Real-World Prescription Pattern and Healthcare Cost Among Patients with Ulcerative Colitis in Japan: A Retrospective Claims Data Analysis

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ABSTRACT

Introduction: The prevalence of ulcerative colitis (UC) is increasing in Japan but recent disease burden estimates are unavailable. This study was conducted to explore the prescription pattern and to estimate the economic burden in Japanese patients with UC.

Methods: This retrospective cohort study was conducted from 1 January 2009 to 30 June 2018 using healthcare claims data from the Japan Medical Data Center (JMDC) database. Patients with a UC diagnosis before the index date (the first UC treatment claim) or within 6 months after the index date, a UC treatment claim registered within ≥ 6 months during the selection period, and a continuous enrollment for 6 months pre-index and 12 months follow-up period were included in the study. Prescription pattern was analyzed by calendar years and lines of treatment (LoT). Healthcare resource utilization and cost per month were determined by LoTs.

Results: Among 10,337 patients with UC diagnosis, 1,861 (18.0%) met the eligibility criteria for this study. 5-Aminosalicylic acid (5-ASA) was the most used treatment over the study period and across all LoTs. 5-ASA was also the most prescribed treatment (88.7%) across all the first LoTs, followed by steroids (20.4%). Use of biologics increased over the study period (biologics + 5-ASA: 0.0% in 2009 to 3.0% in 2018). Biologics were most used as the sixth LoT (7.1%, biologics + 5-ASA; 7.1%, biologics + 5-ASA + steroids). Mean total cost per month was JPY 52,782, with the highest (JPY 112,997) total healthcare cost per month in the fourth LoT and the lowest in the first LoT (JPY 56,782).

Conclusion: Prescription pattern in Japanese patients with UC enrolled in the JMDC database were largely consistent with the clinical guidelines in Japan. UC puts a substantial economic burden on patients, and an effective treatment is warranted to reduce the UC disease burden.

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Key Summary Points

Why carry out this study?

The prevalence of ulcerative colitis (UC) is increasing in Japan but disease burden estimates are unavailable.

We conducted this study to explore the prescription pattern and costs of UC in Japan.

What was learned from the study?

Prescribed treatment in Japan is largely consistent with Japanese clinical guidelines. Moreover, treatment of UC is expensive.

In order to reduce the additional burden due to UC treatment, effective treatment strategies which prevent disease progression are urgently required.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13415177.

INTRODUCTION

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory bowel disease (IBD) characterized by relapsing and remitting mucosal inflammation arising from the rectum, and extending to proximal segments of the colon [1, 2]. UC is more prevalent in the Western world, especially North America and Western Europe, than in Asian countries [1–3]. However, evidence shows that the prevalence of UC in Western countries may have reached a plateau [3], while it is growing in Asian countries [2] including Japan [3]. The global incidence rate of UC is reported as 7.6–245 cases per 100,000 persons per year

[2]. In 2014, a nationwide epidemiological survey conducted in Japanese hospitals reported the prevalence rate of UC to be 172.9 per 100,000 population [4]. In the same year, 170,781 patients received treatment for UC in Japan [5].

A recent US study reported that patients with UC incurred USD 10,304 more in direct healthcare costs per patient per year compared to matched controls without an IBD diagnosis [6]. In Japan, the estimated annual medical cost of UC was approximately USD 249 million and annual per patient cost was USD 1,457 (1 USD = 110 JPY) in the assessment financial year 2014–2015 [7]. Although the majority of this burden is attributed to the direct costs of treatment [6], inappropriate treatment, lack of treatment adherence, or suboptimal treatment may also increase the economic burden [8]. In addition, patients with UC experience diminished quality of life [9] and greater work productivity loss compared to the general population [6].

The current management approach of UC relies heavily on treatment of acute and active disease and maintaining remission [1, 2, 10]. 5-Aminosalicylic acid (5-ASA) is the mainstay of mild to moderate UC management, steroids are used to treat flares, immunomodulators and biologicals are used for moderate to severe UC, and up to 15% of patients may need colectomy for refractory UC or colonic neoplasia [1]. Leukocytapheresis and tacrolimus are also approved for UC treatment in Japan. However, each management approach has its limitations. For example, 5-ASA has moderate efficacy, steroids are not suitable for chronic use, as longterm use is associated with adverse effects, and immunosuppressants and biologics, despite being effective, may be associated with risk of adverse events and malignancies [11–14]. Moreover, as many as 30% of IBD patients may be unresponsive to initial anti-TNF treatment and, in about 45% of patients, the response may diminish over time [10, 15]. Surgery is indicated in patients who are refractory to medical therapy, and approximately 10–15% of patients with UC require surgical intervention. Although effective and tolerable, surgery is

associated with complications [1, 2], and impact the patient's quality of life.

Since there is lack of an effective curative treatment [10], the disease burden of UC remains high; however, with the advancement of new treatment, the demands are shifting toward a management approach, from symptom control to sustained clinical and endoscopic remission [8] using effective and individualized treatments. However, no recent UC burden estimates are available in Japan. Therefore, we conducted a real-world study using a large dataset to explore prescription patterns (pattern of treatment regimens utilized by patients) and assess the economic burden of UC in Japanese patients.

METHODS

Data Source

Data were derived from the Japan Medical Data Center (JMDC) healthcare claims database. This database contains medical and pharmacy claims data for inpatient, outpatient, dispensing services, and annual health checkup of salaried workers and their family members from > 50 Japanese insurance societies belonging to the Health Insurance Association, which includes insurance plans linked to large companies. The database includes approximately 7.3 million (as of April 2020) [16] insured persons, which is about 5.7% of the total population of Japan [17].

Data related to various diagnoses were retrieved using the International Classification of Disease-10th Revision (ICD-10) codes, drugs were identified using the anatomical therapeutic chemical classification, and diagnostic/therapeutic procedures were identified using procedure code information from the JMDC database based on Medical Remuneration in Japan (see Table S1). This article does not contain any studies with human participants or animals performed by any of the authors. As only anonymized de-identified data were used, this study was exempt from institutional review.

Study Design and Sample Selection

The study period for this retrospective cohort analysis was from 1 January 2009 to 30 June 2018, and the sample selection period was between 1 July 2009 and 30 June 2017 (inclusive). The first claim record associated with UC treatment, whether drug or therapeutic procedure, during the selection period was assigned as the index date. Prescription patterns were assessed by analyzing utilization of various treatment regimens and determining lines of treatment (LoT) by identifying events such as treatment initiation, discontinuation, switch, reduction, or add-on.

Patients with a record of at least two claims associated with a UC diagnosis (ICD K51.xx, ulcerative colitis) registered before the index date or within 6 months after the index date, a UC treatment claim registered within at least 6 months during the selection period, and a continuous enrollment for 6 months pre-index and 12 months follow-up period were included in the study. Patients who had at least one claim associated with colorectal cancer or dysplasia diagnosis registered before or at the index date, or had a UC treatment claim registered before the index date, were excluded from the prescription pattern analysis. The exclusion was to ensure a treatment record wash out period before we could have the same baseline for following the prescription pattern. Record of diagnosis claims with ICD C18.xx (malignant neoplasm of colon), ICD C19.xx (malignant neoplasm of rectosigmoid junction), ICD C20.xx (malignant neoplasm of rectum), ICD C21.xx (malignant neoplasm of anus and anal canal), ICD D12.xx (benign neoplasm of colon, rectum, anus and anal canal) were identified and were not included in the analysis.

Study Measures

Prescription Pattern
Prescription pattern in UC was assessed for both drugs and therapeutic procedures. Drugs were classified as 5-ASA, steroids, biologics, immunomodulators, and other agents. Therapeutic procedures were classified as

proctocolectomy and Brooke ileostomy, abdominal colectomy and ileorectal anastomosis, proctocolectomy and Kock pouch, restorative proctocolectomy with ileal pouch–anal anastomosis, and cytapheresis. Concomitant prescriptions of drugs and therapeutic procedures were also considered.

To define a prescription's start and end dates, the initial prescription claim date and number of supply days of the prescribed drug were accounted in the analysis. For missing prescription dates, an approximation from the date of the related claim was used, and missing numbers of supply days were imputed from the median of observed non-missing values. For drugs not administered by the number of days' supply (e.g., infusion/injection), the duration was calculated at each prescription following the guideline description.

A treatment line was defined as a group of consecutive prescriptions of the same treatment class or concomitant usage of treatment classes, without discontinuation (i.e., a gap exceeding 180 days) between the theoretical end date of a prescription and the following prescription. A concomitant prescription was defined by the overlap of prescription records for a duration of at least 30 days. Treatment lines were constructed at the treatment class level, without differentiating individual drugs within a class.

Only the first sequence of treatment lines was analyzed to determine events. Treatment was termed to be: (1) discontinued, if the gap between two drug class/concomitant prescriptions was > 180 days or if there was no record of another drug class/concomitant prescription, (2) switched, if a drug class/concomitant prescription was discontinued and a new drug class/concomitant prescription was recorded with an observed gap < 180 days between the discontinued drug class/concomitant prescription and the new drug class/concomitant prescription with a maximum overlap of 29 days, (3) add-on, if an additional drug class/concomitant prescription was prescribed with an overlap of at least 30 days, and (4) reduced, if one component of the concomitant prescription was discontinued. Therapeutic procedure was identified if a therapeutic procedure claim was observed before one of the events described

above occurred. The sequence of treatment lines continued with all events except when the discontinuation or therapeutic procedure were observed.

Economic Burden

Resource Utilization

Each identified treatment line was defined by the presence of at least one healthcare resource utilization (HRU) outcome occurrence and the number of occurrences per patient-time. These outcomes included number of diagnostic visits and therapeutic procedures, number of hospital admissions, and cumulative inpatient days. A UC-related hospital admission was identified by treatment line as an inpatient/DPC claim associated with a UC ICD-10 diagnosis code in the JMDC 'Diagnosis' dataset. The number of hospital admissions was determined as counts of distinct admission dates in the claims table within the start and end dates of each treatment line and during the follow-up period. The association between treatment categories and number of UC-related hospitalizations was also assessed.

Cost

Healthcare costs per month was determined by three follow-up periods (12, 24, and 36 months) by including patients with < 12, < 24, or < 36 months follow-up, respectively. To calculate the cost per month, we divided the sum of number of claim events (i.e., number of claim events of the patients) by the sum of number of months (i.e., follow-up months of the patients). Healthcare cost per month was also estimated at each treatment line (up to the sixth line). It was identified using the "total medical expense per claim" in the JMDC claims dataset, and defined as the sum of the costs in JPY from all healthcare resources utilized. These costs were defined within the start and end dates of each treatment line during the pre-index and the follow-up periods. UC treatment cost (drugs and therapeutic procedures) up to the sixth line was defined as the sum of the costs in JPY of UC-related drug and therapeutic procedure claims. The patients who were not prescribed any

treatment for UC 6 months prior to the index date were considered treatment-naïve, and patients who had prescription records prior to the index date were considered treatment non-naïve.

Statistical Analysis

Descriptive analyses were conducted for patient characteristics, prescription patterns, HRU, and UC disease progression events. For continuous variables, mean, median, standard deviation (SD), minimum, maximum, and quartiles (Q1 and Q3), and 95% confidence interval were reported. For categorical variables, frequency tables with counts and proportions were presented. Missing and invalid observations were tabulated as a separate category. Calculation of proportions did not include the missing/invalid category. The association between treatment categories in each LoT and the number of UC-related hospitalizations was evaluated using negative binomial models adjusted for age group and gender. Models for the fourth, fifth, and sixth LoT could not be fitted due to low outcome counts. Measures of association with 95% CI and p values were reported. Analysis was performed using SAS v.9.3 software (SAS, Cary, NC, USA).

RESULTS

Study Sample Characteristics

Among 10,337 identified patients with UC, 1,861 (18.0%) met the eligibility criteria (Fig. 1). Sample characteristics of patients in the analysis set were comparable with 'all patients with UC diagnosis', although patients in the analysis set were slightly younger (mean age: 37.2 years) than 'all patients with UC diagnosis' (mean age: 40.1 years). The proportion of male patients was higher than females in both the groups (analysis set: 61.1%, all patients: 61.6%) (Table 1).

Prescription Pattern

Although 5-ASA was the most used treatment option throughout the study period, the prescription rate of 5-ASA monotherapy decreased slightly from 66.0% in 2017 to 60.0% in 2018. The proportions of patients being treated for UC from 2009 to 2017 with 5-ASA and steroids had a trend of gradual increase from 2009 to 2017 (18.5 to 30.2%) (see Table S3). 5-ASA was the choice (88.7%) across all the first-line treatments (5-ASA: 77.5%, 5-ASA + steroids: 9.7%, 5-ASA + immunomodulators: 0.4%, 5-ASA + immunomodulators + steroids: 0.3%, 5-ASA + biologics: 0.3%, 5-ASA + biologics + steroids: 0.5%) followed by steroids (20.4%) (steroid: 9.9%, 5-ASA + steroid: 9.7%, 5-ASA + immunomodulators + steroids: 0.3%, 5-ASA + biologics + steroids 0.5%) (Fig. 2). The concomitant use of biologics and 5-ASA increased over the study duration (0.0–3.0%) (see Table S3). The maximum prescription rate of biologics, either concomitant to 5-ASA (7.1%) or 5-ASA + steroids (7.1%) was observed in the sixth LoT (Fig. 2; see Fig. S1).

Among steroids, systemic prednisolone was the most prescribed drug within the steroid class (see Table S1). Although treatment change occurred in most of cases, 11% of the UC patients received systemic prednisolone therapy throughout the LoT (Fig. 3), with the observed frequency shown across LoT 1–4 (see Fig. S2).

Treatment switch most often occurred in the second LoT (4.3%), particularly in patients using steroids (15.4%) or immunomodulators (50.0%). Add-on was mostly observed in the sixth LoT (25.9%) among patients using steroids or immunomodulators (100%), followed by the third LoT (21.8%) with 5-ASA + biologics (37.5%) or steroids (33.3%). Treatment discontinuation was highest in the first LoT (39.6%), particularly with steroids (66.0%) or 5-ASA (41.9%). On the other hand, patients in the fifth LoT continued their medication the most (49.2%); in particular, all patients who were prescribed biologics or 5-ASA + biologics continued their treatment (100%). Treatment reduction was observed mostly in the sixth LoT (44.4%), especially with
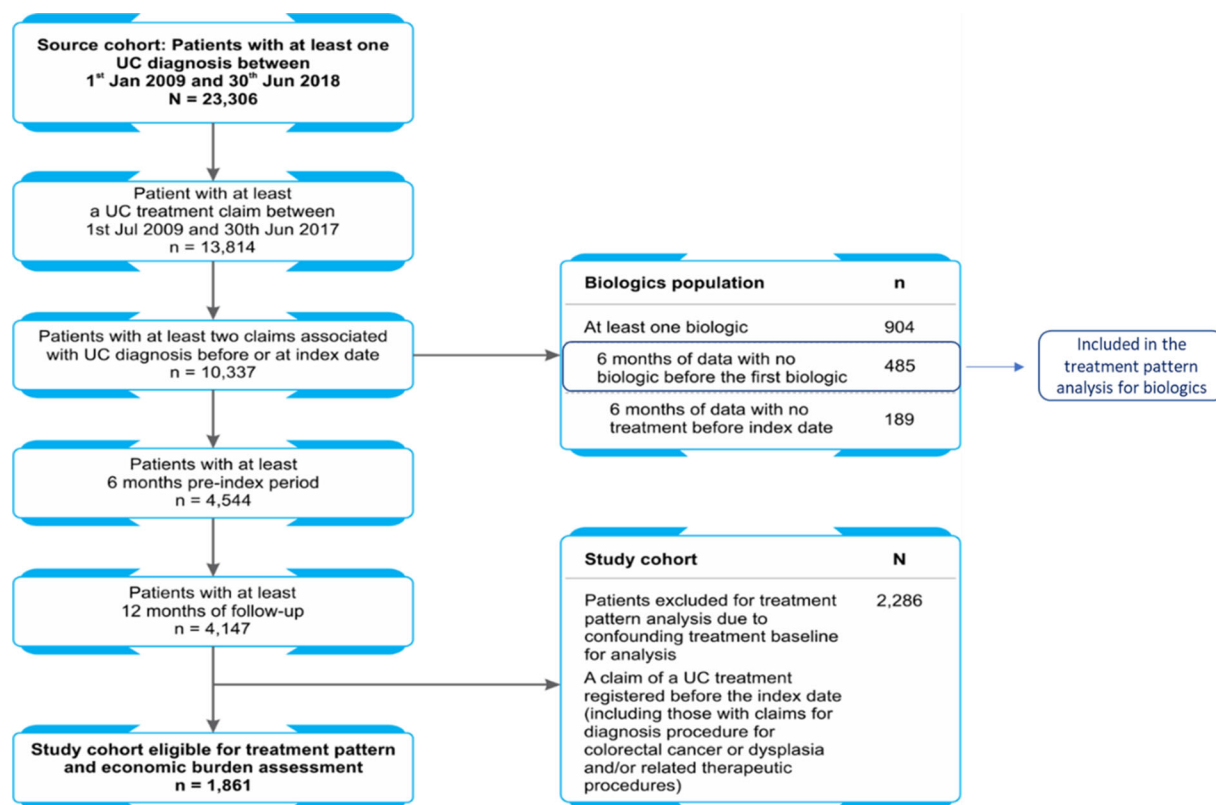
Fig. 1 Patient attrition. *UC* ulcerative colitis

5-ASA + biologics + steroids (100%) or 5-ASA + steroids (80.0%) (Table 2).

Median duration of biologic usage (*n* = 485) was 3.2 years, with a discontinuation rate at 1 year of 32.7% (95% CI 28.4–37.4). However, median duration of biologics usage for patients who did not receive any treatment before initiating biologics (*n* = 186) was 0.6 years, with a discontinuation rate at 1 year of 64.5% (95% CI 57.1–71.8%) (Table 3). Among the 485 patients using biologics, 29.9% switched to a non-biologic product and 8.5% discontinued treatment. Among those who discontinued, the majority had no record for another treatment (65.9%), while 21.9% started another treatment option. Among patients with such long claim gaps, the majority returned to conventional treatments (> 60%), while the rest mostly resumed the same biologic therapy (Table 3).

Economic Burden

Resource Utilization

The diagnostic/therapeutic procedures performed on patients with UC are listed in Table S1. On average, patients with UC had 1.5 diagnostic and therapeutic procedures per month with the number varying as per the LoT. The number of hospital admissions were minimal throughout the treatment lines, with patients on their fourth LoT having the longest mean hospital stay (10.2 days) (Table 4). We observed a significantly higher incidence of UC-related hospitalizations in patients prescribed 5-ASA + steroids compared with 5-ASA only in the first LoT [incidence risk ratio 2.57; 95% CI (1.29–5.11); *p* = 0.007], suggesting that these patients could require more medical support resulting in higher costs. None of the other comparisons showed a significant difference (Table 5).

Table 1 Study sample characteristics before or at index date

	Analysis set (n = 1,861)	All patients with UC diagnosis (n = 10,337)
Gender, n (%)		
Male	1,138 (61.1)	6,368 (61.6)
Female	723 (38.9)	3,969 (38.4)
Age at index date (years), mean (SD)	37.2 (13.1)	40.1 (13.0)
Age at index date (years), n (%)		
< 20	198 (10.6)	602 (5.8)
20–30	389 (20.9)	1,894 (18.3)
30–40	489 (26.3)	2,599 (25.1)
40–50	442 (23.8)	2,752 (26.6)
50+	343 (18.4)	2,490 (24.1)
Median (range) follow-up time (years)	3.2 (1.0, 8.9	3.1 (0.1, 8.9)
Insurance type, n (%)		
Dependent	616 (33.1)	3,170 (30.7)
Insured	1,245 (66.9)	7,167 (69.3)
6 months pre-index: number of UC diagnostic procedures per month, mean (SD)	0.1 (0.1)	0.0 (0.1)
6 months pre-index: number of hospital admissions per month, mean (SD)	0.1 (0.1)	0.0 (0.1)

UC ulcerative colitis, *SD* standard deviation

Costs

Monthly total costs, total pharmacy costs, and total inpatient costs reduced marginally as the follow-up period increased from 12 to 36 months in treatment-naïve patients (those without UC treatment records 6 months prior to the index date). The contribution of outpatient costs was higher than that of pharmacy or inpatient costs; the contribution of inpatient cost was the least among the three (Table 6). Treatment costs in the overall population are reported in Table S4.

Highest and lowest mean total healthcare costs per month were observed in the fourth (JPY 112,997) and the first (JPY 56,782) LoT,

respectively. Mean UC pharmacy and therapeutic procedure costs per month were highest in the sixth LoT (JPY 51,746), while other costs were highest in the fourth LoT (JPY 72,589). The fourth LoT also had the highest mean costs per month for ASA (JPY 17,842), immunomodulators (JPY 3,956), and other drug agents (JPY 19,514). Cost of steroids (JPY 2,571) and biologics (JPY 194,835) were highest in the second and sixth LoT, respectively (see Table S2).

DISCUSSION

The present study was conducted to assess the prescription pattern and economic burden of UC in Japanese patients, using a large health
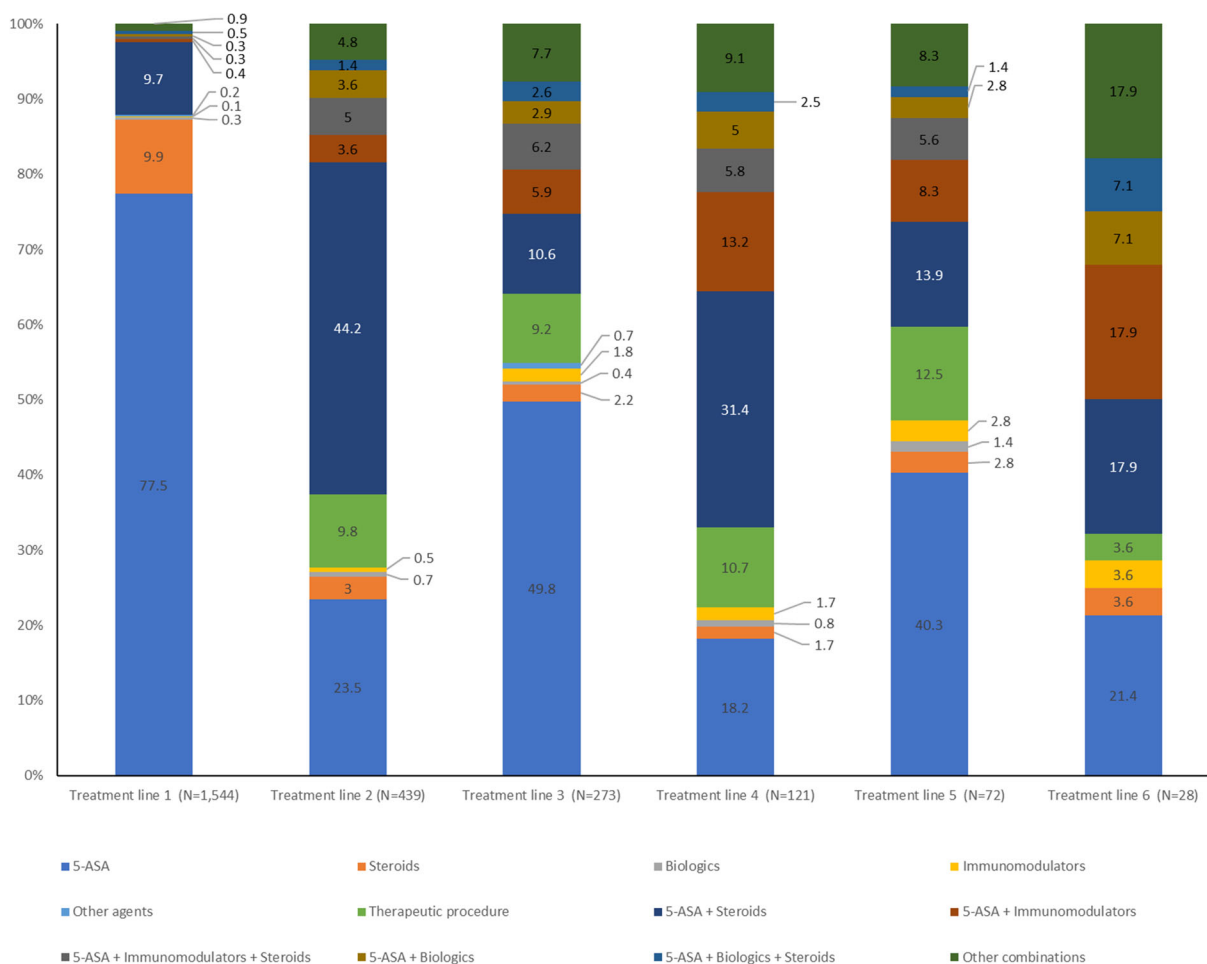
Fig. 2 Trend in ulcerative colitis treatment utilization in Japan, distributed by treatment lines. *5-ASA* 5-aminosalicylic acid. Percentages were calculated from the total number of patients available in each category. The trend of UC treatment by treatment category shows that the trend of 5-ASA and add-on meditation has been increasing. Add-on of 5-ASA with other class of drugs could been observed as patients proceed to the next line of treatment

claims dataset. Findings of this study show that 5-ASA was a commonly used treatment option across all treatment lines. Use of biologics increased marginally during the study period. Additionally, the burden of UC treatment on healthcare system, patients, and the economy was substantial. Since the analysis was conducted using a large representative dataset reflecting routine clinical practice, the findings of the present study are likely to be generalizable. We have compared the Japanese guidelines available during the study to highlight the differences in the treatment landscape (see Table S5).

The Japanese Society of Gastroenterology recommends using 5-ASA as first-line therapy for maintaining clinical and endoscopic remission in mild to moderate UC [18, 19]; recent Cochrane reviews also support the use of 5-ASA [11, 12]. The high prescription rate of 5-ASA observed across all LoTs in our study was consistent with these guidelines. While patients who responded to 5-ASA may not have needed an add-on treatment or change in the treatment class, many who discontinued may have likely achieved adequate response with 5-ASA and terminated the use of other class of drugs or proceeded to the next LoT [20]. However,
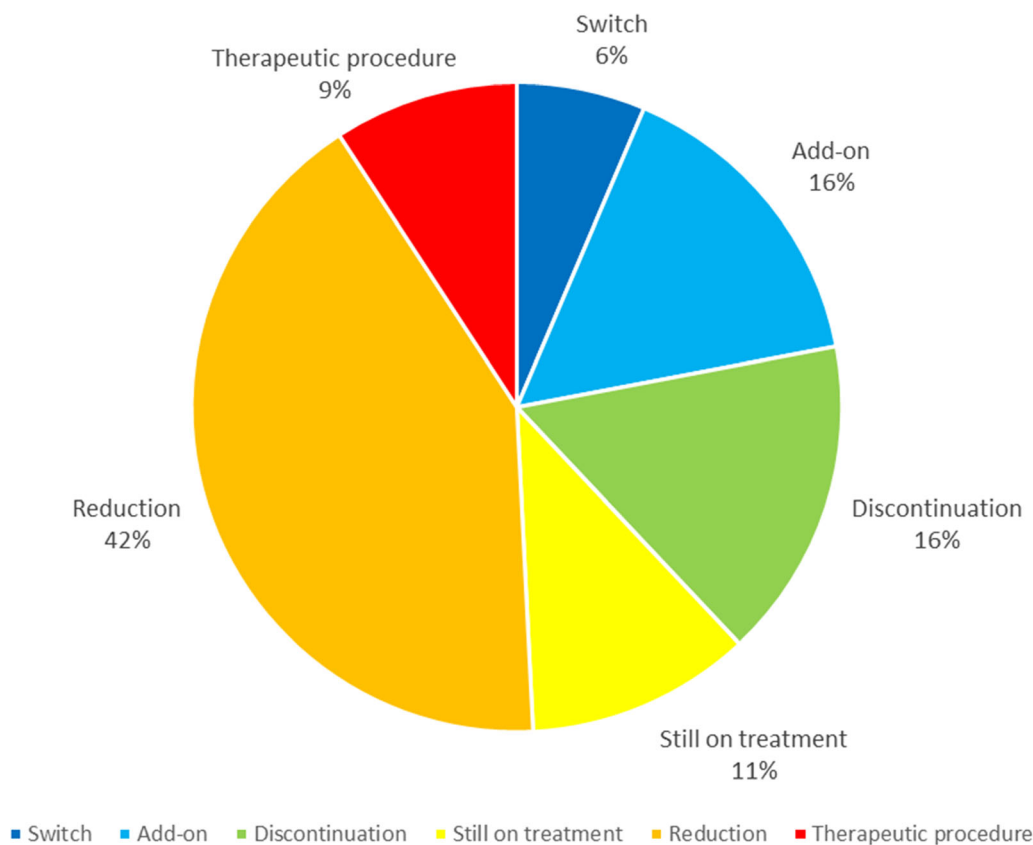
Fig. 3 Treatment event rate in the UC patients prescribed systemic prednisolone monotherapy or 5-ASA + systemic prednisolone. The treatment event rate was calculated from the total number of all treatment events of systemic prednisolone and 5-ASA + systemic prednisolone in all treatment lines

5-ASA's discontinuation rate observed in our study (502 of 1,197 patients who discontinued 5-ASA therapy at first LoT) was higher than we typically expect from clinical experience. Since claims data do not capture information on change in prescription pattern, we relied on a gap in claims record for more than 180 days to determine discontinuation, a method extensively used (with the gap ranging from 30 to 180 days) for prescription pattern analysis using health claims data in the available biomedical literature [21–25]. As the gap in claim records may have occurred due to non-clinical reasons such as family or work-related factors, we cannot rule out the possibility that the patients who discontinued treatment may have resumed their treatment after a gap of 180 days once the follow-up period ended. Hence, it is possible

that we may have overestimated the discontinuation rate [21–25].

An increase in the proportion of patients with 5-ASA add-on prescription (e.g., in combination with steroids or immunomodulators) was observed as the LoT progressed. These patients may have had repeated flares and a higher risk of intractability; however, we do not have enough information to conclude this. Although steroid use in patients refractory to 5-ASA is in agreement with clinical guidelines in Japan, long-term systemic steroid use is not recommended due to an increased risk of adverse events [19]. However, our study showed that about 10% of the patients with UC continued systemic prednisolone (see Fig. 3), especially in the early treatment lines (see Fig. S2). Since we have included patients with at least 12 months of follow-up in this study, we can

Table 2 Treatment events by treatment lines and treatment categories

Treatment line and category, n (%)	Switch	Add-on	Discontinuation	Still on	Reduction	Therapeutic procedure[a]
Treatment line 1 (n = 1,544)	44 (2.8)	250 (16.2)	612 (39.6)	493 (31.9)	102 (6.6)	43 (2.8)
5-ASA, (n = 1,197)	12 (1.0)	207 (17.3)	502 (41.9)	456 (38.1)	0 (0.0)	20 (1.7)
Steroids, (n = 153)	19 (12.4)	14 (9.2)	101 (66.0)	15 (9.8)	0 (0.0)	4 (2.6)
Biologics, (n = 4)	0 (0.0)	1 (25.0)	0 (0.0)	3 (75.0)	0 (0.0)	0 (0.0)
Immunomodulators, (n = 2)	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)
Other agents, (n = 3)	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Therapeutic procedure, (n = 4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (100.0)
5-ASA + steroids, (n = 149)	12 (8.1)	20 (13.4)	9 (6.0)	11 (7.4)	85 (57.0)	12 (8.1)
5-ASA + immunomodulators, (n = 6)	0 (0.0)	3 (50.0)	0 (0.0)	1 (16.7)	1 (16.7)	1 (16.7)
5-ASA + immunomodulators + steroids, (n = 5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100)	0 (0.0)
5-ASA + biologics, (n = 4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (50.0)	0 (0.0)
5-ASA + biologics + steroids, (n = 7)	0 (0.0)	1 (14.3)	0 (0.0)	1 (14.3)	4 (57.1)	1 (14.3)
Other concomitant prescriptions, (n = 10)	1 (10.0)	0 (0.0)	0 (0.0)	3 (30.0)	5 (50.0)	1 (10.0)
Treatment line 2, (n = 396)	17 (4.3)	67 (16.9)	32 (8.1)	91 (23.0)	164 (41.4)	25 (6.3)
5-ASA, (n = 103)	1 (1)	31 (30.1)	18 (17.5)	51 (49.5)	0 (0.0)	2 (1.9)
Steroids, (n = 13)	2 (15.4)	2 (15.4)	5 (38.5)	2 (15.4)	0 (0.0)	2 (15.4)
Biologics, (n = 3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100)	0 (0.0)	0 (0.0)
Immunomodulators, (n = 2)	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)
5-ASA + steroids, (n = 194)	7 (3.6)	22 (11.3)	5 (2.6)	16 (8.2)	131 (67.5)	13 (6.7)
5-ASA + immunomodulators, (n = 16)	1 (6.3)	3 (18.8)	1 (6.3)	9 (56.3)	1 (6.3)	1 (6.3)
5-ASA + immunomodulators + steroids, (n = 22)	1 (4.5)	2 (9.1)	1 (4.5)	1 (4.5)	14 (63.6)	3 (13.6)
5-ASA + biologics, (n = 16)	2 (12.5)	2 (12.5)	1 (6.3)	6 (37.5)	4 (25.0)	1 (6.3)
5-ASA + biologics + steroids, (n = 6)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	2 (33.3)	2 (33.3)
Other concomitant prescriptions, (n = 21)	2 (9.5)	4 (19.0)	1 (4.8)	1 (4.8)	12 (57.1)	1 (4.8)

Table 2 continued

Treatment line and category, n (%)	Switch	Add-on	Discontinuation	Still on	Reduction	Therapeutic procedure[a]
Treatment line 3, (n = 248)	4 (1.6)	54 (21.8)	23 (9.3)	104 (41.9)	50 (20.2)	13 (5.2)
5-ASA, (n = 136)	0 (0.0)	38 (27.9)	18 (13.2)	77 (56.6)	0 (0.0)	3 (2.2)
Steroids, (n = 6)	0 (0.0)	2 (33.3)	0 (0.0)	3 (50.0)	0 (0.0)	1 (16.7)
Biologics, (n = 1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)
Immunomodulators, (n = 5)	0 (0.0)	0 (0.0)	2 (40.0)	3 (60.0)	0 (0.0)	0 (0.0)
Other agents, (n = 2)	0 (0.0)	0 (0.0)	2 (100)	0 (0.0)	0 (0.0)	0 (0.0)
5-ASA + steroids, (n = 29)	1 (3.4)	5 (17.2)	1 (3.4)	3 (10.3)	18 (62.1)	1 (3.4)
5-ASA + immunomodulators, (n = 16)	1 (6.3)	4 (25.0)	0 (0.0)	6 (37.5)	4 (25.0)	1 (6.3)
5-ASA + immunomodulators + steroids, (n = 17)	0 (0.0)	2 (11.8)	0 (0.0)	2 (11.8)	11 (64.7)	2 (11.8)
5-ASA + biologics, (n = 8)	0 (0.0)	3 (37.5)	0 (0.0)	2 (25.0)	3 (37.5)	0 (0.0)
5-ASA + biologics + steroids, (n = 7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)	5 (71.4)	0 (0.0)
Other concomitant prescriptions, (n = 21)	2 (9.5)	0 (0.0)	0 (0.0)	5 (23.8)	9 (42.9)	5 (23.8)
Treatment line 4, (n = 108)	3 (2.8)	18 (16.7)	7 (6.5)	29 (26.9)	42 (38.9)	9 (8.3)
5-ASA, (n = 22)	0 (0.0)	8 (36.4)	4 (18.2)	9 (40.9)	0 (0.0)	1 (4.5)
Steroids, (n = 2)	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)
Biologics, (n = 1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)
Immunomodulators, (n = 2)	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)
5-ASA + steroids, (n = 38)	0 (0.0)	3 (7.9)	2 (5.3)	2 (5.3)	27 (71.1)	4 (10.5)
5-ASA + immunomodulators, (n = 16)	1 (6.3)	3 (18.8)	1 (6.3)	8 (50.0)	3 (18.8)	0 (0.0)
5-ASA + immunomodulators + steroids, (n = 7)	1 (14.3)	0 (0.0)	0 (0.0)	1 (14.3)	5 (71.4)	0 (0.0)
5-ASA + biologics, (n = 6)	0 (0.0)	1 (16.7)	0 (0.0)	3 (50.0)	2 (33.3)	0 (0.0)
5-ASA + biologics + steroids, (n = 3)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)
Other concomitant prescriptions, (n = 11)	0 (0.0)	1 (9.1)	0 (0.0)	3 (27.3)	4 (36.4)	3 (27.3)
Treatment line 5, (n = 63)	2 (3.2)	10 (15.9)	4 (6.3)	31 (49.2)	15 (23.8)	1 (1.6)

Table 2 continued

Treatment line and category, n (%)	Switch	Add-on	Discontinuation	Still on	Reduction	Therapeutic procedure[a]
5-ASA, (n = 29)	1 (3.4)	4 (13.8)	3 (10.3)	21 (72.4)	0 (0.0)	0 (0.0)
Steroids, (n = 2)	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)
Biologics, (n = 1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)
Immunomodulators, (n = 2)	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)
5-ASA + steroids, (n = 10)	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	6 (60.0)	1 (10.0)
5-ASA + immunomodulators, (n = 6)	0 (0.0)	1 (16.7)	0 (0.0)	5 (83.3)	0 (0.0)	0 (0.0)
5-ASA + immunomodulators + steroids, (n = 4)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	3 (75.0)	0 (0.0)
5-ASA + biologics, (n = 2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)	0 (0.0)	0 (0.0)
5-ASA + biologics + steroids, (n = 1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)
Other concomitant prescriptions, (n = 6)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	5 (83.3)	0 (0.0)
Treatment line 6, (n = 27)	0 (0.0)	7 (25.9)	0 (0.0)	7 (25.9)	12 (44.4)	1 (3.7)
5-ASA, (n = 6)	0 (0.0)	2 (33.3)	0 (0.0)	4 (66.7)	0 (0.0)	0 (0.0)
Steroids, (n = 1)	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immunomodulators, (n = 1)	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5-ASA + steroids, (n = 5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (80.0)	1 (20.0)
5-ASA + immunomodulators, (n = 5)	0 (0.0)	2 (40.0)	0 (0.0)	1 (20.0)	2 (40.0)	0 (0.0)
5-ASA + biologics, (n = 2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)
5-ASA + biologics + steroids, (n = 2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)	0 (0.0)
Other concomitant prescriptions, (n = 5)	0 (0.0)	1 (20.0)	0 (0.0)	1 (20.0)	3 (60.0)	0 (0.0)

The number of patients in treatment line 1 (n = 1,544) varies from the number of patients included in the study (n = 1,861) as 317 patients had a short duration of treatment (< 30 days) hence, were excluded from this analysis. Patients who discontinued treatment, were still on the prescribed treatment, or underwent a therapeutic procedure, were not considered in the next treatment line. E.g. in treatment line 1, patients who discontinued treatment (n = 612), were still on treatment (n = 493), or underwent a therapeutic procedure (n = 43) were not included in treatment line 2 (n = 396; 1544–612–493–43)

5-ASA 5-aminosalicylic acid

[a] Number of patients who underwent colectomy are 3, 2, and 1 in the first, second, and third treatment lines, respectively

Table 3 Overall biologics prescription pattern and time gap without biologics claims after initial biologics prescription

	All biologics ($n = 485$)
Median duration of biologic use, years (95% CI)	3.2 (2.2–5.4)
Median duration of biologic use in treatment-naïve UC patients ($n = 189$), years (95% CI)	0.6 (05–0.8)
Discontinuation rate at 1 year, % (95% CI)	32.7 (28.4–37.4)
Discontinuation rate at 1 year in treatment-naïve UC patients ($n = 189$), % (95% CI)	64.5 (57.1–71.8%)
Line event, n (%)	
Switch	145 (29.9)
Discontinuation	41 (8.5)
Continuation	291 (60.0)
Therapeutic procedure	8[a] (1.7)
Patients who discontinued ($n = 41$), n (%)	
No treatment record	27 (65.9)
Restart the same biologic	4 (9.8)
Start another treatment	9 (21.9)
Therapeutic procedure	1[b] (2.4)
Median period of no treatment record, years (95% CI)	2.1 (1.0–4.9)
Continued treatment claims within 1 year, % (95% CI)	29.9 (16.6–50.2)
Treatment claim gap < 120 days ($n = 1$), n (%)	
Restart the same biologic	0
Start conventional treatment	1 (100)
Therapeutic procedure	0
Treatment claim gap < 180 days ($n = 3$), n (%)	
Restart the same biologic	2 (66.7)
Start conventional treatment	1 (33.3)
Therapeutic procedure	0
Treatment claim gap < 270 days ($n = 8$), n (%)	
Restart the same biologic	3 (37.5)
Start conventional treatment	5 (62.5)
Therapeutic procedure	0
Treatment claim gap < 360 days ($n = 9$), n (%)	
Restart the same biologic	3 (33.3)
Start conventional treatment	6 (66.7)
Therapeutic procedure	0
Treatment claim gap ≥ 360 days ($n = 5$), n (%)	

Table 3 continued

	All biologics (*n* = 485)
Restart the same biologic	1 (20.0)
Start conventional treatment	3 (60.0)
Therapeutic procedure	1[c] (20.0)

CI confidence interval

[a] Adalimumab – two cytapheresis and one colectomy; infliximab – five cytapheresis

[b] Infliximab—one colectomy

[c] No data available

Table 4 Healthcare resource utilization per month by treatment line

	Treatment line 1	Treatment line 2	Treatment line 3	Treatment line 4	Treatment line 5	Treatment line 6
Number of diagnostic and therapeutic procedures						
n	1,530	432	272	119	71	28
Mean (SD)	1.7 (2.9)	1.7 (3.0)	1.3 (2.4)	1.7 (4.2)	0.9 (1.8)	1.6 (4.6)
Number of hospital admissions						
n	1,530	434	269	120	72	27
Mean (SD)	0.0 (0.2)	0.1 (0.2)	0.0 (0.2)	0.1 (0.3)	0.0 (0.1)	0.0 (0.0)
Mean cumulative inpatient days						
n	218	63	33	11	7	1
Mean (SD)	3.1 (5.7)	4.7 (7.0)	3.0 (5.5)	10.2 (9.5)	4.2 (5.8)	

The account of resource utilization period was generated within the start and end dates of each treatment line during the follow-up period. Diagnostic and therapeutic procedures were identified by the procedure codes designated by medical remuneration in Japan. Numbers of hospital admissions stay (inpatients and day cases) were generated as the count of distinct admission dates in the claims table within the start and end dates of each treatment line and during the follow-up. Cumulative inpatient days were generated as count days of medical care in the claims table within the start and end dates of each treatment line during the follow-up. Patients whose data were missing were excluded; e.g., patients with missing HRU data were excluded

HRU healthcare resource utilization, *SD* standard deviation

state that some patients seem to take inappropriate systemic steroid treatment that is inconsistent with clinical guidelines in Japan.

5-ASA + biologics was commonly prescribed as the second LoT, which seems inconsistent with Japanese clinical guidelines, as they

Table 5 Association between treatment categories and number of UC-related hospitalizations

Treatment line	Treatment category	n	Incidence risk ratio (95% CI)	p value
1	5-ASA	1,197		
	Steroids	153	0.44 [0.09–2.07]	0.3
	Other agents	45	2.36 [0.68–8.22]	0.18
	5-ASA|steroids	149	2.57 [1.29–5.11]	0.007
2	5-ASA	103		
	Other agents	138	4.97 [0.57–43.04]	0.15
	5-ASA|steroids	194	5.61 [0.67–46.90]	0.11
3	5-ASA	136		
	Other agents	108	13.31 [0.35–510.87]	0.16
	5-ASA|steroids	29	11.06 [0.19–650.96]	0.25

Models for the fourth, fifth, and sixth line of treatment could not be fitted due to low outcome counts

5-ASA 5-aminosalicylic acid, *CI* confidence interval, *UC* ulcerative colitis

recommend using immunomodulators prior to biologics in corticosteroid-dependent patients [19]. However, because it is known that approximately 20% of UC patients experience a severe flare during their disease [26], our data might indicate that some patients require early intensive treatment. However, as the data on the disease severity and clinical response to treatment were not available, it cannot be determined if prescribing 5-ASA + biologics as second-line therapy was appropriate.

Treatment discontinuation was observed largely in the first LoT, although, as explained above, we may have overestimated the discontinuation rate owing to the algorithm used for determining discontinuation events. Add-on treatment and treatment reduction were the most frequent patterns observed from the second to the sixth LoT. Add-on treatment was commonly observed when immunomodulators were prescribed concomitantly with other therapies. The rate of switching was low across all LoTs.

A marginally increasing trend in the prescription of biologics was observed during the study period. The maximum prescription rate (5.5%) of biologics with or without concomitant treatments (0.6% + 3.4% + 1.5%) was observed in the year 2015, which was lower than estimates reported in a US retrospective claims database analysis (5.1 to 16.2% from 2007 to 2015) [27]. As the high costs associated with biologics may limit their wider usage, the MHLW provides financial aid to patients who are prescribed biologics [28]. However, in the present study, the impact of biologics' cost was not significant, apparently due to a very low proportion of biologic users.

The median duration of biologic treatment among treatment-naïve patients in the current study was 7.2 months, and 64.5% of those who received biologics discontinued after 1 year. Null et al., in a retrospective analysis of US health claims data, reported that about 50% of patients receiving infliximab or adalimumab discontinued during the first 12 months, and a substantial percentage of those patients did not restart or switch to another biologic therapy [29]. The reasons for discontinuation, though poorly understood, may include side effects or a lack of efficacy [30], although the reasons for discontinuation were unavailable in our study.

The number of hospital admissions per month in the present study was slightly lower than 0.28 admissions per month reported by Yamabe et al. [31], who retrospectively analyzed

Table 6 Costs (Japanese Yen) at each timepoint in treatment-naive patients with < 12/24/36 months follow-up

	Over 12 months	Over 24 months	Over 36 months	Overall follow-up
Total cost/month				
n	1,860	1,860	1,860	1,860
Mean ± SD	50,959.8 ± 12,3674.9	45,988.3 ± 95,254.2	44,799.5 ± 90,410.9	43,911.0 ± 88,318.9
Median	23,716.4	21,905.0	21,310.7	20,898.3
[Q1, Q3]	[12,073.1, 39,504.8]	[10,651.9, 38,251.7]	[9,883.9, 37,722.5]	[9,912.5, 37,889.5]
[min, max]	[60.5, 1,741,647]	[370.0, 1,520,816]	[303.3, 1,520,816]	[199.4, 1,520,816]
Total pharmacy cost/month				
n	1,860	1,860	1,860	1,860
Mean ± SD	12,110.6 ± 16,405.6	11,632.3 ± 16,432.2	11,488.9 ± 17,065.0	11,307.8 ± 17,814.7
Median	7,324.2	6,700.9	6,525.3	6,695.3
[Q1, Q3]	[1,735.9, 18,086.2]	[1,566.7, 16,982.3]	[1,560.8, 16,551.5]	[1,596.3, 15,941.7]
[min, max]	[0.0, 259,218.5]	[0.0, 253,377.3]	[0.0, 245,922.3]	[0.0, 324,017.7]
Total inpatient cost/month				
n	1,860	1,860	1,860	1,860
Mean ± SD	20,596.6 ± 108,014.2	16,420.5 ± 75,695.8	15,246.5 ± 69,058.3	14,223.1 ± 66,810.0
Median	0.0	0.0	0.0	0.0
[Q1, Q3]	[0.0, 0.0]	[0.0, 0.0]	[0.0, 0.0]	[0.0, 1,903.3]
[min, max]	[0.0, 1,730,764]	[0.0, 1,511,313]	[0.0, 1,511,313]	[0.0, 1,511,313]
Total outpatient cost/month				
n	1,860	1,860	1,860	1,860
Mean ± SD	18,252.7 ± 38,381.4	17,935.4 ± 37,074.2	18,064.1 ± 38,098.6	18,380.1 ± 38,641.6
Median	10,407.2	9,378.2	9,285.1	9,119.9
[Q1, Q3]	[5,688.2, 17,641.6]	[5,318.8, 16,444.2]	[5,187.5, 16,219.1]	[5,022.2, 16,312.0]
[min, max]	[60.5, 943,824.0]	[58.4, 799,294.1]	[39.0, 799,294.1]	[25.6, 799,294.1]

Only patients with at least 1 day of follow-up were included. Treatment naïve: patients with no prescription records 6 months prior to the index period

SD standard deviation

data from the 2012–2014 Japan National Health and Wellness Survey. UC treatment costs as well as its contribution to total healthcare costs (72.3%) were highest in the sixth LoT, probably due to increased usage of biologics. Total annual direct costs estimated in the present study (JPY 656,928 and JPY 526,932 for treatment non-naïve and naïve patients, respectively) were substantially less than the cost reported by Yamabe et al. (JPY 2,135,095) [31], who used self-reported survey responses for cost estimation, which may have a potentially unverified resource utilization and inflated cost reporting. The present study also shows

that most of the UC patients were of working age (30–50 years old), and around 30% of them had a dependent insurance status. Although we did not estimate indirect costs due to productivity loss, Yamabe et al. [31] reported that UC accrues an average indirect cost of more than JPY 1.5 million per-patient annually.

Our study has the typical limitations of a claims data analysis as the dataset may have coding errors. Also, since diagnoses were identified by ICD codes and not clinically validated, there may be a potential of misclassification. The database had no information about disease severity; hence, the effect of severity on outcomes could not be evaluated. Missing values had to be imputed while describing treatment pathways, as some claims only had the month and year data. Furthermore, changes in prescription pattern were not explored adequately due to unavailability of information regarding the reason for switching or discontinuing a treatment. Since this study had a follow-up period of 3 years, it is possible that only high up-front costs were captured for a few patients who underwent hospitalization and significant therapy, but were in remission for a prolonged period of time, resulting in skewed cost data. Lastly, these findings should be interpreted cautiously, since they may not represent current clinical practice of UC management in Japan, and only present an overview of treatment utilization among UC patients. Further research with statistically rigorous design is warranted to validate these findings.

CONCLUSION

This study shows that the prescription pattern in Japanese patients with UC enrolled in the JMDC database is largely consistent with Japanese clinical guidelines. Utilization of 5-ASA and 5-ASA + steroids increased and decreased throughout the treatment lines; similar changes were observed for HRU and costs. This suggests that treatment switch occurs whenever flares occur, probably due to inadequate response to treatment with 5-ASA and 5-ASA + steroids. Although not explicitly analyzed in this study, determining the prognosis and providing an appropriate and optimal alternate treatment to patients who are refractory to existing treatment could help extend remission, prevent relapses, and reduce HRU and costs.

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Compliance with Ethics Guidelines. This article does not contain any studies with human participants or animals performed by any of the authors. As only anonymized de-identified data were used, this study was exempt from institutional review.

Data Availability. We do not have additional associated data to disclose, all the

relevant data has been reported in the manuscript or submitted supplementary material.

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