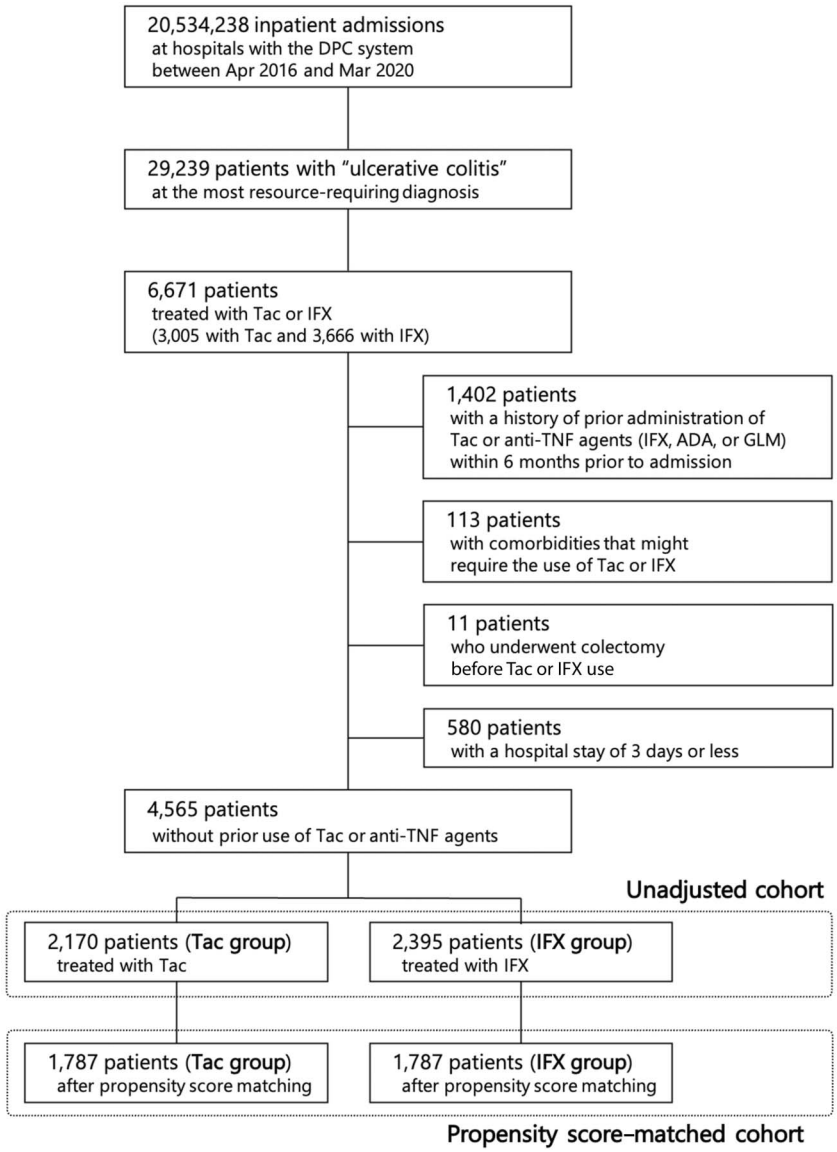

Figure 1. The flow from patient enrollment to PS-matching cohort. Among 6,671 patients treated with Tac or IFX during the index hospitalization, 4,565 patients were eligible for this analysis. After PS matching, 1,787 patients were selected for each of the Tac and IFX groups. ADA, adalimumab; DPC, diagnosis procedure combination; GLM, golimumab; IFX, infliximab; PS, propensity score; Tac, tacrolimus; TNF, tumor necrosis factor; UC, ulcerative colitis.

group (57.3%) than in the IFX group (62.3%, $P < 0.01$). The rate of admission to academic hospitals was higher in the Tac group (45.6%) than in the IFX group (28.4%, $P < 0.01$). There were no differences in other factors between the 2 groups.

After PS matching, 1,787 patients were selected for each of the Tac and IFX groups. The c-statistic of this model was 0.62. Patient characteristics after PS matching are summarized in Table 1. All standardized differences were less than 0.1, confirming no background differences between the 2 PS-matched groups.

Short-term outcomes

Of the 1,787 patients in each group, 214 (12.0%) in the Tac group and 82 (4.6%) in the IFX group switched their drug from Tac or IFX to another molecular-targeted agent (mainly from Tac to IFX or from IFX to Tac) within the index hospitalization. The medication discontinuation rate was higher in the Tac group than in the IFX group (odds ratio [OR] = 2.83, 95% confidence interval [CI]: 2.17–3.68, $P < 0.01$, Figure 2). Excluding patients who changed their medications, 123 (7.8%) of 1,573 patients in the Tac group and 71 (4.2%) of 1,705 in the IFX group underwent colectomy during the mean hospitalization period of 5.1 (SD: 3.3) and 4.5 (SD: 3.6) weeks; the short-term colectomy rate was higher in the Tac group than in the IFX group (OR = 1.95, 95% CI: 1.45–2.64, $P < 0.01$, Figure 2). Consequently, 1,450 (81.1%) patients in the Tac group and 1,634 (91.4%) patients in the IFX group were discharged without colectomy, remaining on the original drug.

When limited to patients who discontinued the original drug (214 patients in the Tac group and 82 patients in the IFX group), 178, 23, and 13 patients in the Tac group switched to IFX, ADA, and GLM, respectively, whereas 70, 4, and 8 patients in the IFX group switched to Tac, ADA, and GLM, respectively. After switching to another agent, 38 (17.8%) of 214 patients in the initial Tac group and 10 (12.2%) of 82 patients in the initial IFX group required colectomy, with no significant difference in the colectomy rate between the 2 switched subgroups (OR = 1.55, 95% CI: 0.74–3.29, $P = 0.23$).

Long-term outcomes

Among 3,084 patients (1,450 in the Tac group and 1,634 in the IFX group) who were discharged without medication discontinuation and colectomy, we analyzed the cumulative medication discontinuation, UC-related rehospitalization, and colectomy rates after discharge (Figure 3). During the mean postdischarge observation period of 64.9 (SD: 58.0) and 70.7 (SD: 58.9) weeks, 412 (28.4%) and 280 (17.1%) patients discontinued their medications and switched to other molecular-targeted agents in the Tac and IFX groups, respectively. The cumulative rates of

Table 1. Clinical characteristics of the study population

	Before PS matching			After PS matching[a]			
	Tac group n = 2,170	IFX group n = 2,395	*P* value	Tac group n = 1,787	IFX group n = 1,787	*P* value	Standardized difference[b]
Female (%)	855 (39.4)	949 (39.6)	0.87	704 (39.4)	702 (39.2)	0.95	0.002
Age, yr (mean ± SD)	44.2 ± 18.3	44.3 ± 19.3		42.2 ± 18.6	41.9 ± 18.6		
Age categories (%)		**<0.01**			0.13		
≥60 yr	401 (18.5)	609 (25.4)		337 (18.9)	341 (19.1)		0.006
<60 yr	1,769 (81.5)	1,786 (74.6)		1,410 (78.9)	1,446 (80.9)		0.050
BMI, kg/m^2 (mean ± SD)	20.6 ± 5.1	20.9 ± 3.8		20.75 ± 5.3	20.76 ± 3.9		
BMI categories (%)		**<0.01**			0.85		
<18.5 kg/m^2	664 (31.9)	628 (26.8)		526 (29.4)	531 (29.7)		0.006
≥18.5 kg/m^2	1,420 (68.1)	1,714 (73.2)		1,261 (70.6)	1,256 (70.3)		0.006
Smoking history (%)	714 (32.9)	846 (35.3)	0.09	598 (33.5)	596 (33.4)	0.94	0.002
CCI (mean ± SD)	0.29 ± 0.64	0.29 ± 0.75		0.29 ± 0.7	0.29 ± 0.7		
CCI categories (%)		0.07			0.82		
0	1,699 (78.3)	1,935 (80.8)		1,416 (79.2)	1,428 (79.9)		0.017
1	345 (15.9)	323 (13.5)		265 (14.8)	261 (14.6)		0.006
≥2	126 (5.8)	137 (5.7)		106 (5.9)	98 (5.5)		0.019
Emergency admission (%)	1,244 (57.3)	1,493 (62.3)	**<0.01**	1,079 (60.4)	1,135 (63.5)	0.05	0.065
Academic hospital (%)	989 (45.6)	679 (28.4)	**<0.01**	669 (37.4)	657 (36.8)	0.68	0.014
Concomitant corticosteroid (%)	1,667 (76.8)	1,857 (77.5)	0.56	1,381 (77.2)	1,378 (77.1)	0.90	0.004
Concomitant AZA or 6-MP (%)	915 (42.2)	955 (39.9)	0.12	733 (41.0)	719 (40.2)	0.63	0.016

AZA, azathioprine; BMI, body mass index; CCI, Charlson comorbidity index; IFX, infliximab; MP, mercaptopurine; PS, propensity score; Tac, tacrolimus.
[a]We estimated a PS by logistic regression analysis with patient profile (sex, age, BMI, smoking history, and CCI), admission and discharge information (emergency hospital admission or not, academic hospital admission or not), and concomitant medications (corticosteroids, AZA or 6-MP) as covariates. Age (younger than 60 or 60 yr or older) and BMI (<18.5 or ≥18.5 kg/m^2) were classified into 2 categories.
[b]After PS matching, covariates between the 2 groups were considered to be well balanced if the standardized difference was <0.1.

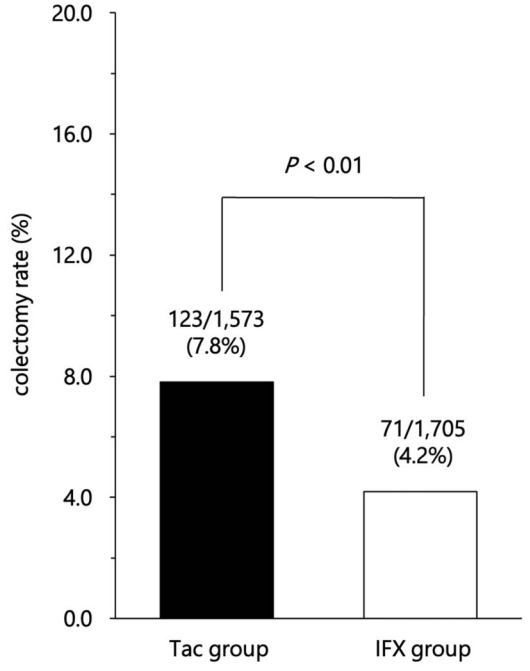

Figure 2. The colectomy rate during the index hospitalization. Of the 1,787 patients in each group, 214 (12.0%) patients in the Tac group and 82 (4.6%) patients in the IFX group switched from Tac or IFX to another molecular-targeted agent during hospitalization. Excluding patients who discontinued the original drug, 123 (7.8%) of 1,573 patients in the Tac group and 71 (4.2%) of 1,705 patients in the IFX group underwent colectomy during hospitalization. IFX, infliximab; PS, propensity score; Tac, tacrolimus.

medication discontinuation at 26, 52, and 156 weeks were 16.6%, 29.6%, and 40.7% in the Tac group and 10.9%, 16.9%, and 24.9% in the IFX group, respectively. The cumulative discontinuation rate was higher in the Tac group than in the IFX group (Log-rank test, $P < 0.01$, Figure 3a).

Regarding rehospitalization, 325 (22.4%) patients in the Tac group and 251 (15.4%) patients in the IFX group required rehospitalization. The cumulative rates of rehospitalization at 26, 52, and 156 weeks were 16.1%, 23.7%, and 38.1% in the Tac group and 11.3%, 15.6%, and 24.3% in the IFX group, respectively. The Tac group had a significantly higher cumulative rehospitalization rate than the IFX group (log-rank test, $P < 0.01$, Figure 3b).

Regarding postdischarge colectomy, 48 (3.3%) patients in the Tac group and 44 (2.7%) patients in the IFX group underwent colectomy. The cumulative rates of colectomy at 26, 52, and 156 weeks were 2.5%, 3.7%, and 5.6% in the Tac group and 2.0%, 2.9%, and 4.3% in the IFX group, respectively. Although the Tac group showed higher colectomy rates at 26, 52, and 156 weeks, there was no significant difference in the cumulative colectomy rates after discharge between the 2 groups (log-rank test, $P = 0.22$, Figure 3c).

DISCUSSION

CsA and IFX are the only 2 drugs with proven efficacy in avoiding surgery for severe refractory UC. Tac is occasionally used as an alternative to CsA in settings where CsA is not available, such as in Japan. However, there are no data comparing the efficacy of Tac and IFX in the management of severe UC. In this study, we sought to compare the effectiveness of Tac and IFX in the management of severe hospitalized UC using data from a large nationwide database. We found that the colectomy rate during the index hospitalization and the cumulative rates of medication discontinuation and UC-related rehospitalization after discharge were significantly higher in patients who received Tac when compared with those who received IFX.

Although outcome measures and subjects vary among studies, our findings of improved short-term and long-term outcomes with IFX compared with Tac are consistent with those appreciated in several small retrospective studies (16,25–27). Regarding the potential to avoid short-term colectomy, previous retrospective studies have reported relatively higher effectiveness for IFX than Tac, although the sample sizes were limited. Among 95 patients with steroid-refractory UC, Endo et al (16) reported clinical remission rates of 55.3% in the Tac group and 68.8% in the IFX group after 2 months. Among 46 patients with moderate-to-severe UC, Nuki et al (25) also reported clinical remission rates of 67% in the Tac group and 76% in the IFX group after 10 weeks. In a small number of subjects with moderate-to-severe UC, Otsuka et al (26) reported comparable clinical remission rates of 72.7% and 77.8% in the Tac and IFX groups, respectively, after 12 weeks. On the contrary, Yamagami et al (27) also reported a higher clinical remission rate of 50.0% for Tac compared with 37.9% for IFX after 14 weeks in 122 patients with moderate-to-severe UC. Although differences in disease severity of included subjects, outcome measures, or timing of evaluating outcomes may have affected differences in outcomes, a meta-analysis by Jia et al (15) that combined these reports found no significant difference in the short-term colectomy rate between Tac and IFX. In contrast to these small retrospective studies, this study using a large nationwide database showed that the colectomy rate in the Tac group was significantly higher than that in the IFX group during the index hospitalization.

As a subgroup analysis, we examined colectomy rates in patients who switched from Tac or IFX to another molecular-targeted agent during the same hospitalization. There are various perspectives on the feasibility of sequential treatment in ASUC. Although reports are limited, IFX has been shown to be effective in patients who were intolerant or refractory to Tac (28–31), and switching from IFX to Tac has also been shown to be effective (32). In this study, even if the first agent was ineffective, colectomy could be avoided in a high percentage of patients by switching from one agent to another. Both Tac to IFX and IFX to Tac were equally effective; therefore, it would be reasonable to use either agent as first line. Sequential treatment may be acceptable with the careful assessment of the increased risk of adverse events related to intense immunosuppressive therapy (33) although we were unable to analyze this risk in the current analysis. Early surgery may be a safe option if the patient fails to respond to Tac or IFX after high-dose intravenous steroid therapy.

Our subgroup analyses also compared the cumulative medication discontinuation, rehospitalization, and colectomy rates as long-term outcomes between the Tac and IFX groups in patients who were discharged without discontinuation and colectomy. As a result, the cumulative discontinuation and rehospitalization rates were higher in the Tac group than in the IFX group. A higher discontinuation rate in the Tac group may indicate that a certain number of patients were unable to bridge smoothly to thiopurines. In fact, a meta-analysis combining small retrospective analyses showed favorable results for long-term colectomy with

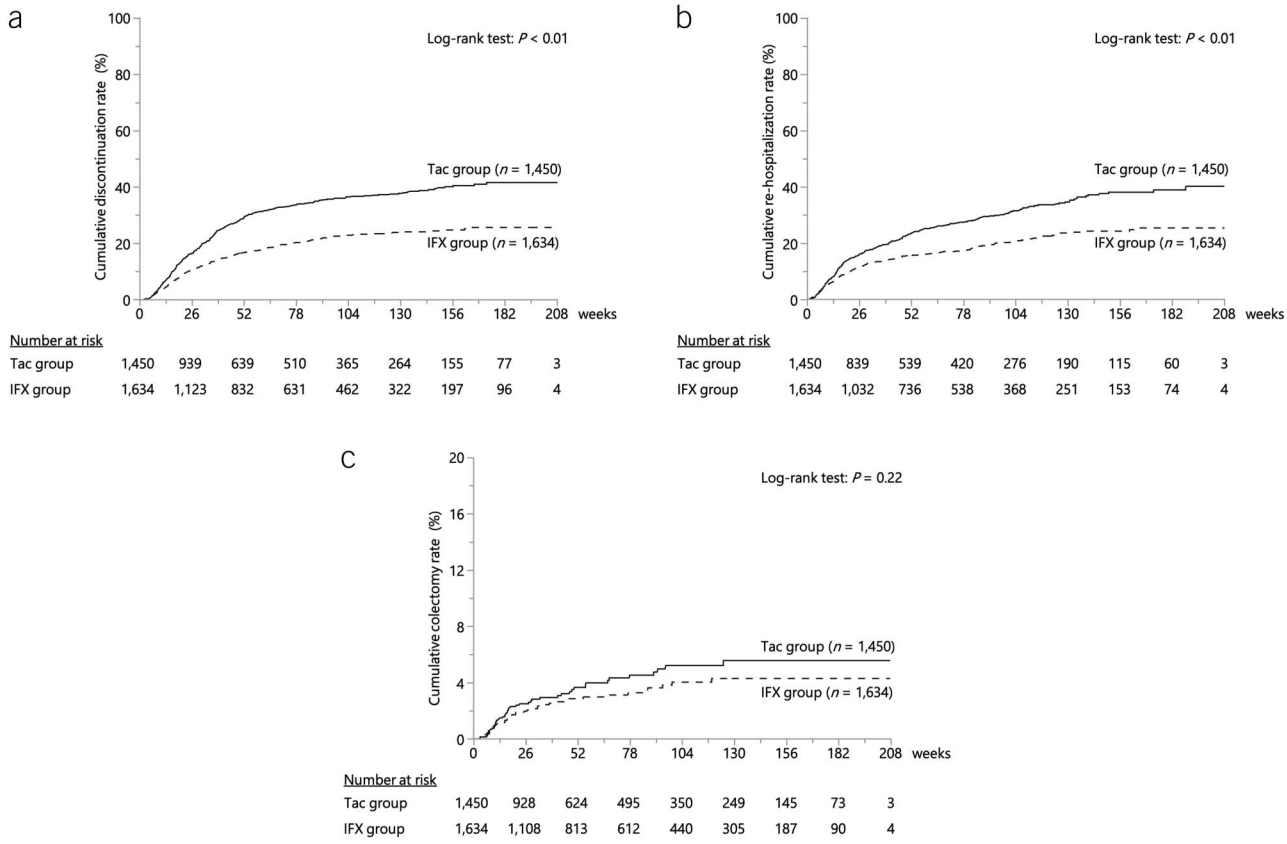

Figure 3. The cumulative medication discontinuation (**a**), rehospitalization (**b**), and colectomy (**c**) rates during postdischarge observation. Among patients who were discharged without medication discontinuation and colectomy (1,450 in the Tac group and 1,634 in the IFX group), we analyzed the cumulative medication discontinuation (**a**), UC-related rehospitalization (**b**), and colectomy (**c**) rates using the Kaplan-Meier method. The cumulative discontinuation and rehospitalization rates were higher in the Tac group than in the IFX group (Log-rank test, $P < 0.01$). There was no significant difference in the cumulative colectomy rates between the 2 groups. IFX, infliximab; Tac, tacrolimus.

IFX, although not significantly (15). Contrary to the cumulative discontinuation and rehospitalization rates, there was no significant difference in the cumulative colectomy rate between the 2 groups. A difference may not have been detected because of the low rates in both groups. Alternatively, once the high-risk group for colectomy is excluded during hospitalization, the long-term ability to avoid surgery may be comparable between the Tac and IFX groups. The aforementioned meta-analysis also showed no significant difference in colectomy rates between the 2 groups at 1 and 3 years, consistent with the results of our study (15).

The use of the DPC database allowed us to compare the effectiveness of the 2 groups on a larger scale than previously reported. However, the most important issue with the DPC database was that it did not include information on blood and imaging tests, which may have led to differences in pretreatment disease severity between the 2 groups. Therefore, we performed PS matching to adjust patient characteristics of the 2 groups. As a result, IFX might be superior to Tac in avoiding surgery. Current guidelines for hospitalized severe UC recommend the use of CsA or IFX to avoid surgery (13). While the short-term efficacy is generally equivalent, IFX is preferred over CsA in the long-term course. On the contrary, in the setting where CsA is not available and either Tac or IFX is used to avoid surgery (2), we found IFX was superior to Tac in preventing colectomy during index hospitalization. In addition, long-term outcomes were better in the IFX group. However, there are several limitations to make our findings to be generalized.

First, the DPC database does not include information on blood and imaging tests including colonoscopy, which limits the precise assessment of disease severity. By restricting the subjects to hospitalized patients, we were able to identify only patients with severe disease including ASUC. However, given the relatively low surgery rate in this study, the proportion of ASUC among the target population may not be so high. Second, although we adjusted for the bias in disease severity between the Tac and IFX groups using PS matching, we could not fully adjust for unmeasured confounding factors. They may include genes related to Tac-metabolizing enzymes and laboratory and endoscopic findings related to the severity of the disease. Third, because the DPC database does not track individuals through multiple hospitals, data might be duplicated for patients transferred to other hospitals.

In conclusion, this study showed that Tac and IFX were effective for avoiding surgery in hospitalized patients with UC, based on analyses derived from a large nationwide database. However, regarding the short-term outcome, the IFX group had a significantly lower colectomy rate than the Tac group. Regarding the long-term outcomes, the cumulative discontinuation and rehospitalization rates were lower in the IFX group; however, there was no significant difference in the cumulative colectomy

rate between the 2 groups. Both prospective studies comparing Tac and IFX and large retrospective or prospective studies comparing Tac and CsA are warranted.

CONFLICTS OF INTEREST

Guarantor of the article: Hisashi Shiga, MD, PhD.

Specific author contributions: T.T. and H.S.: conceived the study, wrote the study protocol, collected and analyzed the data, and wrote the manuscript. K.T., K.Fus., and K.Fuj.: collected the data. Y.S., T.N., R.M., M.K., Y.Ka., Y.Ki., and A.M.: contributed to discussions. All authors had full access to all the data in this study and approved the final version of the manuscript.

Potential competing interests: H.S. received lecture fees from Mitsubishi Tanabe Pharma Corp., AbbVie Inc., EA Pharma Co. Ltd., Janssen Pharmaceutical K.K., Takeda Pharmaceutical Co. Ltd., and Pfizer Inc. Y.Ka. received research grants from AbbVie Inc., Daiichi Sankyo Co. Ltd., Kyowa Kirin Co. Ltd., PRECISION IBD, and Janssen Pharmaceutical K.K. and received lecture fees from Mitsubishi Tanabe Pharma Corp. and Janssen Pharmaceutical K.K. A.M. received research grants from Zeria Pharmaceutical Co. Ltd., JIMRO Co. Ltd., Mochida Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corp., AbbVie Inc., EA Pharma Co. Ltd., and Takeda Pharmaceutical Co. Ltd. and received lecture fees from AbbVie Inc., EA Pharma Co. Ltd., and Takeda Pharmaceutical Co. Ltd. For the remaining authors, none were declared.

Financial support: None to report.

IRB approval statement: The study protocol was reviewed and approved by the Ethics Committee of Tohoku University Graduate School of Medicine (2021-1-815).

Study Highlights

WHAT IS KNOWN

- ✓ Several studies have analyzed comparative efficacy of cyclosporine and infliximab (IFX) for acute severe ulcerative colitis.
- ✓ Comparative efficacy of tacrolimus (Tac), another calcineurin inhibitor, and IFX has not been reported.

WHAT IS NEW HERE

- ✓ Four-year effectiveness of Tac and IFX for hospitalized patients with ulcerative colitis was compared using a large nationwide database.
- ✓ During the index hospitalization, colectomy rate was higher in the Tac group.
- ✓ Among patients discharged without colectomy, cumulative discontinuation and rehospitalization rates were also higher in the Tac group.
- ✓ This large database analysis leads to future prospective studies.

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