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ORIGINAL ARTICLE

Long-term prognosis and clinical practice for new-onset ulcerative colitis in the era of biologics: A Japanese retrospective study

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Key words
biologics, long-term prognosis, molecular targeting drugs, steroid, surgery, ulcerative colitis.

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Abstract

Background and Aim: There is a scarcity of data on long-term outcomes in patients with new-onset ulcerative colitis (UC) in the era of biologics. We aimed to clarify the long-term prognosis of UC and the clinical practice of prescriptions for UC.

Methods: We collected 6689 new-onset UC cases using a medical claim database provided by DeSC Healthcare, Inc. We investigated the surgery-free, systemic steroid-free, and molecular targeting drug-free rates and compared their differences based on UC-onset age. We used multivariate analysis to identify clinical factors affecting long-term prognosis and investigated the transition of prescriptions for UC.

Results: The surgery-free, systemic steroid-free, and molecular targeting drug-free rates at 5 years post-UC diagnosis were 98.5%, 61.0%, and 88.7%, respectively. Pediatric patients had higher surgery-free rates compared with elderly patients and non-pediatric/non-elderly patients ($P = 0.022$), whereas the systemic steroid-free and molecular targeting drug-free rates were significantly lower ($P < 0.0001$, $P < 0.0001$, respectively). The retention rate of the first molecular targeting drug did not differ between drugs. The prescription rates of systemic steroid, immunomodulator, and molecular targeting drug increased from the second quarter in 2014 to the fourth quarter in 2021 (29.8%–39.1%, 6.8%–17.7%, and 7.6%–16.4%, respectively).

Conclusions: We clarified the long-term prognosis and clinical practice of new-onset UC cases. The long-term outcome after UC onset might improve because of increasing use of new therapeutic agents. Further investigations are warranted.

Introduction

Ulcerative colitis (UC) is an inflammatory bowel diseases (IBD) that mainly affects the entire colon and is characterized by repeating exacerbations and remissions.[1–3] Although most UC patients have shown good results with 5-amynosalicylic acid (5ASA), a certain number of cases require stronger therapies including systemic steroid administration and molecular targeting drugs. Furthermore, several cases eventually need to undergo surgery.[1–3] The molecular targeting drugs such as biologics and small molecule agents have become available worldwide and are believed to have changed long-term UC outcomes.[4] In Japan, tacrolimus was first approved for the treatment of UC in 2009, followed by infliximab in 2010 and other drugs. However, data pertaining to the long-term prognosis of new-onset UC cases after approval of such new therapeutic agents are still scarce. The current clinical practice and prescription rates for UC treatment in this era of biologics are also unclear. Clarifying these uncertainties will be essential for guiding current clinical practice with reference to UC patients.

We have previously conducted several studies regarding IBD using a Diagnosis Combination Procedure (DPC) database.[5–10] The DPC is a patient medical claims database in Japan and is useful for analyzing rare diseases and complications because of large amounts of data available in this repository. Although the DPC database has several benefits, it consists mainly of inpatient data and has no outpatient data. Outpatient data are necessary for analyzing the uncertainties of UC treatment and outcome described above. We contracted with DeSC Healthcare, Inc. to obtain a dataset that consists of both inpatient and outpatient data. The DeSC dataset is expected to be helpful in resolving our research objectives related to UC treatment and prognosis.

The aim of this study is to clarify the long-term prognosis of new-onset UC cases in the present biologics era and to clarify the factors pertaining to clinical practice that impact long-term

UC outcomes. Analyzing the clinical practice of prescriptions for UC treatment is another aim of this study.

Methods

Data source. In this study, we used a dataset comprising UC patients' prescription claims receipts developed and maintained by DeSC Healthcare, Inc. We contracted with DeSC Healthcare, Inc. and obtained their permission to use this dataset for our research. This dataset contains anonymized UC inpatient and outpatient prescription claims records that include age, sex, medical treatment, surgery, and clinical diagnosis based on International Classification of Diseases 10th version (ICD-10) from a health insurance association in Japan ranging from April 2014 to February 2022.

Extraction of eligible patients and data collection. We extracted eligible patients from the DeSC Healthcare database, as shown in the flowchart in Figure S1. UC cases were identified using ICD-10 code K51 and entries of suspicious cases containing the word "suspicious" were excluded. The cases who had Crohn's disease in their clinical diagnosis were also excluded. We subsequently extracted cases who were assumed to have newly developed UC based on the definitions described below.

We collected the following data on patients from the DeSC dataset: sex, birth year and month, the start and end date of observation, and surgery. Information regarding prescribed medications including 5ASA, systemic steroid administration (prednisolone), immunomodulator (azathioprine and 6-mercaptopurine), molecular targeting drugs including biologics (infliximab, adalimumab, golimumab, ustekinumab, and vedolizumab), and small molecule agents (tofacitinib, tacrolimus, and cyclosporine) were also collected.

Definitions. We defined a "new" prescription of each drug as follows: there was no prescription of the medicine within 26 weeks before the first prescription date of the medicine during the observation period. The other types of prescriptions were defined as "old" prescriptions. This criterion of 26 weeks to assume the new prescription was based on the fact that the common longest prescription period in Japan is 3 months (12–13 weeks). If there was no prescription within 26 weeks before, which is double for the longest prescription days (two times of visit) in Japan, we assumed the prescription as a new one.

The prescription was defined as discontinued in case of no prescription for more than 13 weeks from the next scheduled prescription date. The next scheduled prescription date differs between drugs. For instance, the next scheduled prescription date of ustekinumab was after 12 weeks from the last prescription date (infliximab and vedolizumab were 8 weeks, adalimumab and golimumab were number of prescriptions $\times$ 14 days, and other drugs were prescription days).

We also assumed cases in our study who had both (1) new prescription of either 5ASA, systemic steroid or topical steroid drugs and (2) no old prescription of such drugs during the observation period, as a new onset of UC. We estimated the age of UC onset based on this assumption.

Data analysis. We divided new UC development cases into three categories depending on their estimated onset age of UC (elderly onset, pediatric onset, and non-elderly, non-pediatric onset). Pediatric onset is defined under 16 years based on the Montreal classification.[11] The definition of elderly onset is 65 years or older based on the World Health Organization classification.[12]

We evaluated the cumulative surgery-free rate, cumulative systemic steroid-free rate, and cumulative molecular targeting drugs-free rate using the Kaplan–Meier method as the long-term prognosis after new-onset UC. The impact of the difference of onset age on the long-term prognosis was also investigated with the log-rank test. We subsequently compared the cumulative retention rate of first molecular targeting drugs other than tacrolimus and cyclosporine using the Kaplan–Meier method. Multivariate logistic regression analysis was performed to identify the clinical factors that related to systemic steroid administration, usage of molecular targeting drugs, surgery, and discontinuation of the first molecular targeting drug. Univariate analysis using the chi-square test and multivariate analysis using the Cox proportional hazard model were performed to investigate association between clinical factors and discontinuation of the first molecular targeting drug.

We then investigated the clinical practice of UC treatment in the biologics era by clarifying the prescription rate of each drug and its usage trend. This prescription analysis targeted all UC cases in the DeSC dataset regardless of new development of UC. The calculation was performed as follows: (the number of patients prescribed each drug)/(the total number of patients prescribed any drugs). The calculation was conducted every quarter in each year. Duplications in the same quarter were excluded.

Statistics. The threshold for statistical significance was set at $P < 0.05$. All analyses were performed using the JMP Pro16 software (SAS Institute, Tokyo, Jauuuupan).

Ethics approval and patient consent statement. The study protocol was reviewed and approved by the Ethics Committee of the Tohoku University Graduate School of Medicine (2022-1-412). The requirement for informed consent was waived because of the anonymity of patient data.

Results

Background of the study population. We extracted 6698 cases that were assumed to have newly developed UC based on the definitions described above (Figure S1). The characteristics of such cases are summarized in Table 1. The mean observation period was 1757.7 days. The administration rate of systemic steroid at UC onset was 19.0%. Infliximab was used most frequently as the first molecular targeting drug, followed by tacrolimus and vedolizumab. Ninety-six UC patients underwent surgery during the observation period of the study.

The long-term prognosis for new-onset UC. The cumulative surgery-free rate in new-onset UC patients was 98.5% at 5 years after UC onset (Fig. 1a). The cumulative systemic steroid-free rate and molecular targeting drug-free rate at

Table 1 Background of patients assumed to have new-onset UC

	Cases assumed to have new-onset UC, $N = 6698$
Sex (male/female)	3894/2804
Age categories of UC-onset	
Elderly onset	2627
Non-elderly, non-pediatric onset	3973
Pediatric onset	98
Mean observation period (SD)	1757.7 (710.7) days
Administration of systemic steroid at UC-onset	1273 (19.0%)
First molecular targeting drug	
Infliximab	137
Adalimumab	65
Golimumab	44
Ustekunumab	18
Vedolizumab	82
Tofacitinib	17
Tacrolimus	92
Cycrosporine po	19
Cycrosporine iv	3
Surgery	96

iv; intravenous injection; po, per os; SD, standard deviation; UC, ulcerative colitis.

5 years after UC onset were 61.0% and 88.7%, respectively (Fig. 1b,c).

Figure 2 shows differences in long-term prognosis between onset age categories. The surgery-free rate of pediatric onset UC patients at 5 years after UC onset was 100%, whereas it was 97.8% for elderly onset, and 98.8% for non-elderly, non-pediatric onset ($P = 0.022$) (Fig. 2a). The systemic steroid-free rate for pediatric onset UC patients was statistically lower than those of elderly and non-elderly, non-pediatric UC-onset patients ($P < 0.0001$) (Fig. 2b). The cumulative molecular targeting drug-free rate of pediatric onset UC patients was also significantly lower than those of elderly and non-elderly, non-pediatric onset UC cases ($P < 0.0001$) (Fig. 2c).

Multivariate analysis (Table 2) showed that pediatric onset UC was associated with systemic steroid administration (odds ratio [OR] = 2.75, 95% confidence interval [CI]: 1.84–4.12, $P < 0.0001$). Pediatric onset UC (OR = 3.64, 95% CI: 2.23–5.92, $P < 0.0001$) and usage of systemic steroid at UC onset (OR = 1.93, 95% CI: 1.56–2.38, $P < 0.0001$) were identified as the clinical factors that impacted usage of molecular targeting drugs. Elderly onset UC (OR = 2.07, 95% CI: 1.37–3.13, $P = 0.0006$) and usage of molecular targeting drugs (OR = 2.65, 95% CI: 1.53–4.61, $P = 0.0005$) were also identified as the clinical factors associated with surgery.

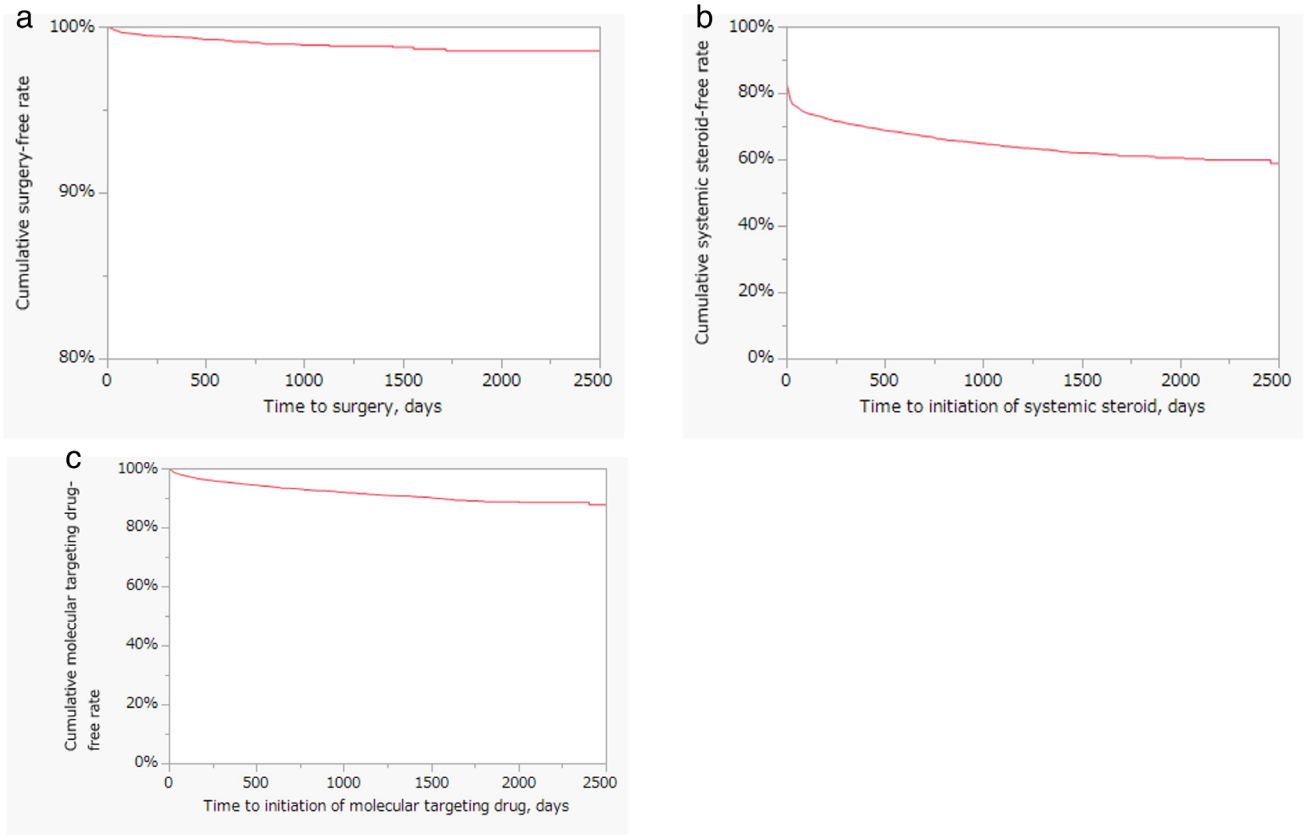

Figure 1 The Kaplan–Meier curve describing the long-term prognosis of new-onset UC cases. (a) The cumulative surgery-free rate in patients with new-onset UC was 98.5% at 5 years after onset of UC. (b) The cumulative systemic steroid-free rate at 5 years was 61.0%. (c) The cumulative molecular targeting drug-free rate at 5 years was 88.7%.

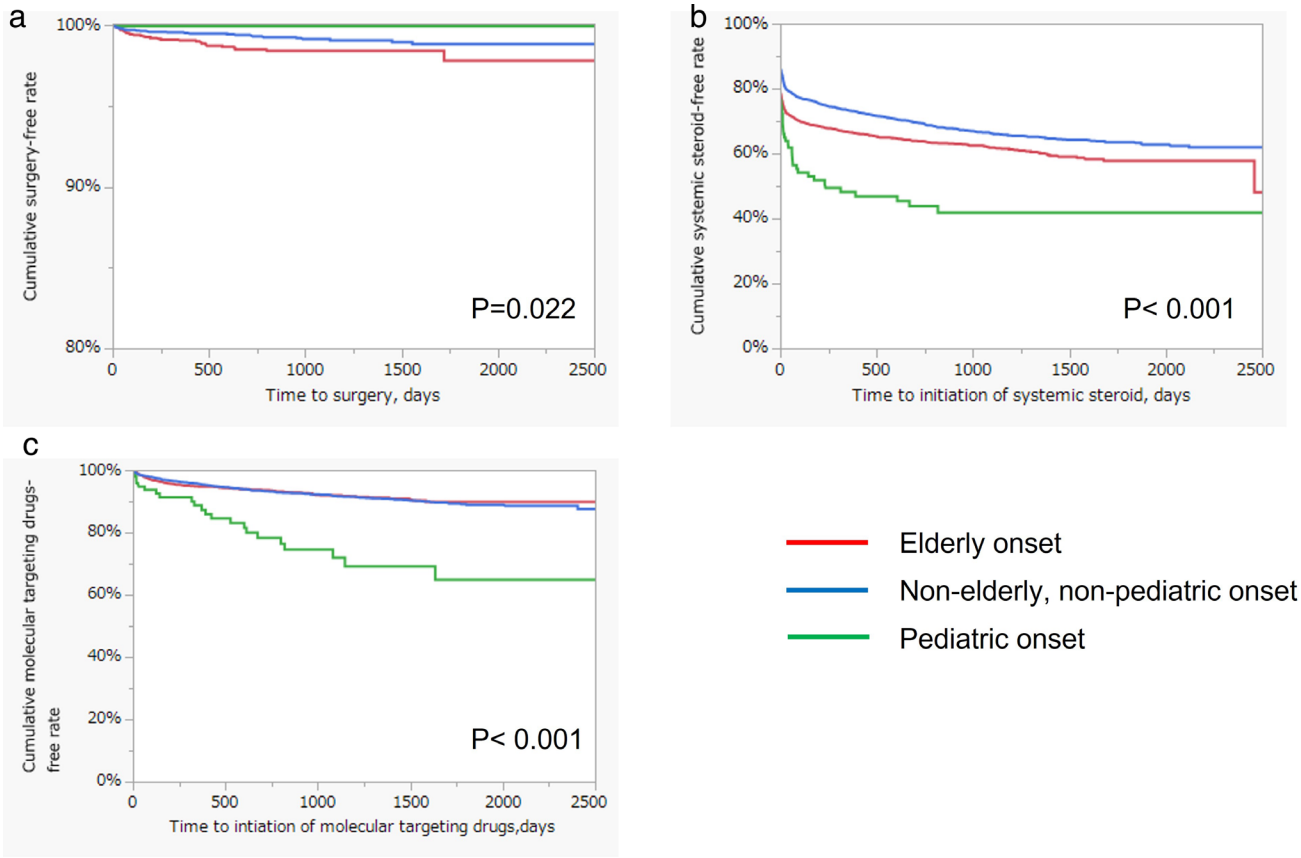

Figure 2 The Kaplan–Meier curve describing the differences of long-term prognosis between onset age categories. (a) The cumulative surgery-free rate of pediatric onset, non-elderly/non-pediatric onset and elderly onset at 5 years was 100%, 99.8%, and 97.8%, respectively ($P = 0.022$). (b) The cumulative steroid-free rate of pediatric onset, non-elderly/non-pediatric onset, and elderly onset at 5 years was 41.8%, 63.5%, and 57.7%, respectively ($P < 0.0001$). (c) The cumulative molecular targeting drug-free rate of pediatric onset, non-elderly/non-pediatric onset, and elderly onset at 5 years was 64.8%, 88.9%, and 89.8%, respectively ($P < 0.0001$).

Retention of the first molecular targeting drug. The cumulative retention rates of each first molecular targeting drug are shown in Figure 3. There was no difference between these drug retention data ($P = 0.083$, log-rank test).

Univariate analysis showed that the kind of first molecular targeting drug was associated with its discontinuation ($P = 0.00060$). However, multivariate analysis revealed that there was no association between the kind of first molecular targeting drug and its discontinuation (Table 3).

The clinical practice of UC prescriptions in the era of biologics. Figure 4 shows the transition of prescriptions for UC. Figure 4a shows that the total amount of prescriptions is rising, especially for molecular targeting drugs and immunomodulators, which have been increasing from the second quarter in 2014 to the fourth quarter in 2021 (6.8%–17.7% and 7.6%–16.4%, respectively). The prescription rate of systemic steroid administration (per oral and intravenous injection) also increased from 29.8% to 39.1% (from the second quarter in 2014 to the fourth quarter in 2021).

Figure 4b,c reveals that newly marketed drugs such as multi-matrix system mesalamine (Lialda) and budesonide form (Rectable) showed increased prescription rates, whereas competitive drugs including pH-dependent release mesalamine (Asacol), prolonged-release mesalazine (Pentasa) enema, prednisolone enema (Predonema), and betamethasone enema (Steronema) showed decreased prescription rates.

A similar trend has also been observed in the prescription of molecular targeting drugs (Fig. 4d). After approvals of ustekinumab, vedolizumab, and tofacitinib, the prescription rates of tacrolimus and cyclosporine have been decreasing. On the contrary, infliximab and golimumab demonstrated stable prescription rates. Additionally, the overall prescription rates for molecular targeting drugs have been increasing as shown in Figure 4a,d.

Discussion

We estimated the long-term outcomes after new-onset UC using the so-called "big data." This study analyzed more than 6000 cases of new-onset UC, even though they were assumed cases.

Table 2 Multivariate analysis[†] of the association among clinical factors and clinical events in patients with ulcerative colitis

Clinical factors	Number of patients, $N = 6698$	Systemic steroid administration			Use of molecular targeting drug			Surgery		
		Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Sex	Male: 3894	Reference		0.14	Reference		0.16	Reference		0.27
	Female: 2804	0.92	0.83–1.03		0.87	0.72–1.06		0.79	0.52–1.20	
Age categories of UC onset	Elderly: 2627	**1.22**	**1.10–1.36**	**0.0002**	0.84	0.68–1.02	0.09	**2.07**	**1.37–3.13**	**0.0006**
	Non-elderly, non-perdiatric: 3973	Reference			Reference			Reference		
	Pediatric: 98	**2.75**	**1.84–4.12**	**< 0.0001**	**3.64**	**2.23–5.92**	**< 0.0001**	0.78	0.11–5.85	0.82
Use of systemic steroid at UC onset	Yes:1273				**1.93**	**1.56–2.38**	**< 0.0001**	1.33	0.84–2.12	0.22
	No: 5425				Reference			Reference		
Molecular targeting drug during clinical course of treatment	Yes: 477							**2.65**	**1.53–4.61**	**0.0005**
	No: 6221							Reference		

[†]Logistic regression analysis.
Note: Bold characters means statistical significance.
UC, ulcerative colitis.

Figure 3 The cumulative retention rates of each first molecular targeting drug. There was no difference between the drugs ($P = 0.083$, log-rank test).

This is one of the attractive points of this study. The dataset used in this study contains both inpatient and outpatient data from all over Japan regardless of referral center. Therefore, our results are expected to reflect the real-world healthcare scenario in Japan with regard to UC patients.

The cumulative surgery-free rate at 5 years after UC onset was 98.5%. Another study targeting UC patients who were diagnosed between 2003 and 2004 reported that the cumulative surgery-risk rate at 5 years after UC onset was 10.1%.[13] These results indicate that the surgery risk might be decreasing because of clinical availability of molecular targeting drugs. A questionnaire survey from Japan reported that the prevalence of UC surgery decreased over the study period while usage of calcineurin inhibitor and anti-tumor necrosis factor antibody was increasing.[14]

The cumulative systemic steroid-free rate for UC patients in this study was 61.0%. This rate might seem to be relatively low. However, a population-based study reported that 50% of UC patients received corticosteroids during a median follow-up period of 15 years.[15] Our findings do not differ from these previous reports and indicate that nearly half of UC patients may receive systemic steroid administration during the course of the disease. Generally, about 50% of UC patients are administered systemic steroid.

Our analysis revealed that about 10% of UC patients are prescribed molecular targeting drugs at 5 year after UC onset. Little is known about clinical practice trends of prescribing molecular targeting drugs to UC patients. One study reported that 6.0% of UC patients received anti-tumor necrosis factor (anti-TNF) α antibody during the follow-up period.[16] Another population-based study also reported that the use of biological agents at 5 years after UC onset is increasing to 10.6% over time.[17] We found similar results in our analysis of a large UC patient dataset.

The Kaplan–Meier curve by categories of onset age (Fig. 2) revealed that pediatric onset UC patients have a lower surgery rate and higher usage rates of systemic steroid and molecular targeting drugs compared with elderly onset and non-elderly/non-pediatric onset UC cases. This result might not necessarily reflect the disease severity of each age category. In fact, a retrospective cohort study reported that relapse incidence in pediatric patients decreased after introduction of biologic

Table 3 Association between clinical factors and discontinuation of molecular targeting drug

Clinical factor	Number of patients, $N = 363$	Univariate[†]	Multivariate[‡]		
		P-value	Odds ratio	95% CI	*P*-value
Sex	Male: 223	0.36	Reference		0.93
	Female: 140		0.98	0.69–1.41	
Age categories at UC onset	Elderly onset: 122	0.45	1.23	0.88–1.90	0.19
	Non-elderly, non-perdiatric onset: 220		Reference		
	Pediatric onset: 21		1.65	0.53–3.15	0.23
Administration of systemic steroid at UC onset	Yes: 94	0.47	Reference		0.81
	No: 269		0.79	0.58–1.16	
First molecular targeting drug used during the clinical course of treatment (excluding tacrolimus and cyclosporine)	Infliximab: 137	**0.0060**	Reference		
	Adalimumab: 65		0.74	0.46–1.20	0.22
	Golimumab: 44		1.01	0.61–1.67	0.98
	Ustekinumab: 18		5.95E-10	0–	0.99
	Vedolizumab: 82		0.82	0.51–1.34	0.43
	Tofacitinib: 17		0.53	0.18–1.55	0.25

[†]Chi-square test.
[‡]Cox proportional hazard model.
Note: Bold characters means statistical significance.
UC, ulcerative colitis.

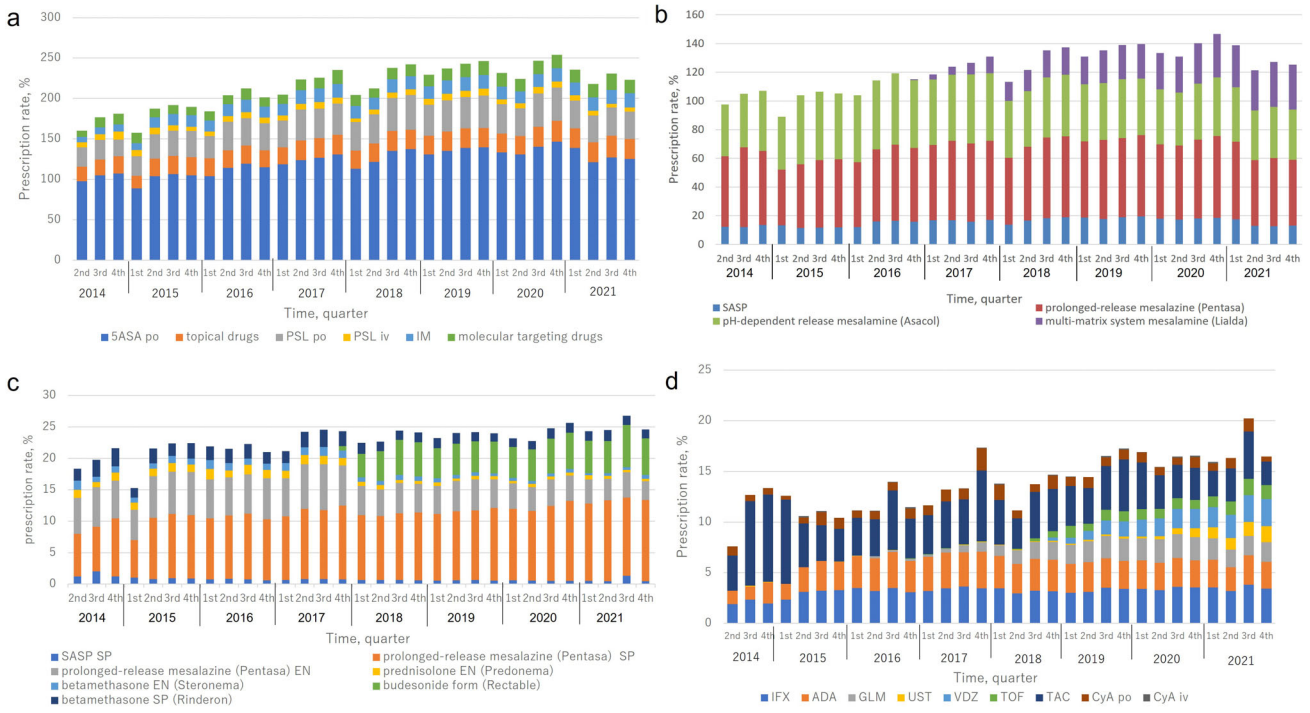

Figure 4 The transition of prescription for ulcerative colitis. (a) The total amount of prescriptions is rising, especially the amounts of molecular targeting drugs and immunomodulator category of medications are increasing. The prescription rate of systemic steroids also increased. Po: per orally, iv: intravenous injection, IM: immunomodulator. (b, c) The prescription rates of newly marketed drugs such as multi-matrix system mesalamine (Lialda) and budesonide form (Rectable) kept on increasing, whereas those of the competitive drugs including pH-dependent release mesalamine (Asacol), prolonged-release mesalazine (Pentasa) enema, prednisolone enema (Predonema), and betamethasone enema (Steronema). SASP: salazosulfapyridine, SP: suppository, EN: enema. (d) As the prescription rates of ustekinumab, vedolizumab, and tofacitinib increase, the prescription rates of tacrolimus and cyclosporine have been decreasing. ADA, adalimumab; Cya, cyclosporine; GLM, golimumab; IFX, infliximab; TAC, tacrolimus; TOF, tofacitinib; UST, ustekinumab.

agents.[18] The use of biologics in pediatric patients may eventually contribute to avoiding surgery by reducing the incidence of relapse. Moreover, the younger age might affect the decision whether surgery should be conducted or not. Regarding elderly patients, two studies reported severe infection in elderly patients with UC administered immunosuppressive therapies could be lethal.[19,20] Therefore, elderly patients might be likely to undergo surgery compared with non-elderly patients.

We also analyzed the prescription rates of each drug available in Japan. The prescription rates of systemic steroid, immunomodulator, and molecular targeting drugs have been increasing as time passes. The prescription rate of molecular targeting drugs is increasing because of more approvals of new therapeutic agents in recent years. The increasing prescription rates of systemic steroid, immunomodulator, and molecular targeting drugs imply that the prevalence rate of UC patients with moderate to severe disease might increase. Moreover, assessment of nucleoside diphosphate-linked moiety X-type motif 15 (NUDT15) polymorphism has been approved by insurance companies in Japan to prevent severe adverse events related to immunomodulator drug use.[21] This epoch-making step may be one reason for the increase in immunomodulator prescription rates.

There are several limitations in our study. First, the study design is retrospective. Prospective cohort studies will be needed in the future to overcome this limitation and to confirm our findings. Second, there was no additional patient information available in the accessed dataset such as blood tests, endoscopic examinations, biopsy specimens, and computed tomography images to determine disease severity. Therefore, the correlation between the long-term outcome of UC and the severity of the disease cannot be elucidated. Furthermore, there was no information on disease onset. We assumed that cases with a new prescription of 5ASA or steroid are new-onset UC patients. The difference in definition of UC onset may affect the result of this study. The reasons for surgery are also unclear. Third, we might not be able to eliminate a bias in the representativeness of data. Our results showed larger proportion of elderly persons compared with general population. This might be due to the nature of DeSC dataset that contains a large data of elderly patients with UC aged 75 years or older. Although this study has several limitations, we were able to derive many useful findings and statistical trends from this very large dataset of UC patients. Our findings are expected to be useful for daily clinical UC practice and for future investigations.

In conclusion, we analyzed the long-term prognosis and clinical practice for new-onset UC in the era of biologics using big data. Further prospective investigations are warranted to confirm these results via prospective nationwide database analyses.

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Declaration of conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

RM, Y. Kakuta, TO, YS, TN, and HS contributed to the study conception and design. Data extraction and collection were performed by Y. Kakuta. Data analysis was performed RM and Y. Kakuta. The first draft of the manuscript was written by RM and revised critically by RM, Y. Kinouchi, and AM. All authors read and approved the final version of the manuscript.

Data availability statement. The corresponding author has opted to not share data because of a contract with DeSC Healthcare, Inc.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. The flowchart for extraction of eligible patients from the patient claims database of DeSC Healthcare, Inc. We extracted 6698 cases of new-onset ulcerative colitis (UC). The long-term prognosis and differences in outcome based on the onset age and the retention rate of the first molecular targeting drug were analyzed. The prescription rate of each drug for UC was analyzed for all cases, regardless of presence of new-onset UC