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ORIGINAL ARTICLE—ALIMENTARY TRACT

Real-world efficacy and safety of advanced therapies in hospitalized patients with ulcerative colitis

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Abstract

Background This multicenter observational cohort study aimed to evaluate the utilization and short-term efficacy of advanced therapy (AT) in hospitalized patients with acute severe ulcerative colitis (ASUC).

Methods In total, 221 patients with ASUC were enrolled between August 2020 and July 2021. The primary endpoint was clinical remission (CR, defined as a patient-reported outcome score < 2 with no blood in the stool) rate on Day 7 and 14 in hospitalized patients who received corticosteroids (CS) and AT.

Results Among patients with ASUC, 120 and 101 patients received CS or any AT as first-line treatment, respectively. The CR rates on Day 7 and 14 were 22.5% and 35.0%, respectively, in hospitalized patients who received CS as first-line treatment. Most patients who used ATs had CS-dependent or frequent recurrences. Eight different ATs (apheresis, tacrolimus, infliximab, golimumab, tofacitinib, vedolizumab, ustekinumab, and cyclosporine) were used as first-line treatment in patients with ASUC, and the CR rates on Day 7 and 14 were 16.8% and 29.7%, respectively. Twenty-five patients received the second ATs after hospitalizations, and the CR rates on Day 7 and 14 were 0% and 12%, respectively. The CR rates on Day 14 were significantly higher in patients who changed to AT than in those whose

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dose of CS increased (34.0% vs 10.7%, $p = 0.020$) among patients who had already used CS before hospitalization. *Conclusion* Most first-use ATs were effective for patients with ASUC, while second-use ATs might have had limited benefits in inducing CR. These findings may contribute to considerations for the management of hospitalized patients.

Keywords Acute severe ulcerative colitis · Advanced therapy · Biologics · Janus kinase inhibitor

Abbreviations

5-ASA	5-Aminosalicylic acid
ADA	Adalimumab
AE	Adverse effect
AGA	American Gastroenterological Association
ASUC	Acute severe ulcerative colitis
AT	Advanced therapy
BSG	British Society of Gastroenterology
CAP	Apheresis
CDI	*Clostridioides difficile* Infection
CI	Confidence interval
CMV	Cytomegalovirus
CR	Clinical remission
CRP	C-reactive protein
CS	Corticosteroids
CSA	Cyclosporine
DVT	Deep vein thrombosis
ECCO	European Crohn's and Colitis Organization
ESR	Erythrocyte sedimentation rate
GLM	Golimumab
IFX	Infliximab
IL	Interleukin
JAK	Janus kinase
MES	Mayo endoscopic subscores
OR	Odds ratio
PRO2	Patient-reported outcome 2
RCT	Randomized controlled trial
TAC	Tacrolimus
TNF	Tumor necrosis factor
TOFA	Tofacitinib
TPN	Total parenteral nutrition
UC	Ulcerative colitis
USD	Ustekinumab
VED	Vedolizumab

Introduction

Ulcerative colitis (UC) is a chronic intestinal disease with abdominal symptoms, characterized by repeated recurrence and remission, with continuous inflammation. Although the etiology and morbidity of UC remain unknown, and a fundamental treatment for UC has not yet been established, its pathophysiology has been extensively studied and found to involve host genetic factors, immune system dysregulation, and environmental factors [1]. Despite receiving 5-aminosalicylic acid (5-ASA) and corticosteroids (CS), some patients do not achieve clinical remission (CR) with these treatments. Therefore, several therapeutic treatments for treatment-refractory UC have been developed, including calcineurin inhibitors, anti-tumor necrosis factor (TNF)-α antibodies, Janus kinase (JAK) inhibitors, anti-integrin antibodies, and anti-interleukin (IL)-12/23 therapy [2–11]. However, treatment positioning for these agents remains unclear because of differences in the clinical background of the patients, such as age, clinical and endoscopic severity, and previous use of CS or biologics. The American Gastroenterological Association (AGA) clinical guidelines on moderate-to-severe UC management described the treatment options of biologics and JAK inhibitors for patients refractory to 5-ASA or CS according to the previous use of infliximab (IFX) [12]. The British Society of Gastroenterology (BSG) consensus guidelines on inflammatory bowel disease management indicated that escalation of thiopurine, anti-TNF agents, vedolizumab (VED), or tofacitinib (TOFA) can be used for CS-refractory or CS-dependent patients [13]. However, these treatments

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were described in parallel, and the drug choice should be determined by clinical factors, patient choice, cost, adherence likelihood, and local infusion capacity.

For hospitalized patients with UC, recent European Crohn's and Colitis Organization (ECCO) guidelines have indicated that treatment options, including cyclosporine (CSA) administration, IFX administration, or surgery, should be considered for non-responders to CS [14]. The AGA and BSG guidelines provided almost the same description [12, 13]. Although many studies have confirmed the clinical efficacy of advanced therapy (AT), including biologics and JAK inhibitors, these treatments mainly target outpatients. Nevertheless, tacrolimus (TAC), VED, ustekinumab (UST), and TOFA, in addition to IFX and CSA, can be used even for hospitalized patients with severe disease, who do not respond to systemic CS in recent Japanese guidelines from the research group of inflammatory bowel disease in the Ministry of Health, Labor, and Welfare. However, few studies have assessed the usefulness of various AT in hospitalized patients with acute severe UC (ASUC) when ATs are used as the first-line treatment. In addition, few studies have investigated the clinical outcomes of hospitalized patients who received a second AT after clinical efficacy was not obtained by the first AT.

Therefore, we aimed to clarify the usefulness and safety of treatments in patients with active UC requiring hospitalization. This multicenter observational cohort study was conducted to clarify the usage status and evaluate the rapid efficacy of the first and second AT in addition to CS in hospitalized patients with ASUC.

Methods

Patients

Hospitalized patients with UC from 39 institutions were prospectively enrolled in this study between August 2020 and July 2021. The data of hospitalized patients who required medical treatment due to exacerbation of clinical symptoms were collected. Hospitalizations owing to other diseases were excluded. Patients meeting all of the following criteria were enrolled: (1) UC diagnostic criteria according to the Japanese Research Group for Intractable Inflammatory Bowel Disorders, Ministry of Health, Labor, and Welfare; (2) hospitalized patients owing to disease aggravation of UC; (3) patients who would use CS, apheresis (CAP), TAC, IFX, adalimumab (ADA), golimumab (GLM), TOFA, VED, UST, or CSA after admission and throughout hospitalization; and 4) patients aged ≥ 16 years. Patients meeting one of the following criteria were excluded: (1) outpatients; (2) those having colitis other than UC (infectious or ischemic colitis); (3) those who underwent or had already undergone colectomy; and (4) those participating in clinical trials of other drugs.

In this study, data on patients with ASUC were collected from all hospitalized patients of this cohort to assess the usefulness of CS, the first AT, and the second AT in patients with ASUC. ASUC was defined in cases of hospitalized patients with the following Truelove–Witts criteria: six or more bloody bowel movements per day with at least one marker of systemic toxicity, including heart rate > 90 beats/min, body temperature > 37.8 °C, hemoglobin level < 10.5 g/dL, and/or erythrocyte sedimentation rate (ESR) > 30 mm/h [15]. As the ESR could not be measured in all institutions, C-reactive protein (CRP) > 3 mg/dL was adopted if ESR data were missing.

Data collection

The day when each treatment (CS, CAP, TAC, IFX, ADA, GLM, TOFA, VED, UST, and CSA) was started was registered as Day 0 of the first treatment after hospitalization. These patients were followed until 28 days after each treatment or the day when colectomy was needed. If other treatments were changed or added within 28 days of the first treatment, they were registered as the second treatment. Data were collected from the medical charts of each institution. We assessed demographic data at entry, including sex, age, disease duration, the extent of disease, the presence of CS-dependent disease, history of disease recurrences within 12 months, and the use of medication for UC before administration. Body temperature (Celsius) and pulse rate (beats/min) were also recorded at entry.

The type of each treatment after admission, and patient-report outcome 2 (PRO2) at Day 0, 3, 7, and 14 from the initiation of each treatment were collected. PRO2 was defined as the sum of all Mayo endoscopic subscores (MES) for daily diarrhea and rectal bleeding. Data on hemoglobin, serum albumin, and CRP levels were also collected. Adverse effects (AE) were also recorded.

Definitions of AT

AT was defined as treatment with CAP, TAC, IFX, ADA, GLM, TOFA, VED, UST, and CSA. Filgotinib and upadacitinib were not allowed for use in 2020.

Outcomes

We evaluated the clinical efficacy of each treatment in hospitalized patients with ASUC. The primary endpoint was the rate of CR at Day 7 and 14 in patients who were treated with CS, first AT, and second AT. CR was defined as PRO2 < 2 with no blood in the stool. Patients requiring alternative treatments or colectomy were defined as those

with no CR. The main secondary endpoints were the clinical improvement (CI) rate on Day 7 and 14 and the proportion of patients requiring colectomy within 28 days. CI was defined as a decrease of at least 50% in PRO2. These outcomes were assessed in patients within the following groups; (1) patients who received CS as the first-line treatment immediately after hospitalization; (2) patients who received any ATs without additional CS as the first-line treatment immediately after hospitalization; (3) patients who received ATs owing to CS refractoriness (CS → AT); and (4) patients who received second ATs throughout their hospitalizations (CS → AT → AT, or AT → AT).

We also evaluated the difference in treatment selection (CS or AT) and therapeutic effects depending on the presence or absence of steroid use before hospitalization.

The difference in PRO2 on Day 0 from PRO2 on Day 3, 7, and 14 was also assessed in patients with CS or each AT. For safety analysis, the number and type of AEs were assessed.

Statistical analyses

Baseline characteristics of patients were described using means with standard deviations for continuous data and absolute numbers with percentages for categorical data. Predictive factors for achieving CR on Day 7 and 14 in patients receiving CS after hospitalizations were also assessed using univariate and logistic regression as multivariate analysis. The change from baseline at each time point in PRO2 was tested using a mixed-effects model for repeated measures with an unstructured covariance matrix. Regarding the change from baseline at each timepoint in PRO2, only treatments with six or more cases were analyzed. Appropriate contrasts were created for the test, and Kenward–Roger adjustment was used for degrees of freedom of error variance SAS version 9.4 (SAS Institute Inc, Cary, NC). To examine whether an increased dose of CS or use of AT should be selected as a treatment after hospitalization in patients who already used CS before hospitalization, clinical outcomes (CR rates on Day 7 and 14 and proportion of necessary for surgery within 28 days) were compared between the CS (increased dose of CS) and AT groups using the Chi-squared or Fisher's direct tests.

Ethics

The study design was reviewed and approved by the Ethics Committees of Kansai Medical University Hospital (2020044) and each participating institution. Written informed consent was obtained while an opt-out approach was also allowed because there was no risk to the participants. Patients were given the opportunity to refuse participation in this study by posting their preferences on the institutional website.

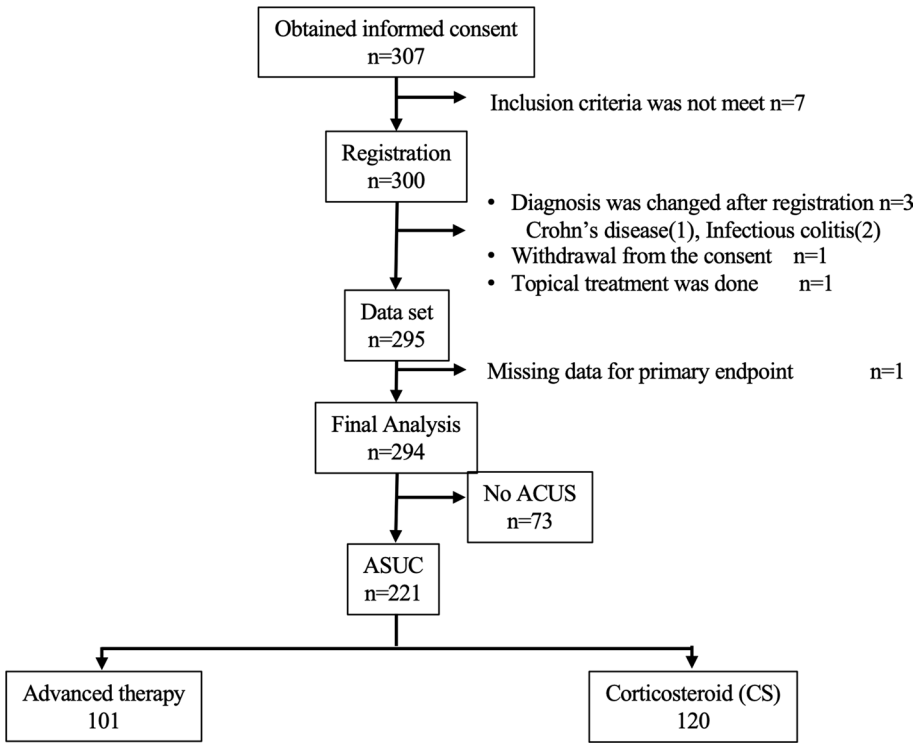

Fig. 1 The flowchart of the entire cohort. To examine the usefulness of corticosteroids (CS) and advanced therapy, the data of patients with acute severe ulcerative colitis (ASUC) were collected

Table 1 Characteristics of hospitalized patients with acute severe ulcerative colitis (ASUC) at entry

Characteristics	Total ($n=221$)	CS ($n=120$)	Advanced therapy ($n=101$)	p value (CS vs. advanced therapy)
Age, years (mean ± SD)	43.4 ± 17.2	41.5 ± 16.7	45.5 ± 17.6	0.087
Female sex, *n* (%)	79 (45.4%)	58 (48.3%)	39 (39.6%)	0.185
Duration of disease, years (mean ± SD)	5.7 ± 7.7	4.7 ± 6.9	6.9 ± 8.5	0.032
Pancolitis, *n* (%)	197 (89.1%)	108 (90.0%)	89 (88.1%)	0.529
Steroid-dependent disease, *n* (%)	57 (25.8%)	25 (20.8%)	32 (31.7%)	0.046
Clinical recurrence ≥ 2 times within the recent 12 months, *n* (%)	36 (16.3%)	11 (9.2%)	25 (24.8%)	0.002
Times of daily diarrhea (mean ± SD)	11.8 ± 5.0	12.2 ± 5.4	11.2 ± 4.5	0.135
Body temperature at registration, ℃ (mean ± SD)	37.4 ± 0.8	37.5 ± 0.8	37.4 ± 0.8	0.281
Pulse rate per minute (mean ± SD)	94.0 ± 16.2	96.1 ± 15.4	91.4 ± 17.8	0.033
Patient-reported outcome 2 (mean ± SD)	5.0 ± 0.9	5.1 ± 0.9	4.9 ± 1.0	0.149
Mayo endoscopic subscore (mean ± SD)	2.7 ± 0.4	2.7 ± 0.5	2.7 ± 0.5	0.351
C-reactive protein, mg/mL (mean ± SD)	6.7 ± 6.6	7.3 ± 6.7	6.2 ± 6.4	0.207
Hemoglobin, g/dL (mean ± SD)	11.1 ± 2.3	11.3 ± 2.9	11.0 ± 2.5	0.380
Erythrocyte sedimentation rate, mm/h (median ± IQR)	47.7 ± 27.0	47.3 ± 25.9	48.0 ± 28.2	0.873
Serum albumin, mg/mL (mean ± SD)	2.9 ± 0.7	3.0 ± 0.7	2.9 ± 0.8	0.299
Use of oral steroids at the entry, *n* (%)	78 (35.3%)	28 (23.3%)	50 (49.5%)	< 0.001
Use of thiopurine at the entry, *n* (%)	39 (17.6%)	11 (9.2%)	28 (27.7%)	< 0.001

CS corticosteroids, *IQR* interquartile range, *SD* standard deviation

Results

Patient characteristics

The study flowchart is shown in Fig. 1. Finally, 221 patients with ASUC were identified in this cohort, while 73 patients needed hospitalization owing to aggravation of UC but did not meet the criteria for the definition of ASUC. The clinical characteristics of the 221 patients with ASUC on admission are shown in Table 1. Among patients with ASUC, 120 and 101 patients received CS or any AT as first-line treatment, respectively. Although disease severities at entry, such as clinical severity, MES, CRP, and serum albumin, were comparable between the CS and AT groups, the proportion of steroid-dependent disease ($p=0.046$), clinical recurrence ≥ 2 times within the recent 12 months ($p=0.002$), use of oral steroids at the entry ($p<0.001$), and use of thiopurine at the entry ($p<0.001$) was significantly higher in the AT group than in the CS group.

Short-term clinical efficacy of CS in patients with ASUC

A total of 120 patients were treated with CS immediately as the first-line treatment after hospitalization (mean daily initial dose: 52.0 ± 11.6 mg). CR on Day 7 and 14 were 22.5% (95% confidence interval: 18.7–26.3) and 35.0% (95% confidence interval (CI): 30.6–39.4) in CS-treated patients (Table 2), respectively. The CI rates on Day 7 and 14 were 45.0% (95% CI 40.5–49.5) and 52.5% (95% CI: 47.9–57.1),

Table 2 Summary of short-term clinical outcomes (number, percentage, 95% CI) in patients receiving the first and second advanced therapies (ATs) after hospitalization

Treatment type	CR on Day 7	CI on Day 7	CR on Day 14	CI on Day 14	Colectomy rate within 28 days
CS after hospitalization ($n=120$)	27 (22.5%) (18.7–26.3)	54 (45.0%) (40.5–49.5)	42 (35.0%) (30.6–39.4)	63 (52.5%) (47.9–57.1)	9 (7.5%) (5.1–9.9)
AT after hospitalization ($n=101$)	17 (16.8%) (13.1–20.5)	40 (39.6%) (34.7–44.5)	30 (29.7%) (25.2–34.2)	44 (43.6%) (38.7–48.5)	12 (11.9%) (8.7–15.1)
AT due to CS refractoriness ($n=48$)	7 (14.6%) (9.5–19.7)	18 (37.5%) (30.5–44.5)	21 (43.8%) (36.6–51.0)	28 (58.3%) (51.2–65.4)	9 (18.8%) (13.2–24.4)
Second AT ($n=25$)	0 (0.0%)	6 (24.0%) (15.3–32.7)	3 (12.0%) (5.4–18.6)	7 (28.0%) (18.8–37.2)	6 (24.0%) (15.3–32.7)

AT advanced therapies, *CI* clinical improvement, *CR* clinical remission, *CS* corticosteroids

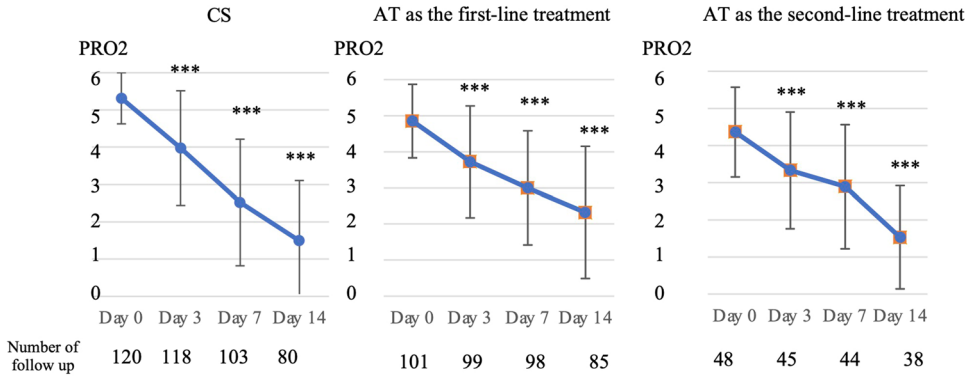

Fig. 2 Changes in patient-report outcome 2 (PRO2) on Day 0, 3, 7, and 14 in patients with acute severe ulcerative colitis (ASUC) who were treated with a) corticosteroids (CS) or b) advanced therapy (AT) as the first-line treatment, or c) in patients with ASUC who were treated with AT as the second-line treatment owing to refractoriness to CS. Differences of PRO2 on Day 0 vs. Day 3, 7, or 14 were compared. ***$p < 0.001$ vs. PRO2 on Day 0

respectively. There were no differences in the CR rates on Day 7 (38.9% vs 19.6%, $p = 0.071$) and 14 (44.4% vs 33.3%, $p = 0.362$) between patients with oral vs intravenous CS. The mean PRO2 rapidly decreased from 5.1 to 3.8 and 2.6 on Day 3 ($p < 0.001$) and 7 ($p < 0.001$), respectively (Fig. 2).

Regarding factors for predicting clinical outcomes in patients who received CS, no use of CS at entry (p = 0.001; OR: 0.21 [95% CI 0.08–0.53]) and PRO2 at baseline ($p = 0.001$; OR: 4.69 [95% CI 1.86–11.79]) were predictive for inducing CR on Day 14 for patients with ASUC (Supplemental Table 1b). No independent factors for inducing CR on Day 7 and the necessity of surgery within 28 days after CS were found in the multivariate analysis (Supplemental Table 1a, c).

Short-term clinical outcomes in patients with ASUC receiving AT as the first-line treatment

The clinical efficacy of AT, including calcineurin inhibitors, biologics, and TOFA, was evaluated in hospitalized patients ASUC. A total of 101 patients used any ATs as the first-line therapy just after hospitalization. IFX and TAC were mainly selected as the first-line ATs, followed by UST and CAP (Supplementary Fig. S1-a). The CR rates on Day 7 and 14 were 16.8% (95% CI 13.1–20.5) and 29.7% (95% CI 25.2–34.2), respectively (Table 2). The CI rates on Day 7 and 14 were 39.6% (95% CI 34.7–44.5) and 43.6% (95% CI 38.7–48.5), respectively. The colectomy rate within 28 days was 11.9% (95% CI 8.7–15.1). The mean PRO2 in patients using ATs also rapidly decreased from 4.9 to 3.7 and 3.0 on Day 3 (p < 0.001) and 7 (p < 0.001), respectively (Fig. 2). For each AT, the mean PRO2 at admission was high in patients receiving TAC (5.3) and TOFA (5.1) (Supplemental Table 2) and clinical responses were rapidly obtained in patients receiving most ATs as the mean PRO2 on Day 3 was significantly lower than that on Day 0 (p < 0.001 for IFX, TAC, CAP; p < 0.05 for TOFA and UST). The mean PRO2 also significantly decreased until Day 14 in patients receiving all ATs (Supplemental Table 2).

Clinical outcomes of AT in patients who were refractory to CS after hospitalization

Among the 120 patients receiving CS after hospitalization, 48 patients were treated with any ATs as second-line treatment due to refractoriness to CS. ATs were used from 3 to 17 days after initiation of CS. Thirty-eight patients (79.2%) received either IFX ($n = 20$) or calcineurin inhibitors ($n = 18$). Few CS-refractory patients received other ATs as the second-line treatment. The CR rates on Day 7 and 14 were 14.6% (95% CI 9.5–19.7) and 43.8% (95% CI 36.6–51.0) (Table 2), respectively. The CI rates on Day 7 and 14 were 37.5% (95% CI 30.5–44.5) and 58.3% (95% CI 51.2–65.4), respectively. The colectomy rate within 28 days was 18.8% (95% CI 13.2–24.4). The mean PRO2 in patients using ATs also decreased from 4.4 to 3.3 and 2.9 on Day 3 ($p < 0.001$) and 7 ($p < 0.001$), respectively (Fig. 2). For each AT, the mean PRO2 on Day 3 was significantly lower than those of Day 0 ($p < 0.001$ for IFX and TAC) (Supplemental Table 3).

Clinical outcomes in patients receiving the second AT

In this study, clinical outcomes for CR induction were analyzed in 25 patients who received the second AT throughout hospitalization (Table 3). Nine, seven, six, two, and one patients received TOFA, IFX, UST, TAC, and VED as the second AT, respectively. No patients achieved CR on Day 7 and the CR and CI rates on Day 14 were 12.0% (95%

Table 3 Clinical characteristics and short-term outcomes in patients who received the second advanced therapy (AT)

Age/Sex	Disease duration (years)	Extent of disease	Type of first CS and/or AT after hospitalization	Type of second AT	Outcome until Day 28	Adverse effects
60 M	4	T	IFX	TOFA	Colectomy	
75 M	1	T	CS → CAP	TOFA	CR	
36F	14	T	ADA	TOFA	CR	
36 M	0	T	CS → TAC	TOFA	Colectomy	
22 M	1	T	CS → TAC	TOFA	Colectomy	CMV reactivation
45 M	1	T	IFX	TOFA	Colectomy	
40 M	11	T	TAC	TOFA	CR	
57F	21	T	CS → IFX	TOFA	CR	
41F	8	L	IFX	TOFA	CR	
46F	3	T	CS → CSA	IFX	Colectomy	Catheter-related blood stream infection
91F	30	T	VED	IFX	Colectomy	
64 M	34	T	TAC	IFX	Change to TOFA	
69F	2	T	TAC	IFX	CR	
18 M	3	T	TAC	IFX	CR	
49 M	5	T	CS → TAC	IFX	Colectomy	Renal dysfunction
43F	2	T	UST	IFX	CR was not obtained	
21F	1	T	CS → TAC	UST	CR was not obtained	DVT
68 M	2	T	CS → CAP	UST	CR	CMV reactivation
55 M	26	T	TOFA	UST	CR was not obtained	
25F	2	T	CS → TAC	UST	CR was not obtained	Renal dysfunction
57 M	0	T	CS → TAC	UST	CR	
50F	4	L	TOFA	UST	CR was not obtained	
53 M	2	T	CS → IFX	TAC	CR	
49F	29	L	CS → GLM	TAC	Change to UST	Renal dysfunction
34F	2	T	CS → CSA	VED	CR was not obtained	

ADA adalimumab, *CAP* apheresis, *CMV* cytomegalovirus, *CR* clinical remission, *CS* corticosteroids, *CSA* intravenous cyclosporine A, *DVT* deep vein thrombosis, *F* female, *GLM* golimumab, *IFX* infliximab, *L* left-sided colitis, *M* male, *PRO2* patient-report outcome 2, *T* total colitis, *TAC* tacrolimus, *TOFA* tofacitinib, *UST* ustekinumab, VED vedolizumab

CI 5.4–18.6) and 28.0% (95% CI 18.8–37.2), respectively. Finally, seven patients (28%) required colectomy. No severe AEs were found in patients receiving the second AT. A summary of short-term clinical outcomes in all patients receiving the first and second ATs is shown in Table 2 and Supplemental Fig. 2.

Clinical outcome in hospitalized patients who used CS before hospitalization

Further analyses were performed to examine the treatment options for ASUC patients who were on CS before hospitalization. Clinical outcomes between hospitalized patients receiving an increased dose of CS or patients receiving AT were compared among patients who already used CS before hospitalization. Among 78 patients who used CS at entry, 28 patients were treated with an increased dose of CS with a median dose of 60 mg (interquartile range

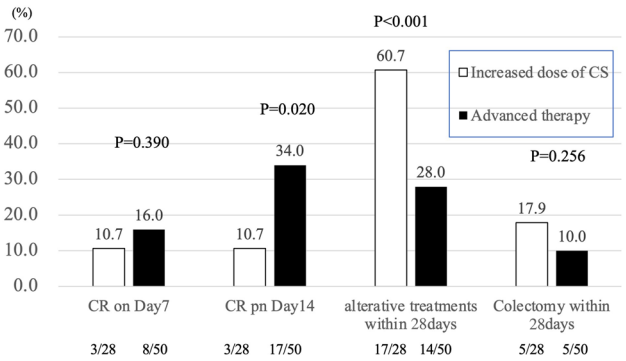

Fig. 3 Clinical remission (CR) rate on Day 7 and 14, proportion of alternative treatments within 28 days, and proportion of surgery within 28 days after first treatments in patients with increased dose of corticosteroids (CS) were compared to that in patients who received advanced therapy

[IQR]: 40–60) daily (CS group), while 50 patients were included in the alternative group (AT group). The CR on Day 14 ($p = 0.020$) was significantly higher in the AT group than in the CS group. Alternative therapies were needed in 60.7% (95% CI 51.5–69.9) of patients with increased doses of CS, while these were in 28.0% (95% CI 21.7–34.3%) in the AT group ($p < 0.001$) (Fig. 3). The proportion of patients who needed surgery within 28 days tended to be higher in the CS group than in the AT group (17.9% vs 10.0%; $p = 0.256$).

Adverse events

A total of 71 AEs were observed in patients with ASUC, including 53 during first-line treatment and 18 during second-line treatment (Table 4). Infection was observed in 39 cases. Cytomegalovirus (CMV) reactivation and *Clostridioides difficile* infection (CDI) occurred in 21 and nine cases, respectively. CMV reactivations were diagnosed by serology ($n = 15$), histology ($n = 2$) or both ($n = 4$). Most CMV reactivation (16/21, 76.1%) and CDI (6/8, 75.0%) were found in patients receiving CS. Seven cases had catheter-related bloodstream infections. Non-infected AEs were observed in 32 cases. Six of the seven renal dysfunction cases occurred in the TAC group. All renal dysfunction cases had elevated serum creatinine levels, and all patients recovered by reducing the TAC dose. Nine patients had liver dysfunction. Occurrence or exacerbation of diabetes was observed in four patients who received a daily CS dose ≥ 40 mg. For cardiovascular disease, deep vein thrombosis (DVT) occurred in two cases, and pulmonary embolism occurred in one patient. All patients were treated with anticoagulants, and none died. No pneumonia, tuberculosis, or death was observed in this cohort.

Table 4 Adverse events in this cohort

Infections	
Cytomegalovirus reactivation	21
Clostridioides difficile infection	8
Catheter-related blood stream infection	7
Sepsis	1
Herpes simplex infection	1
Acne	1
No infections	
Liver dysfunction	9
Renal dysfunction	7
Worsening diabetes	4
Pulmonary embolism/deep vein thrombosis	3
Depression	2
Nausea	2
Headache	1
Retinal detachment	1
Moon face	1
Loss of consciousness	1
Pancytopenia	1

Discussion

We conducted a multicenter cohort study of hospitalized patients with UC. To our knowledge, this study is the first to show real-world data regarding the clinical outcomes of the first and second AT after hospitalization, including most ATs, such as UST, VED, and TOFA, from many facilities. Approximately 40% of patients used AT as the first-line therapy because most of them had either steroid-dependent disease or frequently recurrence within 12 months. The short-term efficacy of the first AT was relatively high. However, limited data were available regarding the efficacy in patients receiving the second AT because only 25 patients received the second AT in this study. However, we confirmed that some patients achieved CR on Day 14 while 28% needed surgery after the second AT. This study's results are useful for the management of hospitalized patients and severe cases, for which evidence is limited.

First, our result indicated that the efficacy of CS was high when used as the first-line treatment in ASUC. Our study also indicated that no baseline CS use was an independent factor for the clinical efficacy of CS on Day 7 and 14. We believe that CS should be selected as the first-line drug for patients who have not been treated with steroids at admission, except for contraindicated cases. Many physicians may take these results for granted, but even now, with many treatments being developed and CS being avoided, CS should still be the mainstay of treatments in patients with UC who needed hospitalization. Our study was conducted from the first to the third wave of COVID-19 pandemic. Consensus statements and expert opinion in the early stages of the COVID-19 pandemic cautioned against use of high-dose CS in patients with inflammatory bowel disease (IBD) because of concerns regarding adverse outcomes of COVID-19 infection [16, 17]. CS were reported to be a risk factor for adverse COVID-19 outcomes in the SECURE-IBD registry [18, 19]. These facts led to concerns regarding the management of patients with ASUC. However, in our cohort, CS was selected as the first-line treatments in more than half of patients with ASUC. Although most of physicians in our study understood the risk of aggravation of COVID-19 infection owing to steroid use, it seems that they used CS appropriately in hospitalized patients with UC of this cohort, emphasizing the efficacy and immediate effect of CS on UC.

ASUC is a potentially life-threatening condition, characterized by clinical and laboratory assessments. For CS,

a dose of 1–1.5 mg/kg/day up to a maximum of 60 mg is recommended [20]. A systematic review of 32 trials of steroid therapy for ASUC reported a 67% overall response rate to CS, with 29% having colectomy, and a 1% mortality rate [21]. Rescue treatment with CSA or IFX is indicated in patients who do not sufficiently respond to CS after 3–5 days, with close monitoring of symptoms and serum CRP and albumin levels [12–14, 22]. Recently, randomized controlled trials (RCTs) comparing the efficacy and safety of IFX and CSA were conducted, and short- and mid-term clinical outcomes were comparable between two groups [23, 24]. A meta-analysis of RCTs of IFX and CSA showed no difference in response for up to 1 year. [25] Based on these results, IFX and CSA are now listed as rescue therapies in these guidelines. In contrast to the evidence of the clinical efficacy of IFX and CSA for ASUC, there is little evidence regarding the efficacy and safety of recently developed molecular targeting agents. No study has evaluated the usefulness of VED alone for patients with ASUC. Alternatively, the efficacy and safety of induction therapy with CSA [26, 27] or TAC [28] in combination with VED were reported in a small number of patients. The clinical efficacy of TOFA may be recognized in some case series [29–32] and case control studies [33]. However, off-label and high-intensity TOFA (30 mg daily) was used in some of these studies. Therefore, clear evidence of TOFA at normal dose has not been well demonstrated. The usefulness of UST was reported as an induction therapy in combination with calcineurin inhibitors for ASUC [34]. The results from recent large case control study showed that infliximab (70%) was most frequently used as rescue therapy, following by VED (10%), TOFA (7%), CSA (6%), and UST (6%) in patients with ASUC with COVID-19 pandemic cohort [18]. However, the clinical efficacy for these treatments was not well described in this study. Although the number of patients with ASUC who used non-IFX biologics was not very high, our study was valuable as it followed the short-term PRO2 transition and CR rate of many treatments.

Of note, approximately 40% of patients (101/221) received any ATs as the first-line treatment just after hospitalizations, although clinical guidelines indicate that CS administration is the first-line treatment for patients with ASUC. One of the reasons why ATs were selected as the first line for a relatively large number of patients may be explained by concerns about the effects of the COVID-19 pandemic, as described above. Another possible reason is that half of the patients who chose ATs as the first-line treatment used oral CS before admission. Physicians might consider that clinical benefits were obtained by changing to ATs from oral CS instead of increasing the dose of CS. In fact, our study indicated that the CR rates on Day 14 were significantly higher in patients who changed to ATs than in those whose dose of CS increased (34.0% vs 10.7%) among patients who already used oral CS before hospitalization. From our study, we were able to confirm some clinical efficacy of the first AT in patients who used CS before hospitalization. In addition, physicians might select AT depending on clinical severity at baseline because the mean PRO2 on Day 0 was different among patients who received each AT, and calcineurin inhibitors were selected in patients with relatively severe disease.

In this study, some critical AEs occurred in this cohort. Although reversible, most renal dysfunctions were observed in the TAC group. Catheter-related bloodstream infections were found in seven cases and DVT was induced in two cases. In these patients, total parenteral nutrition (TPN) was provided because oral intake was not possible because of severe intestinal inflammation. Although insertion of the central venous route was performed for TPN, it has some potential risks, including DVT and severe infections causing deaths. As total colectomy is an effective treatment for patients with severe or fulminant UC, efficacy of short-term medical treatment should be determined to avoid central vein insertion as much as possible.

Although our study is a relatively large study that focused on Japanese hospitalized patients with ASUC to evaluate the usefulness of the first and second AT during the early COVID-19 pandemic, there were some limitations. First, we did not calculate the sample size because this was an observational study to investigate the real-world clinical outcomes of CS, calcineurin inhibitors, biologics, and JAK inhibitors in hospitalized patients during the COVID-19 pandemic. We assumed that there were many cases of patients who used biologics in our cohort because CS was reportedly a risk factor for adverse COVID-19 outcomes in the SECURE-IBD registry. [18] However, there were many cases of patients who used CS, and therefore it was not possible to compare the difference in the therapeutic effects of various biologics in hospitalized cases. Nevertheless, we could confirm that the median PRO2 in patients received first-line ATs decreased in a short time. Second, there was a small number of patients receiving some ATs in this study. This may be explained by the paucity of evidence for the clinical efficacy of ATs in patients with ASUC. Third, although short-term efficacy of CS and AT was assessed in this study, long-term efficacy of AT was not investigated. Longer follow-up periods may have been necessary for UST and VED because of their slow therapeutic effects. However, the purpose of this study was to clarify the efficacy for ASUC. Thus, the short-term efficacy was evaluated. In the future, the mid- to long-term usefulness of UST and VED in hospitalized patients should be evaluated. Fourth, our study was performed only in a Japanese population, and we did not confirm the efficacy of AT for UC in patients of other races. Finally, variations in the treatment selection from each institution might

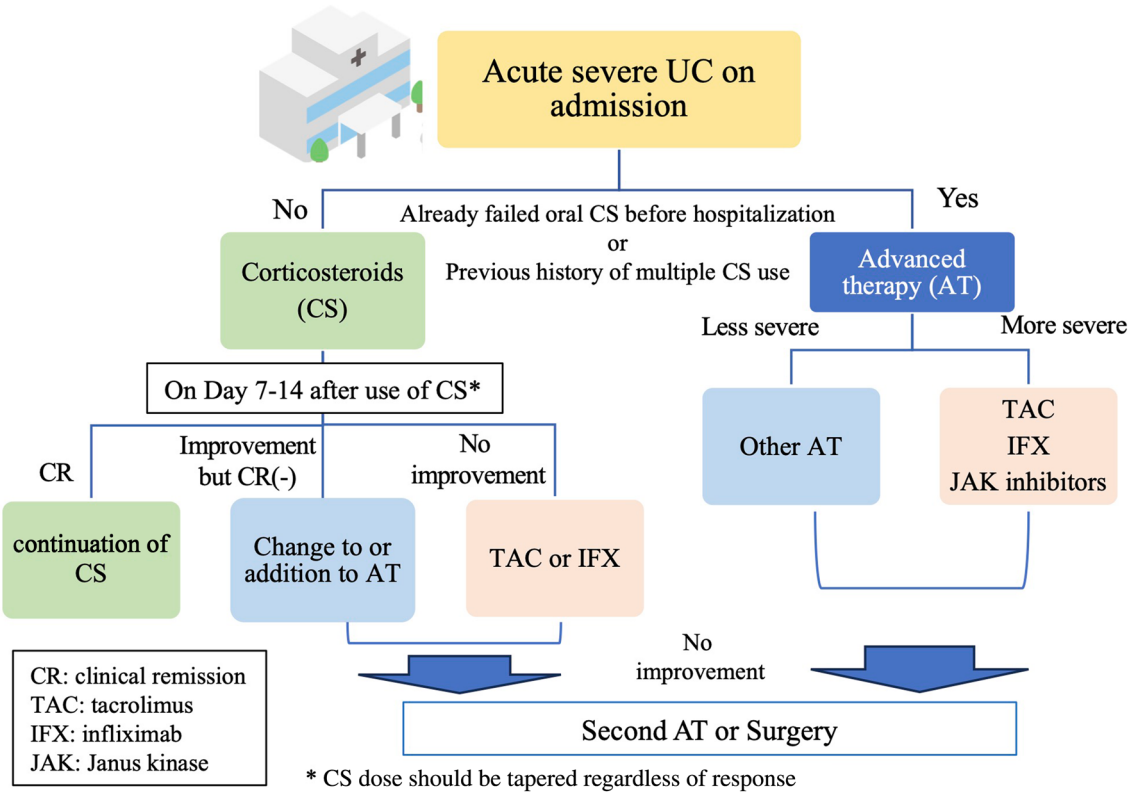

Fig. 4 The optimal treatment strategy for patients with acute severe ulcerative colitis (ASUC)

have affected clinical outcomes in this study. Despite these limitations, we have clarified treatment selection and their therapeutic effects against ASUC in hospitalized Japanese patients.

One of the strengths of our study was the evaluation of the short-term efficacy of the second AT in hospitalized patients. While some patients experienced clinical benefits after the use of the second AT, the efficacy of the second AT was limited as compared to that of the first AT. Second AT in cases of ASUC refractory to the first AT may delay the need for surgery. Therefore, it should only be used in specialized cases.

The optimal treatment strategy for patients with ASUC is presented in Fig. 4. Although intravenous CS is the first-line treatment for patients with ASUC, the choice of AT is useful for these patients who have already received oral CS before hospitalization (Fig. 3). The choice of AT as the first-line treatment may also be useful in patients who have received multiple courses of treatment with CS (Fig. 4). For patients with refractoriness to CS after hospitalization, use of calcineurin inhibitors or infliximab is better treatment options. Other ATs, such as UST and VED administration, may be useful for patients who have partially responded to CS but CR is not obtained until 7–14 days. When AT is used as the first-line treatment for patients with ASUC, administration of TAC, IFX, or TOFA is a better treatment option for more severe cases while other ATs may be useful for less severe cases among hospitalized patients.

In conclusion, several medical treatments, including biologics, JAK inhibitors, and calcineurin inhibitors, were selected as the first-line treatment for patients with ASUC. The short-term efficacy was satisfactory in patients receiving most treatments in our cohort. Most first ATs were effective for patients with ASUC, while second ATs might have limited benefits in inducing CR. These findings may contribute to future clinical practices for the management of hospitalized patients with UC.

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