Biologics did not reduce surgery rate but prolonged remission duration in patients with ulcerative colitis: analysis of a large retrospective Japanese cohort

Yuya Yokoyama

Chiba University Hospital

Yuki Ohta

Chiba University Hospital

Sadahisa Ogasawara

Chiba University Hospital

Jun Kato (✉ kato.jun@chiba-u.jp)

Chiba University

Ryoko Arai

Chiba University

Hiroataka Koseki

Chiba Aoba Municipal Hospital

Masaya Saito

Seikeikai Chiba medical center

Tatsuya Kaneko

Chiba University

Mamoru Tokunaga

Chiba University

Hiroataka Oura

Chiba University

Tsubasa Oike

Chiba University

Yushi Imai

Chiba University

Kengo Kanayama

Chiba University

Naoki Akizue

Chiba University

Junichiro Kumagai

Chiba University

Takashi Taida

Chiba University
Kenichiro Okimoto
Chiba University

Keiko Saito
Chiba University

Yoshihiko Ooka
Chiba University

Tomoaki Matsumura
Chiba University

Tomoo Nakagawa
Chiba University

Makoto Arai
Chiba University

Tatsuro Katsuno
Chiba University

Yoshihiro Fukuda
Seikeikai Chiba medical center

Yoshio Kitsukawa
Chiba Aoba Municipal Hospital

Naoya Kato
Chiba University

Research Article

Keywords: ulcerative colitis, inflammatory bowel disease, biologics, antitumor necrosis factor therapy.

Posted Date: February 18th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1265976/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Objective: To gain better understanding of the effects of biologics, we evaluated clinical outcomes in patients with moderate to severe exacerbations of ulcerative colitis (UC).

Methods: This retrospective, multicenter study retrieved the entire clinical courses of UC patients who began treatments between 2004 and 2018. All exacerbations and clinical parameters, including treatment details for exacerbations and both remission and re-exacerbation dates, were identified during the observation period. Two different endpoints, the cumulative incidence rates of surgical resection and re-exacerbation, were evaluated separately in moderate to severe exacerbation events.

Results: Among 1401 patients, 1626 exacerbation events were determined according to a partial Mayo score (remission: <2, mild: 2–4, moderate: 5–7, and severe: >7). During the observation period, as administration rates of biologics increased, both surgical resection and hospitalization rates decreased, for 959 moderate to severe exacerbation events. We confirmed that biologics significantly reduced the cumulative re-exacerbation rate in moderate to severe exacerbation events during the study period compared with suboptimal therapies (a 0.507-fold decrease risk according to COX regression analysis, $P < 0.001$). However, they had not enough impact in reducing the cumulative incidence rate of surgical resection in moderate to severe exacerbation events that were corticosteroid-refractory or dependent (a 0.878-fold decrease risk according to COX regression analysis, $P = 0.606$).

Conclusions: Biologics may improve remission duration, but these agents had no significant impact in reducing the risk of surgical resection in moderate to severe active UC.

Introduction

Ulcerative colitis (UC), a subtype of inflammatory bowel disease (IBD), is a chronic inflammatory disease of the colon, representing the most common distressing period of productive age and resulting in disability [1]. Although UC is associated with the Caucasian population in the United States and Europe, its incidence in newly developed countries, primarily in Asia, has been increasing rapidly over the past few decades [2–5]. Japan ranks second in the world in terms of the number of UC patients after the United States [3–6]. The sharp increase of UC cases in Japan appears to be associated with Westernized diets and environments, which affect the intestinal microbiome and increase the risk for UC in genetically susceptible individuals [7, 8].

The primary treatment goals for UC patients are to induce and maintain remission. Specifically, a surgical resection of the total colon due to an induction failure and an early re-exacerbation after remission are the two worst clinical outcomes in patients with UC [1]. 5-aminosalicylates (5-ASA), which are anti-inflammatory agents, are the major choice of treatment to induce and maintain remission in patients with mild to moderate active UC [9, 10]. Corticosteroids are a classical and most widely used treatment for inducing remission based on their confirmed high rates of immediate effectiveness [11–13]. Over half a century since the first report, corticosteroids remain the first-line treatment for moderate to severe

exacerbations or when 5-ASA proves ineffective, as recommended by global guidelines [14–17]. However, roughly one-third of patients have not achieved clinical response or remission, while almost two-thirds of patients had required reintroduction of corticosteroids within two years and even they had achieved remission [18, 19].

During the past two decades, there has been a dramatic paradigm shift in UC treatment with the introduction of biologics, primarily antitumor necrosis factor (anti-TNF) therapy, for both inducing and maintaining remission [9, 14, 15, 17]. Well-designed randomized controlled trials have confirmed that biologics, including infliximab, adalimumab, golimumab, and vedolizumab, both improved induction and sustained remission rates compared with placebo in patients with moderate to severe active UC who had failed corticosteroid therapy or who had a history of corticosteroid refractory or dependent [20–24]. The rates of surgical resection and hospitalization in UC patients have decreased in both Eastern and Western populations [25, 26]. However, the effects of biologics for patients with active UC, particularly focusing on overall long-term effectiveness of these new agents for maintaining remission, remain controversial and have not yet been clarified sufficiently. Therefore, this study was conducted to evaluate the clinical outcomes of biologics in UC patients with moderate to severe exacerbations using a large retrospective Japanese cohort over a long observation period.

Methods

Study population and study design

Chiba City is inhabited by approximately 1 million people (the 12th largest population in Japan) with less migration compared with the central metropolitan area of Japan. Chiba University Hospital, Chiba Aoba Municipal Hospital, and Chiba Medical Center are the only three institutions to which well-trained specialists in IBD belong.

We retrospectively investigated the entire clinical courses of UC patients by reviewing the electronic medical records (EMR) in three institutions and identified all exacerbations according to the partial Mayo score [27]. We identified all exacerbation events during the entire observation period and acquired the following data: the date of exacerbation diagnosis, laboratory data and disease extent at the time of exacerbation, requirement of hospitalization, and medical treatments for exacerbation.

All participating hospitals received approval from IRB. The Institutional Review Board of Chiba University Hospital approved this study (approval number: 3399).

Informed consent

was waived because this was a survey study using medical records and no written or verbal consent could be obtained from the research subjects. However, materials regarding opting out were posted to give patients the opportunity to refuse to participate in the study. We conduct our research in accordance with the "Ethical Guidelines for Medical Research Involving Human Subjects" established by the Ministry

of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of Japan.

Treatment strategies for UC

UC diagnosis was based on the combination of conventional clinical, endoscopic, radiological, and pathological criteria [28]. 5-ASA is the first choice for inducing and maintaining remission in patients with mild to moderate active UC. Corticosteroids are introduced for patients with moderate to severe active UC, and/or in those unresponsive to 5-ASA, and are tapered off over 8–12 weeks. Biologics (infliximab, adalimumab, golimumab and vedolizumab), and immunomodulators (i.e., thiopurines; azathioprine/6-mercaptopurine), were considered in case of corticosteroid failure. Calcineurin inhibitors, apheresis, and surgical resection were considered rescue medical treatments in patients who were unresponsive to corticosteroids. Since tofacitinib was approved in Japan in May 2018 and had been use only a few patients, we excluded these patients form this study.

Definition of exacerbations according to partial Mayo score

The degree of exacerbations during the observation period was assessed according to the partial Mayo score using three noninvasive parameters (stool frequency, rectum bleeding, and physician's global assessment) [26]. Each of the three categories were rated from 0 to 3 that was summed up to derive a total score in the ranges of 0–9 (remission: <2, mild: 2–4, moderate: 5–7, and severe: >7). Moderate and severe exacerbations were defined as partial Mayo scores 5–7 and >7, respectively. The remission date was defined as the first date after the exacerbation event that we confirmed as clinical improvement according to a partial Mayo <2. The re-exacerbation date was defined as the first date after remission that we confirmed a change in clinical status according to a partial Mayo score ≥ 2 .

Assessments of clinical outcomes of corticosteroids

Clinical outcomes of corticosteroids were evaluated for each exacerbation event. Corticosteroid-refractory was defined if remission, which was assessed according to a partial Mayo score <2, could not be achieved by corticosteroid monotherapy. Meanwhile, cases of active disease revival while receiving reduced doses of corticosteroids were regarded as corticosteroid-dependent. We collectively reviewed the cases that showed corticosteroid-refractory or -dependent (COR-REF or DEP) in the analysis.

Definition of effectiveness evaluation and COR-REF or DEP cohorts

All moderate to severe active events in UC patients were classified as an effectiveness evaluation cohort for assessing the clinical outcomes of treatments during induction of, and maintaining remission after, excluding events that were induced by 5-ASA alone. COR-REF or DEP cohorts were defined when any of the following conditions were observed: 1) met the abovementioned criteria of COR-REF or DEP after taking corticosteroids for moderate to severe exacerbations or 2) had a previous history of the criteria of COR-REF or DEP induced for exacerbations using treatments without corticosteroids.

Statistical analysis

Pearson's chi-squared test or Fisher's exact test was used, as appropriate. ANOVA test was used to compare the mean between independent groups. The cumulative incidence of surgical resection was analyzed using Kaplan–Meier plots, which was defined as the duration from the date of exacerbation till the date of surgical resection, with the censoring date defined as the day of the last follow-up or the date of re-exacerbation. The cumulative re-exacerbation incidence was analyzed using Kaplan–Meier plots, which was defined as the duration from the date of exacerbation to the date of re-exacerbation, with the censoring date defined as the day of the last follow-up. Cox regression analyses were performed to evaluate the factors for the cumulative risk of surgical resection and re-exacerbation in UC patients with moderate to severe exacerbations. All statistical analyses were conducted using the SPSS statistical software (version 25; SPSS-IBM, Chicago, IL, USA).

Results

Study population and baseline characteristics

Between January 2004 and December 2018, 1401 patients were started on treatments for UC at the three institutions and were included in the present retrospective cohort. The final data were locked on December 2019, and the median observation period was 48.3 months (95% CI: 44.7–51.9). Supplementary Figure 1 depicts the study population trend per year. The number of follow-up patients per year increased dramatically, and hospitalization rates per year decreased in the present cohort.

Table 1 shows the baseline characteristic of the study population at the time of the initial visit during the study period. The mean age was 39.8 years, and one-fourth of the patients were aged ≤ 22.0 years. Supplementary Figure 2 presents the correlations between the year of onset and the mean age at initial UC diagnosis. The mean age at initial diagnosis appeared to be significantly higher along with the calendar year of onset ($P < 0.001$).

Table 1
Baseline characteristics at the initial visit

Demographics/characteristics	Any (n = 1401)
Gender, male (<i>n</i> [%])	762 (54.4)
Age at the time of first consultation, years	39.8 (17.3)
Mean (SD)	38.0 (0–93)
Median (range)	26.0
Percentile (25%)	38.0
Percentile (50%)	52.0
Percentile (75%)	
Age at the time of initial diagnosis, years	35.0 (16.7)
Mean (SD)	31.5 (0–93)
Median (range)	22.0
Percentile (25%)	31.5
Percentile (50%)	46.0
Percentile (75%)	
Height, cm, median (SD)	162.9 (9.7)
Body weight, kg, median (SD)	57.0 (12.0)
Body mass index, median (SD)	19.0 (7.6)
Smoking	676 (48.3)
None (<i>n</i> [%])	186 (13.3)
Previous smoker (<i>n</i> [%])	80 (5.7)
Current smoker (<i>n</i> [%])	459 (32.8)
Unknown (<i>n</i> [%])	
Prior history of appendectomy (<i>n</i> [%])	24 (1.7)
Initial diagnosis of UC at the time of first consultation (<i>n</i> [%])	419 (29.9)

Demographics/characteristics	Any (n = 1401)
Partial Mayo grade at the time of first consultation	475 (33.9)
Inactive (<i>n</i> [%])	451 (32.2)
Mild (<i>n</i> [%])	329 (23.5)
Moderate (<i>n</i> [%])	146 (10.4)
Severe (<i>n</i> [%])	
Type of UC at the time of first consultation	367 (26.2)
Proctitis (<i>n</i> [%])	368 (26.3)
Left-sided colitis (<i>n</i> [%])	488 (34.8)
Pancolitis (<i>n</i> [%])	95 (6.8)
Right-sided or segmental colitis (<i>n</i> [%])	83 (5.9)
Unknown (<i>n</i> [%])	

Clinical characteristics, treatments, and clinical outcomes for moderate to severe exacerbations

We identified 1639 exacerbation events from the study cohort. Then, 13 exacerbation events were excluded from this analysis due to using tofacitinib for the treatment. Of 1626 exacerbation events to be analyzed, 959 were classified as moderate to severe as follows: 207 in 2004–2008 (21.6%), 304 in 2009–2013 (31.7%), and 448 in 2014–2018 (46.7%) (Figure 1, upper row). Of the moderate to severe exacerbation events among the entire study population, 878 (91.5%) were confirmed as remission, and 81 (8.4%) were converted into surgical resection without achieving remission.

Next, we extracted the first and second exacerbation events of clinical courses during the observation period for each patient from the overall exacerbation events. Of the identified 994 and 401 first and second exacerbation events during the study period, respectively, 525 and 266 were distinguished as moderate to severe exacerbations, respectively (Figure 1, middle and lower rows). From now on, we will refer to first exacerbation of study period as initial exacerbation, and second exacerbation of study period as relapse exacerbation. Table 2 shows the clinical characteristics of the overall, initial, and relapse exacerbations in patients with moderate to severe active UC.

Table 2
Clinical characteristics and treatments in patients with moderate to severe UC exacerbations

Characteristics	Overall exacerbations (n = 959)	Initial exacerbations (n = 525)	Relapse exacerbations (n = 266)
Age, year, mean (SD)	38.6 (17.4)	38.1 (17.9)	38.3 (16.9)
Partial Mayo, severe (n [%])	246 (25.6)	155 (29.5)	59 (22.2)
Pancolitis UC (n [%])	403 (42.0)	210 (40.0)	115 (43.2)
Laboratory data, mean (SD)	8924.8 (3769.8)	9201.2 (3891.9)	8736.7 (3637.8)
White blood cell	3.76 (0.71)	3.61 (0.79)	3.99 (0.532)
Serum albumin	2.70 (4.36)	3.23 (4.83)	2.06 (3.42)
C-reactive protein			
Hospitalization (n [%])	372 (38.8)	236 (45.0)	85 (31.7)
Treatments for exacerbations (n [%])	330 (34.4)	292 (55.6)	29 (10.9)
5-ASAs	124 (12.9)	106 (20.2)	15 (5.6)
Single use	628 (65.5)	342 (65.1)	179 (67.2)
Corticosteroids	78 (8.1)	39 (7.4)	20 (7.5)
Immunomodulators	204 (21.3)	110 (21.0)	61 (22.9)
Calcineurin inhibitors	164 (17.1)	55 (10.5)	41 (15.4)
Biologics	254 (26.5)	133 (25.3)	78 (29.3)
Apheresis	81 (8.4)	42 (8.0)	22 (8.3)
Surgical resection			

5-ASA was administered in 330 of 959 moderate to severe exacerbation events (34.4%), of which 122 (12.7%) were treated with 5-ASA alone. Single-use rates of 5-ASA for moderate to severe exacerbations were similar in the three time periods (Figure 2). We excluded those events that were introduced by 5-ASA alone (n = 122) and set an effectiveness evaluation cohort in the present study (Figure 1, n = 837). Median time periods to remission and re-exacerbation of overall moderate to severe exacerbations in the effectiveness evaluation cohort were 1.7 months (95% CI, 1.6–18.9) and 36.4 months (95% CI, 29.5–43.3), respectively.

Corticosteroids were used for 628 events (65.5%) of moderate to severe active UC, of which 126 (13.0% of overall moderate to severe exacerbations and 20.0% of inductions by corticosteroids) had a previous history of corticosteroid refractory. The proportions of previous history of COR-REF or DEP were almost in

concordance with the three time periods (Figure 2, $P = 0.581$). During the study period, 56.4% of events were confirmed as remission by corticosteroids. The remission rates of corticosteroids were significantly higher if there was no previous history of COR-REF or DEP (absence: 60.6%, presence: 39.7%, $P < 0.001$). Of 837 events in the effectiveness evaluation cohort, we classified 360 events as COR-REF or DEP cohort, based on our earlier definition (Figure 1, the rightmost column).

Figure 2C depicts the transitions of treatments for moderate to severe exacerbations. Biologics showed an increasing tendency during the study period. In contrast, surgical resection and apheresis showed a gradually decreasing trend during same period.

Cumulative risk of surgical resection in UC patients with moderate to severe exacerbations

Based on the effectiveness evaluation cohort of overall exacerbation events, we analyzed factors for the cumulative risk of surgical resection in patients with moderate to severe active UC. A multivariate Cox regression model revealed age ≥ 60 years, severe exacerbations, history of COR-REF or DEP, induction by apheresis, and calcineurin inhibitors were independent risk factors for surgical resection (Table 3). On the other hand, steroids tended to reduce the risk of surgery, although the multivariate analysis did not show a significant difference. Biologics had no significant effect on the cumulative risk of surgical resection.

Table 3

Cox regression analysis of the factors for cumulative risk of surgical resection in patients with moderate to severe UC exacerbations

Variables	Univariate analysis		P	Multivariate analysis		P
	Hazard ratio	95% CI		Hazard ratio	95% CI	
Age, ≥ 60 years	1.895	1.133–3.170	0.015	2.269	1.341–3.840	0.002
First attack	0.825	0.436–1.560	0.554	0.997	0.511–1.945	0.993
Pancolitis UC	1.432	0.924–2.221	0.108	1.156	0.737–1.813	0.528
Severe exacerbation	3.954	2.545–6.142	<0.001	2.973	1.860–4.754	<0.001
History of COR-REF or DEP	3.986	2.576–6.167	<0.001	2.920	1.806–4.720	<0.001
Corticosteroids	0.569	0.368–0.879	0.011	0.666	0.419–1.057	0.085
Apheresis	2.021	1.302–3.136	0.002	1.807	1.132–2.884	0.013
Calcineurin inhibitors	5.059	3.246–7.884	<0.001	2.695	1.657–4.383	<0.001
Biologics	1.355	0.849–2.164	0.203	0.913	0.556–1.499	0.719

We next verified the cumulative incidence of surgical resection in the effectiveness evaluation cohorts of overall, initial, and relapse exacerbation events in subgroups (Figure 3). Classified as COR-REF or DEP were significantly high risk for surgical resection in moderate to severe exacerbation events (Figure 3, the left column). However, biologics did not have a significant effect in reducing the risk for surgical resection (Figure 3, the right column).

Cumulative risk of re-exacerbation in UC patients with moderate to severe exacerbations

Results of the multivariate Cox regression model in overall moderate to severe exacerbation events in patients with UC are shown in Table 4. Biologics significantly reduced the risk of re-exacerbation. In contrast, induction by corticosteroids significantly increased the risk of re-exacerbation. Figure 4 shows the Kaplan–Meier curve of the cumulative incidence of re-exacerbation caused due to the administration of biologics. Our results confirmed that biologics reduced the risk of re-exacerbation in the whole, initial, and relapse exacerbations population in effective evaluation cohort (Figure 4, the left column). We also

evaluated that impact of induction of biologics on cumulative incidence rate of re-exacerbation in patients with COR-REF or DEP cohort. The cumulative incidence rate of re-exacerbation in whole exacerbations population was significantly decreased as well as initial exacerbations cohort (Figure 4, the right column).

Table 4

Cox regression analysis of the factors for cumulative risk of re-exacerbation in patients with moderate to severe UC exacerbations

Variables	Univariate analysis		P	Multivariate analysis		P
	Hazard ratio	95% CI		Hazard ratio	95% CI	
Age, ≥60 years	0.828	0.611–1.115	0.214	0.813	0.603–1.096	0.174
First attack	0.976	0.771–1.236	0.839	0.803	0.612–1.054	0.113
Pancolitis UC	1.227	1.015–1.484	0.035	1.217	1.065–1.391	0.004
Severe exacerbation	1.238	1.000–1.533	0.050	1.133	0.902–1.424	0.283
History of COR-REF or DEP	0.846	0.664–1.077	0.173	0.930	0.716–1.209	0.589
5-ASA	1.046	0.859–1.274	0.652	1.161	0.911–1.480	0.226
Corticosteroids	1.436	1.164–1.772	0.001	1.473	1.183–1.833	0.001
Apheresis	0.992	0.803–1.226	0.944	0.977	0.785–1.216	0.837
Calcineurin inhibitors	1.115	0.886–1.404	0.353	1.206	0.939–1.549	0.142
Immunomodulators	1.051	0.754–1.467	0.768	1.066	0.760–1.480	0.712
Biologics	0.527	0.389–0.713	<0.001	0.501	0.367–0.683	<0.001

Discussion

We demonstrated the effect of biologics in patients with moderate to severe active UC in the Japanese real-world practice by setting two different endpoints, i.e., cumulative incidence rate of surgical resection and re-exacerbation. Our findings indicated the distinctive potential of biologics and the strategic directions of using these drugs in patients.

This study established a unique endpoint, i.e., the cumulative incidence rate of re-exacerbation, and focused on the clinical impact of biologics on maintaining remission in moderate to severe exacerbation events of UC. In general, the clinical outcomes of biologics were assessed using the remission rate. Most randomized controlled trials of biologics have generally compared with placebo by selecting 44-, 52-, or 54-week remission rate as the primary endpoint [20–24]. Recent studies that confirmed the effectiveness of biologics used similar indicators [29, 30]. Even remission rate is a define and convenient endpoint to assess effectiveness both induction and maintenance of remission in UC patients, endpoints with 44-, 52-, or 54-week remission rate appears to be suitable for clinical trials because it does not require long observation periods. However, considering the disease characteristics of UC, the potential of treatments should be evaluated separately based on induction and maintenance of remission. We believe that our study is the first one to demonstrate the cumulative incidence rate of re-exacerbation of biologics in moderate to severe active UC using cohorts from the real-world practice. Our results suggested that administration of biologics significantly reduced the risk of re-exacerbation and prolonged remission duration in moderate to severe UC exacerbation. The cumulative risk of re-exacerbation events, which achieved remission by corticosteroids, was significantly higher than that achieved using biologics in the COR-REF or DEP cohort of our study. Altogether, these results demonstrated an important finding that the conspicuous effect of biologics is maintaining remission in patients with active UC. Based on the results of present study, biologics may be used not only in COR-REF or DEP patients, but also in patients achieving remission by corticosteroids for maintaining remission. We suggest that subpopulation of patients achieving remission by corticosteroids who have high risk of surgical resection in case of re-exacerbation have indications for biologics. Although the medical cost of biologics is a huge medical problem [31, 32], biosimilar and generic drugs may help to solve the issue [33]. Further trials focusing on maintaining remission are required to clarify this clinical issue of UC.

Our study also confirmed the potential of corticosteroids in reducing the risk of surgical resection in moderate to severe UC exacerbations, although statistical significance was not observed with the multivariate analysis. Corticosteroids' potential for achieving remission and avoiding surgical resection should be re-recognized in moderate to severe active UC as reported previously [11–13, 18, 19]. Conversely, biologics showed no dramatic impact on reducing surgical resection risk compared with suboptimal treatments in the COR-REF or DEP population. Although a randomized controlled trial verified that infliximab reduced the risk of surgical resection compared with placebo [20], a recent study reported by Murthy et al. demonstrated that anti-TNF therapy did not decrease UC-related intestinal resections in the real-world practice [34]. Altogether, these results and ours indicate that biologics might not have the anticipated effectiveness for introducing remission, especially in salvaging the COR-REF or DEP population from surgical resection. Hence, there is a strong need to develop promising agents with similar or higher potential of achieving remission compared to corticosteroids.

The characteristics of the present retrospective cohort were generally illustrative to represent of the Japanese UC population during the past few decades. First, both the number of UC patients and the median age at onset had been increasing [35–37]. Second, the rates of hospitalization and surgical resection in the entire population had decreased gradually, including other countries as well [26, 38].

Surgical resection rates of the present cohort were similar those of a Korean cohort [26], although these rates were lower than those of a Western cohort [39]. Remarkably, the proportion of using immunomodulators (i.e., thiopurines) in the present cohort was lower than that in Western countries [40]. It is well known that the incidence rates of adverse events, primarily leukopenia and hair loss, are higher in East Asian populations, including Japan, than in Caucasian populations [41, 42]. Recently, Moriyama et al. reported that a variant in the nudix hydrolase 15 (NUDT15) gene (R139C, c415C > T) was associated with early severe leukopenia in Asians [43]. Currently, the assessment of NUDT R139C has been approved by the Japanese regulatory authority. Consequently, the opportunity to use thiopurines should increase. It would be necessary to confirm the clinical impact of thiopurines in Japanese UC patients in the near future. Regarding biologics, the administration rate is increasing, as in the rest of the world, and is almost equal or slightly higher than those in other countries due to the well-supported system of medical costs [26, 34]. Biologics will become more essential agents for treating active UC patients, due to active development of biologics in the coming years [44, 45]. We anticipate further studies in the future to investigate the effectiveness of biologics focusing on maintaining remission in other cohorts from all over the world.

Conclusion

Our study has confirmed that biologics significantly improved the duration of maintaining remission compared with suboptimal treatments in patients with moderate to severe active UC in a large retrospective Japanese cohort. However, they could not exert a significant effect in reducing the risk of surgical resection in patients with moderate to severe active UC with corticosteroid refractory. We believe that our study results would help gain a deeper understanding of the characteristics of biologics used for treating UC patients.

Declarations

Funding: This research did not receive any grants.

Disclosure:

Sadahisa Ogasawara received honoraria from Bayer, Eisai, Eli Lilly, Otsuka Pharma Co., Ltd., EA Pharma Co., Ltd., consulting or advisory fees from Bayer, Eisai, Merck & Co., Inc., Chugai Pharma, Eli Lilly, AstraZeneca, and research grants from Bayer, Eisai, Eli Lilly. Naoya Kato received honoraria from Abbvie, Mitsubishi Tanabe Pharma, Nippon Kayaku, Nichi-Iko Pharmaceutical Co., Ltd., Takeda, Zeria, Mochida Pharmaceutical Co., Ltd., EA Pharma Co., Ltd., research grants from Abbvie, Mitsubishi Tanabe Pharma, Nippon Kayaku, Takeda, Mochida Pharmaceutical Co., Ltd., EA Pharma Co., Janssen. The other authors involved in this study have nothing to declare regarding funding or conflict of interest with respect to this study.

Availability of Data and Materials: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

IRB did not permit data sharing, because we did not inform patients of data sharing.

Acknowledgments

We would like to respect and thank all physicians, surgeons, and the other medical staffs in Chiba who have been treating IBD patients enthusiastically since IBDs were rare diseases in Japan.

References

1. Ungaro R, Mehandru S, Allen PB, et al. Ulcerative colitis. *Lancet* 2017;389:1756–70.
2. Molodecky NA, Soon IS, Rabi DM, et al. Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases With Time, Based on Systematic Review. *Gastroenterology* 2012;142:46-54.e30.
3. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018;390:2769–78.
4. Thia KT, Loftus EV Jr., Sandborn WJ, et al. An update on the epidemiology of inflammatory bowel disease in Asia. *Am J Gastroenterol* 2008;103:3167–82.
5. Yang Y, Owyang C, Wu GD. East Meets West: The Increasing Incidence of Inflammatory Bowel Disease in Asia as a Paradigm for Environmental Effects on the Pathogenesis of Immune-Mediated Disease. *Gastroenterology* 2016;151:e1-e5.
6. Murakami Y, Nishiwaki Y, Oba MS, et al. Estimated prevalence of ulcerative colitis and crohn's disease in japan in 2014: An analysis of a nationwide survey. *Journal of Gastroenterology* 2019;54:1070–7.
7. Kaplan GG, Ng SC. Understanding and Preventing the Global Increase of Inflammatory Bowel Disease. *Gastroenterology* 2017;152:313-21.e2.
8. Ng SC, Tang W, Leong RW, et al. Environmental risk factors in inflammatory bowel disease: a population-based case-control study in Asia-Pacific. *Gut* 2015;64:1063–71.
9. Bressler B, Marshall JK, Bernstein CN, et al. Toronto Ulcerative Colitis Consensus Group. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. *Gastroenterology* 2015;148:1035-58.e3.
10. Ford AC, Achkar JP, Khan KJ, et al. Efficacy of 5-Aminosalicylates in Ulcerative Colitis: Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2011;106:601–16.
11. Truelove SC, Witts LJ. Cortisone in ulcerative colitis. *BMJ* 1955;2:1041–8.
12. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid Therapy in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2011;106:590–9; quiz 600.
13. Garcia-Planella E, Mañosa M, Van Domselaar M, et al. Long-term outcome of ulcerative colitis in patients who achieve clinical remission with a first course of corticosteroids. *Dig Liver Dis*

2012;44:206–10.

14. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology* 2020;158:1450–61.
15. Matsuoka K, Kobayashi T, Ueno F, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease. *J Gastroenterol* 2018;53:305–53.
16. Ooi CJ, Fock KM, Makharia GK, et al. Asia Pacific Association of Gastroenterology Working Group on Inflammatory Bowel Disease. The Asia-Pacific consensus on ulcerative colitis. *J Gastroenterol Hepatol* 2010;25:453–68.
17. Harbord M, Eliakim R, Bettenworth D, et al. Third european evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: Current management. *Journal of Crohn's and Colitis* 2017;11:769–84.
18. Järnerot G, Rolny P, Sandberg-Gertzén H. Intensive intravenous treatment of ulcerative colitis. *Gastroenterology* 1985;89:1005–13.
19. D'Haens G, Lemmens L, Geboes K, et al. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. *Gastroenterology* 2001;120:1323–9.
20. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis. *New England Journal of Medicine* 2005;353:2462–76.
21. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011;60:780–7.
22. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012;142:257-65.e1-3.
23. Sandborn WJ, Feagan BG, Marano C, et al. PURSUIT-Maintenance Study Group. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014;146:96-109.e1.
24. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. *New England Journal of Medicine* 2013;369:699–710.
25. Parragi L, Fournier N, Zeitz J, et al. Colectomy Rates in Ulcerative Colitis Are Low and Decreasing: 10-year Follow-up Data From the Swiss IBD Cohort Study. *Journal of Crohn's and Colitis* 2018;12:811–8.
26. Cha JM, Park SH, Rhee KH, et al. Long-term prognosis of ulcerative colitis and its temporal changes between 1986 and 2015 in a population-based cohort in the Songpa-Kangdong district of Seoul, Korea. *Gut* 2019;gutjnl-2019-319699.
27. Lewis JD, Chuai S, Nessel L, et al. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis* 2008;14:1660–6

28. Loftus EV Jr, Silverstein MD, Sandborn WJ, et al. Ulcerative colitis in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. *Gut* 2000;46:336–43.
29. Sands BE, Peyrin-Biroulet L, Loftus EV, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *New England Journal of Medicine* 2019;381:1215–26.
30. Narula N, Peerani F, Meserve J, et al. Vedolizumab for Ulcerative Colitis: Treatment Outcomes from the VICTORY Consortium. *Am J Gastroenterol* 2018;113:1345.
31. Wu B, Wang Z, Zhang Q. Cost-Effectiveness of Different Strategies for the Treatment of Moderate-to-Severe Ulcerative Colitis. *Inflamm Bowel Dis* 2018;24:2291–302.
32. Stawowczyk E, Kawalec P. A Systematic Review of the Cost-Effectiveness of Biologics for Ulcerative Colitis. *Pharmacoeconomics* 2018;36:419-34.
33. Meyer A, Rudant J, Drouin J, et al. The effectiveness and safety of infliximab compared with biosimilar CT-P13, in 3112 patients with ulcerative colitis. *Aliment Pharmacol Ther* 2019;50:269–77.
34. Murthy SK, Begum J, Benchimol EI, et al. Introduction of anti-TNF therapy has not yielded expected declines in hospitalisation and intestinal resection rates in inflammatory bowel diseases: a population-based interrupted time series study. *Gut* 2020;69:274–82.
35. Komoto S, Higashiyama M, Watanabe C, et al. Clinical differences between elderly-onset ulcerative colitis and non-elderly-onset ulcerative colitis: A nationwide survey data in Japan. *J Gastroenterol Hepatol* 2018;33:1839–43.
36. Higashiyama M, Sugita A, Koganei K, et al. Management of elderly ulcerative colitis in Japan. *J Gastroenterol* 2019 Jul;54(7):571–86.
37. Fujimoto T, Kato J, Nasu J, et al. Change of clinical characteristics of ulcerative colitis in japan: Analysis of 844 hospital-based patients from 1981 to 2000. *European Journal of Gastroenterology & Hepatology* 2007;19:229–35.
38. Fumery M, Singh S, Dulai PS, et al. Natural History of Adult Ulcerative Colitis in Population-based Cohorts: A Systematic Review. *Clin Gastroenterol Hepatol* 2018;16:343-56.e3.
39. Frolkis AD, Dykeman J, Negrón ME, et al. Risk of Surgery for Inflammatory Bowel Diseases Has Decreased Over Time: A Systematic Review and Meta-Analysis of Population-Based Studies. *Gastroenterology* 2013;145:996–1006.
40. Eriksson C, Cao Y, Rundquist S, et al. Changes in medical management and colectomy rates: a population-based cohort study on the epidemiology and natural history of ulcerative colitis in Örebro, Sweden, 1963-2010. *Aliment Pharmacol Ther* 2017;46:748–57.
41. Hibi T, Naganuma M, Kitahora T, et al. Low-dose azathioprine is effective and safe for maintenance of remission in patients with ulcerative colitis. *J Gastroenterol* 2003;38:740–6.
42. Takatsu N, Matsui T, Murakami Y, et al. Adverse reactions to azathioprine cannot be predicted by thiopurine S-methyltransferase genotype in Japanese patients with inflammatory bowel disease. *J Gastroenterol Hepatol* 2009;24:1258–64.

43. Moriyama T, Nishii R, Perez-Andreu V, *et al.* Nudt15 polymorphisms alter thiopurine metabolism and hematopoietic toxicity. *Nature Genetics* 2016;48:367–73.
44. Sabino J, Verstockt B, Vermeire S, Ferrante M. New biologics and small molecules in inflammatory bowel disease: An update. *Therapeutic Advances in Gastroenterology* 2019;12:175628481985320.
45. Danese S. New Drugs in the Ulcerative Colitis Pipeline: Prometheus Unbound. *Gastroenterology* 2020;158:467–70.

Figures

Figure 1

Study flow

Figure 2

Transitions of treatments in patients with moderate to severe ulcerative colitis exacerbations. A: 5-Aminosalicylates, B: Corticosteroids(“present” means previous history of COR-REF or DEP), C: Other treatments.

Figure 3

Cumulative incidences of surgical resection in patients with moderate to severe ulcerative colitis exacerbations. The left column: the impact of classified as COR-REF or DEP cohort on cumulative incidence of surgical resection in patients with the effective evaluation cohort. The right column: impact of induction by biologics on cumulative incidence of surgical resection in patients with the COR-REF or DEP cohort.

Figure 4

Cumulative incidences of re-exacerbations in patients with moderate to severe ulcerative colitis exacerbations. The left column: the impact of induction of biologics on cumulative incidence of re-exacerbation in patients with the effectiveness evaluation cohort. The right column: the impact of induction of biologics on cumulative incidence of re-exacerbation in patients with the COR-REF or DEP cohort.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplFigure1.tiff](#)
- [SupplFigure2.tiff](#)
- [suppl.docx](#)