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Differences in Clinical Practice and Disease Course Between Elderly-Onset and Long-Standing Elderly Ulcerative Colitis: A Single-Center Study in Japan

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The optimal immunosuppressive therapy for elderly patients with ulcerative colitis (UC) remains unclear. We aimed to evaluate clinical practice and prognosis in elderly patients with UC through comparing between those with elderly-onset UC (EOUC) and those with long-standing elderly UC (LEUC). In this retrospective single-center cohort study, we evaluated elderly patients with UC aged ≥ 60 in August 2022 through collecting medical record data from the time of diagnosis of UC until August 2022. The patients were divided into two groups based on age at disease onset: EOUC (age at onset, ≥ 60 years) and LEUC (age at onset, < 60 years). We assessed the cumulative rates of systemic steroid and molecular targeted drug (MTD) initiation, and colectomy. We enrolled 97 eligible patients (EOUC group, n = 30; LEUC group, n = 67). The cumulative rates of initiating systemic steroid (46% vs. 22% at 1 year, respectively; *P* = 0.002) and MTD (17% vs. 5% at 1 year, respectively; *P* = 0.002) were higher in the EOUC group than in the LEUC group. In multivariate analysis, elderly onset was significantly associated with systemic steroid (hazard ratio [HR] 2.74, 95% confidence interval [CI] 1.43-5.29; *P* = 0.003) and MTD (HR 2.76, 95% CI 1.30-5.87; *P* = 0.008) initiation. Cumulative colectomy rates did not differ significantly between the two groups. Patients with EOUC were initiated on systemic steroids and MTDs sooner following disease onset than patients with LEUC. Our findings suggest rapid progression and refractoriness in patients with EOUC.

Keywords: biologics; elderly patients; molecular targeted drugs; systemic steroids; ulcerative colitis
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Introduction

Ulcerative colitis (UC) is an idiopathic, chronic inflammatory disorder of the colonic mucosa (Xavier and Podolsky 2007). UC exhibits a bimodal onset pattern, with the main peak occurring between 20-30 years of age, and the second peak occurring between 50-70 years of age (Ordás et al. 2012; Ananthakrishnan 2015). The prevalence of UC is rapidly escalating in Asia (Thia et al. 2008; Prideaux et al. 2012), including Japan (Japan Intractable Diseases Information Center 2024). Along with the increased prevalence of UC and Japan's aging population, the incidence of elderly-onset UC (EOUC) has risen compared with previous years (Fujimoto et al. 2007; Takahashi et al. 2014). The disease course appears to differ between patients with EOUC and those with long-standing elderly UC (LEUC), which refers to individuals who were diagnosed with UC at a younger age and have subsequently aged. There have been reports that patients with EOUC have higher rates of hospitalization and surgery compared to those with LEUC (Matsumoto et al. 2013; Okabayashi et al. 2022).

The fundamental principles of medical management for elderly patients with UC are largely the same as those in other age groups (Gisbert et al. 2015; Sturm et al. 2017). However, elderly patients with UC exhibit an elevated risk of infection and neoplastic complications when treated with systemic corticosteroids, immunomodulators, or biologics (Stepaniuk et al. 2015; Sturm et al. 2017). Moreover, the risk of postoperative mortality increases in elderly patients undergoing surgery for UC (Ikeuchi et al. 2014; Sturm et al. 2017).

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The optimal immunosuppressive therapy for elderly patients with UC remains unclear (Lobatón et al. 2015; Ananthakrishnan et al. 2016; Kumar et al. 2017). Additionally, it remains controversial whether differences in the disease prognosis exist depending on the age at UC onset (Ha et al. 2010; Okabayashi et al. 2022).

In this study, we aimed to evaluate clinical practice and prognosis in elderly patients with UC through comparing between those with EOUC and those with LEUC.

Materials and Methods

Study design and patients

This retrospective cohort study was conducted at Tohoku University Hospital in Japan. We included the following patients: (i) those aged ≥ 60 years as at August 2022, (ii) those who attended Tohoku University Hospital between August 2017 and August 2022, (iii) those who met the diagnosis criteria for UC (Jeuring et al. 2016; Sturm et al. 2017; Park et al. 2021), and (iv) both those who had undergone a colectomy previously and those who had not. We excluded the following patients: (i) those who were diagnosed with Crohn's disease or inflammatory bowel disease unclassified, (ii) those who were observed for fewer than three months, and (iii) those whose medical records were inaccessible because they had been treated at other facilities. Eligible patients were divided into EOUC (age at onset, ≥ 60 years) and LEUC (age at onset, < 60 years) groups. The cut-off for the elderly age (60 years) was defined based on previous relevant studies (Jeuring et al. 2016; Sturm et al. 2017; Park et al. 2021).

Data collection

We investigated the medical records of eligible patients from the time a diagnosis of UC was made to the end of data collection (August 2022) or loss to follow-up, or death, whichever occurred first. The following data were collected at the time of UC diagnosis: age, sex, smoking status, disease extension, body mass index (BMI), and Charlson comorbidity index (CCI). Subsequently, we collected medical treatment data and responses to treatment during the follow-up period.

Specific data regarding the treatment of UC, including administration of systemic steroids, immunomodulators (thiopurines), molecular targeted drugs (MTDs), surgery (colectomy), and medication-related adverse events (AEs), were collected. The term "steroid-refractory" includes "steroid-resistant" and "steroid-dependent" conditions, which are defined as follows: Steroid-resistant cases show no significant improvement within 1-2 weeks despite proper steroid use. Steroid-dependent cases remain stable with ongoing steroid treatment but worsen or relapse when steroids are tapered (Dignass et al. 2012). MTDs were defined as follows: tumor necrosis factor α antagonists (anti-TNFs), including infliximab, adalimumab, and golimumab; $\alpha 4\beta 7$ integrin antibody (vedolizumab [VDZ]); a monoclonal antibody against the p40 subunit of interleukin-12 and interleukin-23 (ustekinumab [UST]); tacrolimus (Tac); and JAK inhibitors (JAKi), including tofacitinib and filgotinib.

Treatment strategy

In Japanese guidelines, the treatment strategies for UC patients do not differ from those in Western countries (Nakase et al. 2021). A step-up approach is mainly adopted and more potent therapies are administered if patients are refractory to, or intolerant of, first-line therapies. MTDs are used in cases of steroid dependence and resistance, as well as in cases where complications from systemic steroids are a concern. Regarding the choice of each MTD, factors such as disease activity, risk of complications, administration method, drug compliance, and patient preferences are taken into consideration.

Outcome measures

The primary outcome measures were the cumulative rate of initiation of systemic steroids and MTDs, and colectomy. We also evaluated the cumulative retention rate of MTDs and drug-related AEs. The cumulative retention rate of anti-TNF was compared between the EOUC and LEUC groups, and that of anti-TNF was compared with that of VDZ among all eligible patients.

Statistical analyses

Continuous variables were analyzed using a Mann-Whitney *U* test, whereas categorical variables were analyzed using Fisher's exact test. We used Kaplan-Meier analysis and a log-rank test to assess the cumulative rates of drug initiation and discontinuation, as well as the cumulative rates of undergoing surgery. A Cox proportional hazards model was used to estimate the association between clinical factors and the initiation of systemic steroids and MTDs and to calculate the hazard ratios (HRs) and 95% confidence intervals (95% CIs). All statistical analyses were performed using R for Windows, version 4.2.0 software. The level of significance was set at $P < 0.05$.

Ethical considerations

The study protocol was reviewed and approved by the Ethics Committee of the Tohoku University Graduate School of Medicine (2020-1-627). The requirement for informed consent was waived owing to the study's retrospective design and the opt-out approach.

Results

Patient characteristics

In total, 97 eligible patients were included in our study, of whom 30 and 67 were assigned to the EOUC and LEUC groups, respectively. Characteristics of the study population are summarized in Table 1. The average age at onset was 65.0 ± 5.6 years and 44.7 ± 11.1 years for the EOUC and LEUC groups, respectively, ($P < 0.001$). The average duration of UC was shorter in the EOUC group compared with the LEUC group (8.75 years vs. 22.3 years, respec-

Table 1. Characteristics of the EOUC and LEUC groups.

	EOUC	LEUC	*P* value
Number of patients	30	67	
Male sex (%)	19 (63.3)	41 (61.2)	1
Age at onset, mean (SD)	65.0 (5.6)	44.7 (11.1)	< 0.001
Disease duration (year), mean (SD)	8.75 (6.83)	22.3 (12.6)	< 0.001
Smoking status at onset (%)			
Non-smoker	6 (20.0)	29 (43.3)	0.039
Former smoker	21 (70.0)	26 (38.8)	0.0078
Current smoker	3 (10.0)	7 (10.4)	1
BMI at onset, mean (SD)	23.0 (2.8)	23.6 (4.5)	0.78
CCI at onset, mean (SD)	1.07 (1.0)	1.09 (1.6)	0.30
Disease extension at onset (%)			
Proctitis	0 (0)	11 (16.4)	0.016
Left-sided colitis	11 (36.7)	21 (31.3)	0.64
Extensive colitis	19 (63.3)	34 (50.7)	0.28
Unknown	0 (0)	1 (1.49)	
Refractory (%)	20 (66.7)	38 (56.7)	0.48
Steroid dependent	18 (60.0)	25 (37.3)	0.048
Steroid resistant	2 (6.67)	8 (11.9)	0.72
Systemic steroids (%)	22 (73.3)	39 (58.2)	0.27
Thiopurines (%)	10 (33.3)	25 (37.3)	0.88
Molecular targeted drugs (%)	14 (46.7)	27 (40.3)	0.72
Anti-TNF	8 (26.7)	19 (28.4)	0.92
Vedolizumab	10 (33.3)	7 (10.4)	0.0095
Ustekinumab	3 (10)	5 (7.5)	0.98
JAK inhibitor	3 (10)	3 (4.5)	0.56
Tacrolimus	3 (10)	16 (23.9)	0.19
Colectomy (%)	3 (10)	11 (16.4)	0.60
UC-associated neoplasm (%)	0 (0)	4 (5.97)	0.42

EOUC; elderly-onset ulcerative colitis, LEUC; long-standing ulcerative colitis, SD; standard deviation, BMI; body mass index, CCI; Charlson comorbidity index, anti-TNF; tumor necrosis factor α antagonists, UC; ulcerative colitis.

tively; $P < 0.001$).

At UC onset, the EOUC group had a lower proportion of non-smokers than the LEUC group (20.0% vs. 43.3%, respectively; $P = 0.039$) and a higher proportion of former smokers than the LEUC group (70.0% vs. 38.8%, respectively; $P = 0.0078$). With regard to disease extension at onset, the EOUC group had a smaller proportion of patients with proctitis compared with the LEUC group (0.0% vs. 16.4%, respectively; $P = 0.016$). There were no obvious differences in the CCI and BMI between the two groups.

In terms of treatment, the EOUC group had a higher rate of steroid-dependent cases compared with the LEUC group (60.0% vs. 37.3%, respectively; $P = 0.048$). Although not significantly different, the EOUC group exhibited a slightly higher rate of refractory cases compared with the LEUC group (66.7% vs. 56.7%, respectively; $P = 0.48$). The proportion of patients who received vedolizumab was higher in the EOUC group than in the LEUC group (33.3% vs. 10.4%, respectively; $P = 0.0095$); however, the usage rates of other medications did not differ significantly between the groups.

Systemic steroids

Fig. 1A shows a comparison between the two groups in terms of cumulative probability of systemic steroid therapy initiation. We performed a complete analysis of 83 cases after excluding 14 cases with missing data. Our analysis revealed a significant increase in the cumulative rate of systemic steroid initiation in the EOUC group ($P = 0.002$). The probabilities of initiating systemic steroids were 46% and 22% at 1 year; 50% and 26% at 2 years; and 64% and 33% at 5 years in the EOUC and LEUC groups, respectively.

Table 2A shows the Cox proportional hazards analysis models used to examine the association between risk factors and systemic steroid initiation. Both univariate and multivariate analysis indicated that elderly onset (HR 2.74, 95% CI 1.43-5.29; $P = 0.003$) and extensive colitis (HR

2.17, 95% CI 1.18-3.98; $P = 0.013$) were significantly associated with systemic steroid initiation.

Molecular targeted drugs

Fig. 1B shows a comparison of the cumulative probabilities of initiating MTDs between the EOUC and LEUC groups. We performed a complete analysis of 96 cases after excluding one case with missing data. Our analysis revealed that the cumulative rate of MTD initiation was higher in the EOUC group than in the LEUC group ($P = 0.002$). The probabilities of initiating MTDs were 17% and 5% at 1 year; 28% and 6% at 2 years; and 45% and 12% at 5 years in the EOUC and LEUC groups, respectively.

Table 2B presents Cox proportional hazards analysis models that show an association between risk factors and the initiation of MTDs. According to multivariate analysis, elderly onset (HR 2.76, 95% CI 1.30-5.87; $P = 0.008$) and extensive colitis (HR 2.03, 95% CI 1.03-3.99; $P = 0.041$)

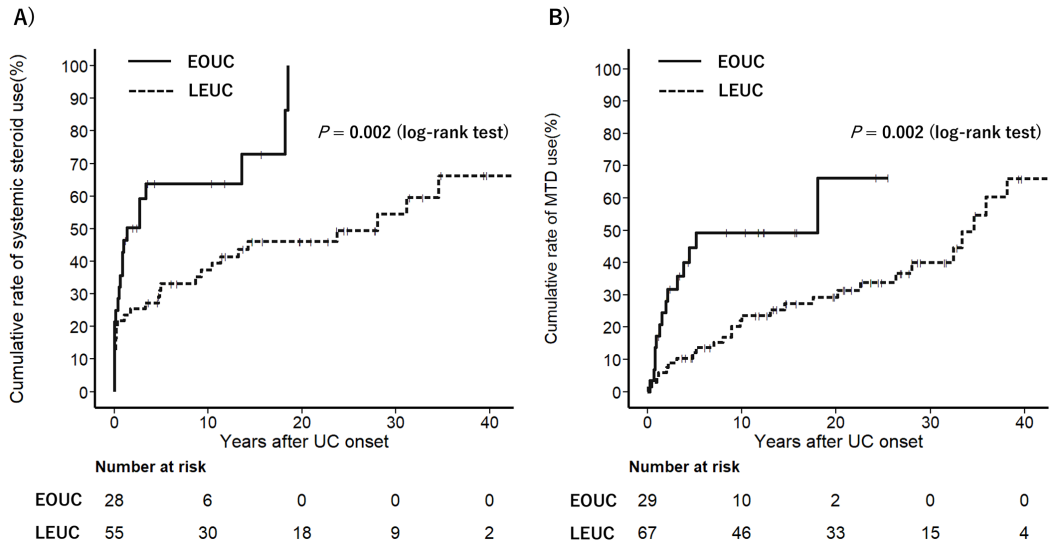

Fig. 1. The cumulative rate of initiation of systemic steroids and MTDs.
Cumulative probability of systemic steroid (A) and MTD (B) use in elderly-onset ulcerative colitis (EOUC) and long-standing elderly ulcerative colitis (LEUC). MTD; molecular targeted drug.

Table 2. Univariate and multivariate analysis of the association between clinical factors and initiation of systemic steroids (A) and molecular targeted drugs (B).

A)

Systemic steroids	Univariate			Multivariate		
	Hazard Ratio	95% CI	*P* value	Hazard Ratio	95% CI	*P* value
Elderly onset	2.55	1.38-4.71	0.003	2.74	1.43-5.29	0.003
Male sex	1.67	0.92-3.05	0.093	3.09	1.02–9.42	0.047
Extensive colitis at onset	2.30	1.27-4.17	0.006	2.17	1.18-3.98	0.013
CCI ≧ 2 at onset	0.82	0.44-1.54	0.54	0.36	0.33-1.35	0.28
BMI < 18.5 at onset	1.21	0.38-3.92	0.75	1.11	0.31-3.93	0.87
Former/Current smoker at onset	1.30	0.71-2.38	0.40	0.46	0.15-1.40	0.17

B)

Molecular targeted drugs	Univariate			Multivariate		
	Hazard Ratio	95% CI	*P* value	Hazard Ratio	95% CI	*P* value
Elderly onset	2.84	1.41-5.74	0.004	2.76	1.30-5.87	0.008
Male sex	1.39	0.73-2.66	0.32	1.09	0.44-2.71	0.85
Extensive colitis at onset	1.93	1.01-3.71	0.047	2.03	1.03-3.99	0.041
CCI ≧ 2 at onset	0.89	0.44-1.78	0.74			
BMI < 18.5 at onset	3.09	0.39-3.09	0.86			
Former/Current smoker at onset	1.56	0.79-3.06	0.20	1.24	0.48-3.22	0.66

BMI; body mass index, CCI; Charlson comorbidity index, CI; confidence interval.

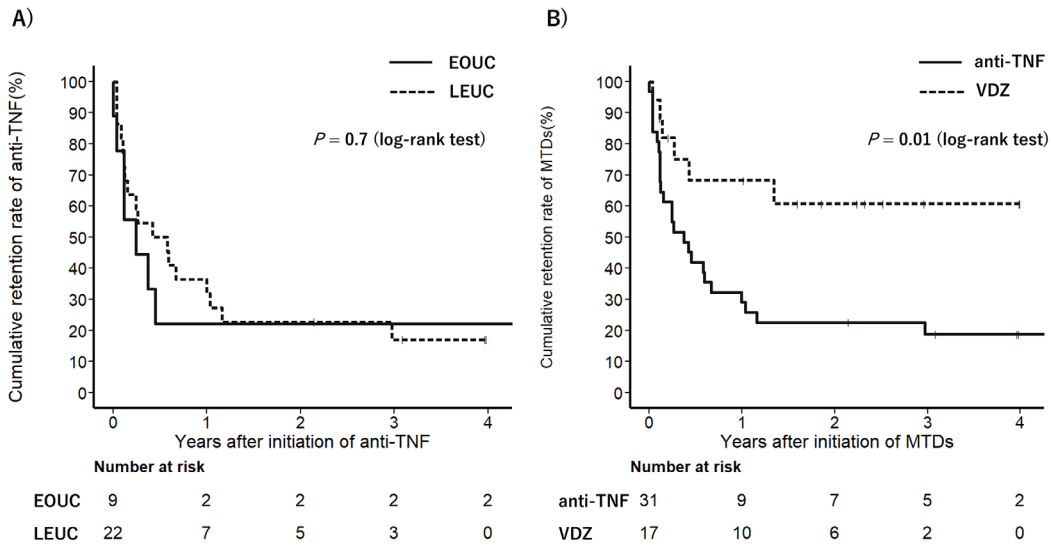

Fig. 2. The cumulative retention rate of anti-TNF.
(A) Cumulative retention rate of anti-TNF in elderly-onset ulcerative colitis (EOUC) and long-standing elderly ulcerative colitis (LEUC). (B) Cumulative retention rate of anti-TNF and VDZ in all eligible patients. MTDs; molecular targeted drugs, anti-TNF; tumor necrosis factor α antagonist, VDZ; vedolizumab.

Table 3. The summaries of adverse events of systemic steroids (A) and molecular targeted drugs (B).

A)			
Systemic steroids	EOUC	LEUC	*P* value
Number of patients	22	39	
Adverse Events (%)	6 (27.3)	10 (25.6)	1.00
Infection (%)	3 (13.6)	3 (7.7)	0.66
Serious Adverse Events (%)	3 (13.6)	1 (2.6)	0.13
B)			
Molecular targeted drugs	EOUC	LEUC	*P* value
Number of use	28	52	
Adverse Events (%)	5 (17.9)	15 (28.8)	0.42
Infection (%)	3 (10.7)	1 (1.9)	0.12
Serious Adverse Events (%)	2 (7.1)	1 (1.9)	0.28

EOUC; elderly-onset ulcerative colitis, LEUC; long-standing ulcerative colitis.

were significantly associated with MTD initiation.

However, we observed no significant difference in the retention of anti-TNF between the EOUC (n = 9) and LEUC (n = 22) groups, as shown in Fig. 2A ($P = 0.7$). The retention rates of anti-TNF were 22% and 32% at 1 year; and 22% and 23% at 2 years in the EOUC and LEUC groups, respectively.

Fig. 2B depicts the cumulative retention rate of anti-TNF (n = 32) and VDZ (n = 17) in all eligible patients. VDZ showed higher retention rates compared with anti-TNF ($P = 0.01$). The retention rates in anti-TNF and VDZ groups were 29% and 68% at 1 year; and 23% and 61% at 2 years, respectively.

Adverse Events

Table 3 presents summaries of treatment responses and AEs associated with the use of systemic steroids and MTDs. For systemic steroids, in the EOUC and LEUC groups, AE rates were 27.3% and 25.6%; infection rates were 13.6% and 7.7%; and serious AE (SAE) rates were 13.6% and 2.6%, respectively. With regard to MTDs, in the EOUC and LEUC groups, AE rates were 17.9% and 28.8%; infection rates were 10.7% and 1.9%; and SAE rates were 7.1% and 1.9%, respectively. While these differences were not statistically significant, we observed a trend toward more frequent infection and SAEs in the EOUC group compared with the LEUC group when using systemic steroids and MTDs. Supplementary Table S1 shows further details on the AEs associated with systemic steroids and MTDs.

Colectomy

The overall colectomy rates were 10% and 16.4% in the EOUC and LEUC groups, respectively ($P = 0.60$). Fig. 3 compares cumulative colectomy rates between the two groups. However, there were no significant differences between them ($P = 0.5$). The probabilities of colectomy were 0% and 2% at 1 year; and 4% and 6% at 5 years in the EOUC and LEUC groups, respectively.

Discussion

This single-center, retrospective study revealed that the cumulative rate of systemic steroid and MTD use was higher in EOUC patients than in LEUC patients. Furthermore, the multivariate analysis identified elderly onset as a clinical factor influencing the use of systemic steroids and MTDs. However, the cumulative colectomy rate showed no significant difference between the two groups.

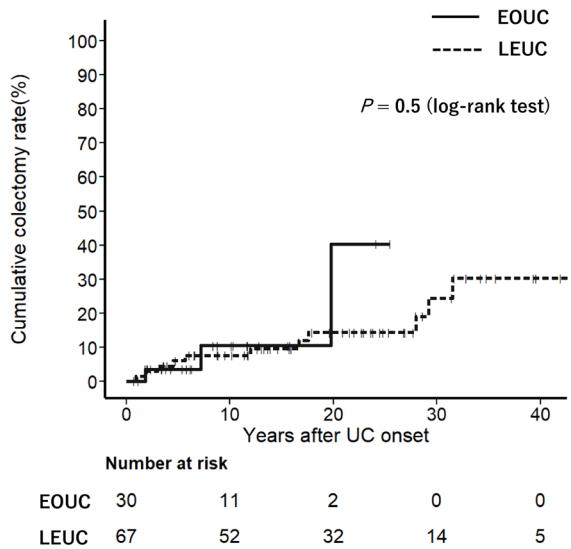

Fig. 3. Cumulative colectomy rate in elderly-onset ulcerative colitis (EOUC) and long-standing elderly ulcerative colitis (LEUC).

Although AE rates did not significantly differ between the EOUC and LEUC groups, a trend toward more frequent infections and SAEs was observed in the EOUC group when using systemic steroids and MTDs.

Our data suggested that patients with EOUC are treated with systemic steroids and MTDs more frequently in the early phases following UC onset than those with LEUC. To our knowledge, this is the first report of this finding in a Japanese cohort. This finding might indicate that the disease activity of EOUC during the early post-onset stage surpasses that of LEUC. Furthermore, patients with EOUC are potentially more likely to develop treatment-resistant conditions than patients with LEUC. A Japanese single-center study indicated a higher requirement for steroid therapy due to UC exacerbation and a higher incidence of steroid refractoriness in an EOUC group than in a LEUC group (Matsumoto et al. 2013). Another multicenter study in Japan reported that intravenous steroid treatment showed lower effectiveness and higher risks of surgery and AEs in elderly patients with EOUC than in those with non-EOUC (Okabayashi et al. 2022). Our results are consistent with these findings, suggesting that patients with EOUC exhibit higher rates of systemic steroid use and steroid refractoriness than those with LEUC.

A limited number of studies have compared immunosuppressive therapies between patients with EOUC and those with LEUC; most studies have compared treatments between patients with EOUC and younger individuals. Two cohort studies from Western countries reported a lower frequency of biological use in an EOUC group than that in an adult-onset UC group (Everhov et al. 2018; Mañosa et al. 2018). This finding differs slightly from our results, which indicated that the cumulative probability of MTD use in EOUC was higher than that in LEUC. One potential reason for this discrepancy is that the patients with EOUC in the prior studies presented with more comorbidities than young patients, which may have influenced the decision to avoid biological use due to concerns about AEs related to the treatment.

Our analysis showed a longer persistence with VDZ than with anti-TNF, and a lower incidence of AEs with VDZ and UST than with the other MTDs in elderly patients with UC. This indicates that VDZ and UST in elderly patients with UC may offer a better therapeutic option in terms of balancing between safety and efficacy. These results are consistent with recent studies that have reported that initiating VDZ and UST was associated with lower rates of infection-related hospitalizations than anti-TNF therapy in elderly patients with IBD with a high comorbidity burden (Cheng et al. 2022; Kochar et al. 2022). However, these previous studies did not account for disease severity when comparing the safety of VDZ and UST to that of anti-TNF. Hence, there could have been selection bias in selecting biologics for patients with varying severity levels. Further, comprehensive investigations are required to ascertain the long-term efficacy and safety of these novel biologics.

We observed no significant difference in the timing of colectomy after UC onset between patients with EOUC and those with LEUC. As this was a single-center study with a limited number of surgical cases, we may have been unable to detect potential differences. A recent large cohort study and meta-analysis reported higher rates of IBD-related surgery and hospitalization in patients with EOUC than in those with non-EOUC (Ananthakrishnan et al. 2016; Komoto et al. 2018). Another study in Japan reported that the main surgical indications for EOUC were being refractory to medical treatment and severe or fulminant disease whereas for LEUC, they were colitis-associated cancer or dysplasia (Kuwahara et al. 2022). In light of our results, clinicians may need to consider transitioning from immunosuppressive therapy to surgery at an earlier phase after UC onset in patients with EOUC, due to the increased risk of refractoriness and complications from immunosuppressive therapy.

Our study had several limitations. First, this was a single-center, small-scale, retrospective study with a long observation period. The results may have been affected by patient selection bias and changes in treatment strategies over time. Particularly, MTD therapy is a recently introduced advanced therapy, and patients with a longer disease duration may not have had the opportunity to receive it at the time of their disease onset. Supplementary Table S2 shows the decades of onset for the EOUC and LEUC groups, and the year when each MTD became available in Japan. The difference in the decades of disease onset between the two groups may influence the timing of starting MTDs. Further investigations are warranted despite our analysis demonstrating earlier initiation of systemic steroids and MTDs in patients with EOUC compared to those with LEUC. Second, since we could not access comprehensive

past medical data for all cases, we could not evaluate certain factors in detail, including endoscopic findings and disease activity scores at onset. Therefore, a large-scale, prospective study is recommended to address these issues.

In conclusion, systemic steroid and MTD initiation occurred earlier after onset in patients with EOUC than in those with LEUC, potentially indicating a tendency toward rapid progression and refractoriness of EOUC.

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Author Contributions

M.S., R.M., H.N., Y.S., T.N., H.S., and Y.K. contributed to the study conception and design. Material preparation, data collection, and analyses were performed by M.S. and R.M. The first draft of the manuscript was written by MS and critically revised by R.M., Y.K., and A.M. All the authors have read and approved the final version of this manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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