Imaging and treatment patterns in newly-diagnosed patients with Crohn's disease: analysis of a Japanese claims database

Fumihito Hirai (fuhirai@cis.fukuoka-u.ac.jp)
Fukuoka University Chikushi Hospital https://orcid.org/0000-0002-5493-5675
Akihito Uda
Takeda Pharmaceutical Company Limited
Mihoko Ota
Takeda Pharmaceutical Company Limited
Yukiko Takemura
Takeda Pharmaceutical Company Limited
Keisuke Tanaka
Takeda Pharmaceutical Company Limited
Ryuichi Iwakiri
Takeda Pharmaceutical Company Limited

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Abstract

Background: The biologics adalimumab, infliximab, and ustekinumab are approved to treat Crohn's disease (CD) in Japan; they are recommended to induce/maintain remission in steroid-dependent/steroid-refractory CD. However, little is known about biologic use in real-world clinical practice, particularly in the initial treatment stage following endoscopic/radiographic diagnosis (intestinal inspection).

Methods: This observational, retrospective, longitudinal cohort study assessed patients in the Japan Medical Data Center claims database who were diagnosed with CD from 2009–2019, and prescribed ≥ 1 biologic (adalimumab, infliximab, ustekinumab). Primary outcomes were type of first-line treatment prescribed on/within 6 months of first CD diagnosis, and time from first diagnosis to biologic introduction.

Results: The study included 1346 patients with newly-diagnosed CD who were prescribed a biologic (adalimumab, n = 434; infliximab, n = 892; ustekinumab, n = 20). Most common first-line treatments were 5-aminosalicylic acid (5-ASA) monotherapy (26.8%), 5-ASA plus biologic (26.3%), and biologic monotherapy (12.9%). First-line steroids (monotherapy/in combination) were prescribed in 10.8% of patients. The first-line biologic prescription rate was lower in patients who had undergone intestinal inspection within 12 months before biologic introduction versus those who had not (5.3% vs 17.4% in monotherapy; 19.9% vs 65.4% in combination with other agents). Mean time from diagnosis to first biologic prescription was 4.1 months.

Conclusions: The study demonstrated high use of biologics (particularly infliximab) and low use of steroids in initial treatment of Japanese patients with newly-diagnosed CD who received biologics during their treatment course. Biologic prescription was more common in patients who had not undergone prior intestinal inspection.

Background

Crohn's disease (CD) is a chronic, progressive inflammatory bowel disease of unknown etiology, involving mainly the small and large intestine, and perianal region, but occasionally the entire gastrointestinal tract [1-3]. It is characterized by a young onset, relapsing–remitting course, and troublesome symptoms, such as abdominal pain, diarrhea, hematochezia, fever, perianal lesions, weight loss, and fatigue, which can impact markedly on patient quality of life (QoL) [1-5]. In addition to enteric complications (eg, stricture, abscess, fistula, hemorrhage), CD may also result in extra-intestinal inflammatory complications in the joints, skin, eyes, mouth, and other organ systems [1-3]. In Japan, the prevalence of CD was 55.6 per 100,000 persons in 2014 [6]. As of December 2014, 40,885 patients in Japan were receiving treatment for CD [7].

Standard management of CD involves drug therapy and nutritional interventions, with surgery reserved for intestinal complications and cases that do not respond to non-invasive treatments [1-3]. The choice of treatment varies depending on the anatomic location of the disease, disease severity, presence of

complications, and whether the treatment goal is to induce or to maintain remission [1-3]. In all cases, the main aims of treatment are to reduce bowel inflammation (by healing the intestinal mucosa), halt disease progression, reduce and control symptoms, reduce the likelihood of complications, maintain nourishment, and optimize patient QoL. Options for the pharmacological treatment of CD, which may be used in monotherapy or in combination, include 5-aminosalicylates (5-ASA; a group of drugs which tend to be used primarily in mild-to-moderate/low-risk CD), corticosteroids, biologics, thiopurine immunomodulators, antimicrobials, and other immunosupressants [1-3].

Currently, 3 biologics are approved to treat CD in Japan: infliximab (antitumor necrosis factor-α [TNFα]), adalimumab (anti-TNFα), and ustekinumab (anti-interleukin-12/-23; introduced in 2017) [8, 9]. These biologics are currently recommended as treatments to induce and maintain remission in patients with steroid-dependent or steroid-refractory CD [1]. However, little is known about how these biologics are used in real-world clinical practice, particularly if and how they are used in the initial stage of treatment following endoscopic/radiographic diagnosis (intestinal inspection), how effective they are, and how long patients are maintained on therapy. This real-world, claims-based study was therefore undertaken to investigate treatment patterns in Japanese patients with newly diagnosed CD previously prescribed biologic therapy (2009–2019), including evaluation (incidence and timing) of initial treatment (particularly first-line use of biologics), intestinal inspections, biologic treatment switches or discontinuations, complications, surgery, biologic persistence, and medical costs. These outcomes were defined for the overall study population and according to whether patients underwent prior intestinal inspection.

Methods

Study design

This was an observational, retrospective longitudinal cohort study of treatment patterns in an overall population of patients, and according to whether these patients underwent prior intestinal inspection, who were included in the Japan Medical Data Center (JMDC) claims database who had been newly diagnosed with CD between 2009 and 2019, and prescribed at least 1 biologic agent (adalimumab, infliximab, or ustekinumab). The JMDC is an administrative database containing information on medical (inpatient and outpatient) and pharmacy claims for salaried workers and their families from several Japanese insurance societies belonging to the Japan Health Insurance Association, which includes insurance plans linked to medium-to-large companies [10]. Using this database, it is possible to track medical consultations for each patient chronologically, even if the patient attends multiple institutions or transfers from one hospital to another.

Claims data were analyzed for the 10-year period from January 1, 2009 to January 1, 2019 (index period). Ethics approval for the analysis was obtained from the Japanese Research Institute of Healthcare Data Science (http://rihds.org/about/). All patient-level data were anonymized.

Patients

Patients were included in this analysis if they had at least 1 confirmed diagnosis code for CD (International Classification of Diseases 10th revision [ICD-10] code [11], K50, and standard disease name) and evidence of at least 1 prescription for a biologic (adalimumab, infliximab, or ustekinumab) after the CD diagnosis between January 1, 2009 and January 1, 2019, without having had a CD diagnosis code in the 4 years prior to the start of the index period (January 1, 2005 to December 31, 2008). Exclusion criteria included: no prior prescription for a biologic between January 1, 2005 and December 31, 2018; evidence of at least 1 prescription for a biologic before the first CD diagnosis; at least 1 diagnosis code for a comorbidity requiring a biologic used in CD (rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, ulcerative colitis, intestinal Behçet's disease, ankylosing spondylitis, axial spondyloarthritis, or juvenile idiopathic arthritis; identified using their ICD-10 codes) in the 12 months prior to first biologic prescription; and > 6 months between first CD diagnosis and first prescription of any drug.

Outcomes

The primary outcomes were the type of first-line treatment prescribed on or within 6 months of the date of first CD diagnosis (index date; first-line treatment with biologics, 5-ASA, immunomodulators [azathioprine or 6-mercaptopurine], other immunosuppressants [ciclosporin, tacrolimus, or methotrexate], enteral nutrition, steroids, antimicrobials, or cytapheresis [CAP]/granulocytapheresis [GCAP]; identified using their Anatomical Therapeutic Chemical codes or J041-2 procedure code [CAP/GCAP]), and time from first confirmed CD diagnosis to biologic introduction (first prescription of adalimumab, infliximab, or ustekinumab). If 2 different drug categories were prescribed within 7 days, the categories were classified as a combination. However, this definition may not be sufficient to identify all combinations with biologics, particularly immunomodulators.

Secondary outcomes of interest included: incidence of intestinal inspection (as defined in the online supplementary information) in the 12 months, and at any time, prior to biologic introduction, and time from last intestinal inspection to biologic introduction (for patients with an intestinal inspection at any time prior to biologic introduction); incidence of treatment switch following biologic introduction and time from biologic introduction to treatment switch; incidence of discontinuation following biologic introduction and time from biologic introduction to discontinuation; incidence of complications (ileal stenosis, intestinal perforation, or intestinal rupture, identified by their ICD-10 codes) any time after biologic introduction and time from biologic introduction to first complication (for patients with a reported complication); incidence of first surgery any time after biologic introduction and time from biologic introduction to first surgery (for patients with a reported surgical procedure); and biologic persistence (incidence and time from biologic introduction to loss of persistence, where persistence was defined as

the absence of a switch or discontinuation of adalimumab, infliximab, or ustekinumab) [12]. A switch from first biologic treatment was defined as a situation when the drug(s) prescribed in first line was no longer prescribed (ie, the gap between any 2 consecutive prescriptions of a given drug was longer than the minimum gap allowed [defined as the 90th percentile of the time between 2 fills]) or when 1 or more new drugs, which were not prescribed in first line, were initiated. Direct medical costs (mean cost per patient per year) were calculated using all claims in the JMDC database from the start of first-line treatment, or from 6 months prior to the start of first-line treatment. Costs included drugs prescribed, surgeries, hospitalizations, and inspection procedures.

Statistical analysis

Analyses were undertaken in the total study population, and according to whether patients had a reported intestinal inspection (endoscopic procedure or computed tomography [CT]/magnetic resonance imaging [MRI] scan) in the 12 months prior to biologic introduction (yes vs no). Baseline characteristics, tuberculosis and hepatitis screening, and incidence data are reported using standard, descriptive summary statistics. Categorical variables were compared between the 2 intestinal inspection subgroups using a 2-sided chi-square test (if $\leq$ 20% of cells had a frequency of < 5) or Fisher's exact test (if > 20% of cells had a frequency of < 5). A Student's *t* test (for normally distributed data) or Wilcoxon signed-rank test (for non-normally distributed data) was used to compare continuous variables.

Time to events were analyzed using Kaplan–Meier methodology and multivariate Cox proportional hazard models with adjustment for baseline characteristics. Kaplan–Meier estimates were compared using a log-rank test; patients without an event were censored at the end of the observation period. Covariates tested in the Cox models included: sex (female vs male); age (continuous variable); anal fistula (confirmed ICD-10 code, K60) in the 6 months prior to diagnosis (no vs yes); surgery in the 6 months prior to diagnosis (no vs yes); CD category (CD, unspecified vs small intestine, large intestine, or other CD); intestinal inspection at any time prior to biologic introduction (no vs yes); number of days from last intestinal inspection to biologic introduction (continuous variable); and type of facility used for the last intestinal inspection (university hospital vs clinic, other hospital, or public hospital). Results from these analyses are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs).

Analyses were performed using SAS version 9.3. Data extraction and analysis was undertaken by Creativ-Ceutical K.K. (Tokyo, Japan), as directed by the authors.

Results

Patients

Overall, 1346 patients with newly diagnosed CD who had been prescribed a biologic agent(s) after first diagnosis (2009–2019) met the eligibility criteria for inclusion in the study (Fig. 1). Of these, 434, 892, and 20 patients had been prescribed adalimumab, infliximab, and ustekinumab as their first biologic, respectively.

Baseline characteristics are shown for all patients and by intestinal inspection in Table 1. In the overall population, patients had a mean age of 32.5 years, with males accounting for 80.8% of the study population. About one-quarter of patients (23.6%) had a history of anal fistula in the 6 months prior to CD diagnosis and mean Charlson Comorbidity Index score for the population was 0.6. The most common disease category was CD, unspecified, which accounted for 75.8% of patients. Mean time from first diagnosis to first prescription of any drug was 9.7 days.

A total of 508 (37.7%) patients had undergone intestinal inspection (endoscopy or CT/MRI) within 12 months prior to biologic introduction and 838 (62.3%) had not undergone intestinal inspection. Patients who underwent an intestinal inspection prior to biologic introduction were younger, had a higher incidence of anal fistula within the 6 months prior to diagnosis, and had a longer time from first diagnosis to first prescription of any drug, compared with those without an intestinal inspection (Table 1).

In the overall population, screening for tuberculosis and hepatitis was not performed in the majority of patients (Table 1). When the population was stratified by intestinal inspection, the majority of patients who had undergone intestinal inspection were screened for tuberculosis and hepatitis, while those who had not undergone intestinal inspection tended not to have been screened for these diseases.

Treatment patterns

First-line treatments and outcomes for all patients and stratified by intestinal inspection are shown in Table 2 and Table 3, respectively. In the overall population, the most commonly prescribed first-line treatments following diagnosis of CD were 5-ASA monotherapy (26.8%), 5-ASA plus biologic combination (26.3%), and biologic monotherapy (12.9%) (Table 2). 5-ASA in combination with enteral nutrition was prescribed in a very small group of patients (1%) (Table 2). A total of 57.4% of patients were prescribed a first-line biologic with or without a 5-ASA agent, immunomodulator, and/or steroid. Steroids were prescribed as first-line treatment (as monotherapy or in combination with other agents) in 10.8% of patients. The rate of prescribing of a biologic in first line was numerically lower in patients who had undergone intestinal inspection within 12 months prior to biologic introduction compared with those who had not (5.3% vs 17.4% in monotherapy; 19.9% vs 65.4% in combination, respectively) (Table 2). In contrast, the prescribing rate of first-line 5-ASA was numerically higher (55.1% vs 9.6% in monotherapy) in patients who had undergone intestinal inspection within 12 months prior to biologic introduction compared with those who had not (Table 2).

In the overall population, mean time from diagnosis to first biologic prescription was 4.1 months (Table 3 and Fig. 2a). Infliximab was the most common first prescribed biologic (892/1346 [66.3%] patients), adalimumab the second most common (434/1346 [32.2%] patients), and ustekinumab the least most common (20/1346 [1.5%] patients) (Table 3). Very few patients (6.3%) switched treatment following biologic introduction. However, the first biologic was discontinued in 56.2% of patients. Mean time from first biologic prescription to a treatment switch or to discontinuation was 14.8 and 14.0 months, respectively. Just over one-third (37.4%) of patients demonstrated persistence with their first biologic (Table 3). Mean time from biologic introduction to loss of persistence was 14.1 months for all patients.

In total, 32.5% of patients developed an intestinal complication and 21.7% required surgery any time after biologic introduction (Table 3). Mean time from first biologic prescription to first complication was 9.9 months and mean time to first surgery was 21.8 months.

Mean time from last intestinal inspection to biologic introduction was 53.7 months. Compared with patients not undergoing intestinal inspection prior to biologic introduction, those with an inspection had a significantly longer time from first CD diagnosis to biologic introduction (Table 3 and Fig. 2b).

Multivariate analysis

On multivariate analysis of the whole study population (Table 4 and Additional file 1: Table S1), intestinal inspection at any time prior to biologic introduction was significantly associated with time to first biologic introduction (HR, 0.23; $P < 0.0001$; Table 4). Other factors associated with time to first biologic introduction were the number of days from last intestinal inspection to biologic introduction (HR, 1.00; $P < 0.001$, which may be a statistical artifact caused by the similar 95% CI, 1.00–1.00), prior surgery (HR, 0.77; $P = 0.008$), diagnosis of small intestine CD (HR, 1.22 vs CD, unspecified; $P = 0.032$), large intestine CD (HR, 1.44 vs CD, unspecified; $P = 0.006$) or other CD (HR, 1.24 vs CD, unspecified; $P = 0.024$), and 'other hospital' facility used for the last intestinal inspection (HR, 1.36 vs university hospital; $P = 0.005$). Diagnosis of small intestine CD was associated with time to first complication after biologic introduction (HR, 1.40 vs CD, unspecified; $P = 0.021$). While statistically significant, the association between age and time to first complication after biologic introduction and time to loss of biologic persistence (HRs of ~1 in both cases) may be a statistical anomaly caused by the almost identical 95% CIs. No other factors were associated with time to first complication after biologic introduction or loss of biologic persistence, and none of the tested covariates were associated with time to first surgery after biologic introduction.

Medical costs

In the overall population, mean medical costs per patient per year from the commencement of first-line treatment were ¥2.31 million, while mean costs per patient per year from 6 months prior to first-line

treatment initiation were ¥2.33 million (approximately US$21,900; €19,700). Stratification by intestinal inspection showed mean costs per patient per year of ¥2.29 million (US$21,500; €19,400) and ¥2.33 million (US$21900; €19700) in patients with and without an intestinal inspection, respectively, in the period following first-line treatment initiation, and ¥2.32 million (US$21,800; €19,600) and ¥2.34 million (US$22,000; €19,800), respectively, in the period from 6 months prior to first-line treatment. The differences seen between the intestinal inspection groups was not significant ($P > 0.5$).

Discussion

This retrospective database analysis was undertaken to investigate the real-world incidence of intestinal inspection and treatment patterns in Japanese patients with newly diagnosed CD who had been prescribed biologic therapy during their treatment course. The results of the analysis provide interesting and important observations that may be used to inform clinical practice in Japan.

The baseline characteristics of the study population were broadly consistent with those observed previously for patients with CD in Japan [12–14]. There is an established male preponderance in Asian patients with CD [13, 15, 16], and this was maintained in the current study, with the population having a greater proportion of males than females. A previous study in CD using the JMDC database, as in this study, reported a similarly high proportion of males in the study population [12]. In accordance with the guidelines [1–3], most patients were prescribed first-line drug therapy soon after first diagnosis (mean of 9.7 days post diagnosis). Patients with a prior intestinal inspection had a longer time from diagnosis to first prescription of any drug than those without inspection (mean of 15.0 vs 6.5 days, respectively); this finding is likely due to the additional time needed to undertake the investigational procedures and review the findings after the provisional diagnosis has been made.

Following the diagnosis of CD, the differences in the numbers of patients who were prescribed each agent as their first biologic (adalimumab $n = 434$, infliximab $n = 892$, ustekinumab $n = 20$) can be attributed to the approval dates for each agent (2007, 1998, and 2019, respectively). Overall, the proportion of patients who were prescribed a biologic in first line (as monotherapy or in combination with other agents) was high (61.1%), indicating that biologics were introduced relatively early after diagnosis. This finding was somewhat surprising as it appears to contradict guideline recommendations, which recommend that biologics are used in steroid-dependent/refractory disease [1–3]. The rate of first-line biologic prescribing was also higher than has been reported in studies from other countries and regions [17–23], although this may be associated with the population selected for this study in which only patients who received biologics as part of their treatment course were included in the analysis. When these data were analyzed by whether intestinal inspection had been performed, patients who had undergone intestinal inspection in the 12 months prior to biologic introduction had a numerically lower rate of first-line biologic use (either as monotherapy or in combination with other drugs) and a statistically longer time from first CD diagnosis to biologic introduction (mean of 9.4 vs 0.9 months, respectively), compared with patients who had not undergone these investigational procedures. The strong, statistically significant association between prior intestinal inspection and longer time to first biologic prescription was confirmed on

multivariate analysis (HR, 0.23; $P < 0.0001$). These results indicate that biologics are more likely to be used in the early phase of treatment in Japanese patients who have not undergone prior intestinal inspection than in patients who have had these investigations, suggesting that performing intestinal inspections leads to following guideline recommendations more closely and using traditional treatments such as 5-ASAs and steroids. Overall, the prescription rate of steroids as first-line treatment was low, despite the Japanese guideline recommendation that steroids and nutritional therapy should be administered as first-line treatment. This observation suggests that the use of steroids for the treatment of patients with CD in Japan tends to be avoided. This finding might be explained by a reluctance of Japanese physicians to prescribe steroids as a first-line treatment option due to a perceived risk of side effects; these side effects could be viewed as limiting for this study population of young, working-age individuals. Further information on the use of steroids in Japanese patients with CD, for instance dosage, type, duration, and tapering protocol, and the impact of introduction of a biologic on steroid prescription was not examined in this study. However, details of steroid use and its association with the use of endoscopy will be the focus of a future analysis based on data from the JMDC database.

Examination of the small bowel facilitates precise evaluation of CD, and assists in treatment decisions [24]. In Western countries, small bowel examinations are mostly conducted by cross-sectional imaging or capsule endoscopy. However, double balloon and small intestine fluoroscopy are widely used in Japan [25]. While there are regional differences between Western countries and Japan, we consider the precise evaluation of small bowel lesions using the appropriate inspection technique for each individual patient as key to promoting the optimal use of treatment.

The impact of the intestinal inspection technique (endoscopy or CT/MRI) on outcomes was not assessed in this study, but this may represent an interesting topic for future analysis. However, it is important to note that techniques vary widely depending on physician preference and facilities available in each hospital, so accurate detection of disease status is likely to be a more important factor than type of detection technique used.

The effectiveness and tolerability of biologic therapy was indicated by the persistence findings, which account for both treatment switches and discontinuations. In our analysis, over half of patients discontinued biologic treatment during their clinical course, and mean time to loss of biologic persistence was > 12 months, which is comparable to that reported in previous studies [12, 18, 26–29]. The relatively low rate of intestinal complications (33%) and surgery (22%) following biologic introduction, and long mean time between first biologic introduction and first complication (of about 10 months) or first surgery (of just under 2 years) suggests a role of biologics in preventing CD complications and delaying the need for surgical intervention, as seen in other observational studies and clinical trials [30–32]. There were no differences in secondary endpoints, such as treatment switching, discontinuations, and persistence, between those who did and did not undergo intestinal inspection, suggesting that these procedures do not impact on treatment following the introduction of first-line therapy. In contrast, significantly more patients who had intestinal inspection were also screened for tuberculosis and hepatitis, which are important diseases to screen before the introduction of biologics in the real-world setting. This result

suggests that the patients undergoing intestinal inspection may have been cared for by clinicians who were more educated in the important aspects of caring for patients with CD than those who did not undergo this procedure.

In Western countries, prescribing biologics to patients with CD can be associated with insurance and cost barriers, such as variations in reimbursement and affordability from country to country [33]. The increased prescribing of biologics as first-line treatment in this Japanese CD population may reflect the health insurance system in Japan, which provides universal coverage and permits prescribing of expensive medications, such as biologics, if physicians consider them to be the best option in a particular setting and if they are approved for the disease being treated. Furthermore, biologics may be prescribed immediately without thorough investigation in Japan. There may be unnecessary treatment costs incurred by the use of expensive biologics, or treatment without indication, at an early disease stage without performing a small bowel examination, so promoting the optimization of treatment for CD with respect to the prescription of biologics is also important from the viewpoints of selecting appropriate treatment and controlling medical costs. Biologics are a substantial cost to healthcare systems, accounting for the majority of CD-related costs [34], and studies have shown rising costs with increased use of biologics [35]. Our results suggest that in Japan, if physicians choose to perform intestinal inspections (including expensive CT/MRI), medical costs are similar with prescription of biologics when compared with following guideline recommendations.

As this was a non-randomized study, selection bias will be present. However, an attempt was made to minimize the impact of selection bias on the outcome data by using adjusted models for the multivariate analyses. The study was also limited by the information available in the JMDC database. For example, the JMDC database does not collect information on disease severity or activity, reason(s) for prescription, whether a drug is taken as prescribed at the right time of the day, if extra doses are taken to compensate for forgotten doses, or on pill dumping or stockpiling. In addition, the JMDC database includes only working adults and their family members, and so may not be reflective of the true CD population in Japan. For these analyses, it was assumed that all patients filled their prescription(s) and were compliant with their medication. The patient population selected for this study may be considered as a limitation. As all patients were required to have received biologics during their treatment course, some of the results, for instance the proportion of patients receiving a biologic as first line treatment, are not easily comparable to the populations in other real-world studies. It is possible that the selection of different study endpoints, for instance the relationship between first line biologic prescription and patient baseline characteristics, could have provided additional useful insight into CD in the Japanese patient population.

In conclusion, this study demonstrates a high use of biologics (particularly infliximab) and low use of steroids in the initial treatment of Japanese patients with newly diagnosed CD who had been prescribed biologic therapy during their treatment course. Prescription of a biologic was more common in patients who had not undergone a prior endoscopic procedure or CT/MRI of the bowel than in those who had undergone any of these procedures. Moreover, despite early introduction of biologics, treatment

discontinuation was observed in more than half of patients. Further studies are required to establish the reasons underlying the association between the prescription of a biologic and intestinal inspection.

Abbreviations

5-ASA: 5-aminosalicylates; CAP: cytapheresis; CD: Crohn's disease; CCI: Charlson Comorbidity Index; CI: confidence interval; CT: computed tomography; GCAP: granulocytapheresis; HR: hazard ratio; ICD–10: International Classification of Diseases 10th revision; IQR: interquartile range; JMDC: Japan Medical Data Center; MRI: magnetic resonance imaging; QoL: quality of life; ref.: reference; SD: standard deviation; TNF-a: antitumor necrosis factor-α

Declarations

Ethics approval and consent to participate

Ethics approval for the analysis was obtained from the Japanese Research Institute of Healthcare Data Science (http://rihds.org/about/). All patient-level data were anonymized.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available because they were obtained from the Japan Medical Data Center (JMDC) claims database, but are available from the corresponding author on reasonable request.

Competing interests

FH has received honoraria from AbbVie GK, EA Pharma Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Janssen Pharmaceutical K.K., and Takeda Pharmaceutical Co. Ltd. AU, MO, YT, KT and RI are employees of Takeda Pharmaceutical Co. Ltd., Tokyo, Japan.

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Authors' contributions

FH was responsible for conception and design of the study, and analysis and interpretation of data. AU, MO, YT, KT and RI were responsible for conception and design of the study, collection and assembly of data, and analysis and interpretation of data. All authors participated in drafting the manuscript, and provided final approval of the version to be submitted.

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Author details

[1]Department of Gastroenterology, Faculty of Medicine, Fukuoka University, Fukuoka, Japan. [2]Japan Medical Affairs, Takeda Pharmaceutical Company Limited, Tokyo, Japan.

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Tables

Table 1 Patient characteristics at the date of first confirmed diagnosis of Crohn's disease

Characteristic	All patients	By intestinal inspection		*P* value
		Yes[a]	No	
	($N = 1346$)	($n = 508$)	($n = 838$)	
Sex, *n* (%)				
Female	258 (19.2)	97 (19.1)	161 (19.2)	0.958
Male	1088 (80.8)	411 (80.9)	677 (80.8)	
Age, years				
Mean (SD)	32.5 (11.1)	30.6 (11.7)	33.7 (10.6)	< 0.001
Median (IQR)	31.0 (24.0–40.0)	28.0 (22.0–39.0)	33.0 (25.0–41.0)	
Age category, *n* (%)				
< 18 years	88 (6.5)	55 (10.8)	33 (3.9)	< 0.001
18–39 years	899 (66.8)	335 (65.9)	564 (67.3)	
≥ 40 years	359 (26.7)	118 (23.2)	241 (28.8)	
Anal fistula within the 6 months prior to CD diagnosis, *n* (%)				
No	1029 (76.5)	350 (68.9)	679 (81.0)	< 0.001
Yes	317 (23.6)	158 (31.1)	159 (19.0)	
CCI score category, *n* (%)				
0	739 (54.9)	279 (54.9)	460 (54.9)	0.925
1	456 (33.9)	170 (33.5)	286 (34.1)	
≥ 2	151 (11.2)	59 (11.6)	92 (11.0)	
CCI score				
Mean (SD)	0.6 (0.9)	0.6 (1.0)	0.6 (0.8)	0.514
Median (IQR)	0 (0–1.0)	0 (0–1.0)	0 (0–1.0)	
CD category, *n* (%)				
Small intestine	137 (10.2)	56 (11.0)	81 (9.7)	0.584
Large intestine	61 (4.5)	27 (5.3)	34 (4.1)	
Other CD	128 (9.5)	48 (9.5)	80 (9.6)	
CD, unspecified	1020 (75.8)	377 (74.2)	643 (76.7)	
Time from first CD diagnosis to first prescription of any drug, days				
Mean (SD)	9.7 (18.9)	15.0 (21.8)	6.5 (16.1)	< 0.001
Median (IQR)	0 (0–14.0)	8.0 (0–19.0)	0 (0–11.0)	
All tuberculosis screening within 6 months prior to biologics introduction, *n* (%)[b]				
No	877 (65.2)	120 (23.6)	757 (90.3)	< 0.001
Yes	469 (34.8)	388 (76.4)	81 (9.7)	
Tuberculosis-specific screening within 6 months prior to biologics introduction, *n* (%)				
No	1022 (75.9)	210 (41.3)	812 (96.9)	< 0.001
Yes	324 (24.1)	298 (58.7)	26 (3.1)	
Hepatitis screening within 6 months prior to biologics introduction, *n* (%)				
No	921 (68.4)	141 (27.8)	780 (93.1)	< 0.001
Yes	425 (31.6)	367 (72.2)	58 (6.9)	

[a] Patients with an intestinal inspection procedure code within 12 months prior to biologic introduction

[b] Tuberculosis specific + non-specific CT/X-rays followed by diagnosis of tuberculosis within 3 months after screening
CCI Charlson Comorbidity Index, *CD* Crohn's disease, *CT* computed tomography, *IQR* interquartile range, *SD* standard deviation

Table 2 Prescribed first-line treatments

Treatment prescribed in first line, *n* (%)	All patients	By intestinal inspection		*P* value[b]
		Yes[a]	No	
	(*N* = 1346)	(*n* = 508)	(*n* = 838)	
5-ASA	360 (26.8)	280 (55.1)	80 (9.6)	< 0.0001
5-ASA + biologic	354 (26.3)	59 (11.6)	295 (35.2)	< 0.0001
5-ASA + biologic + IM	123 (9.1)	11 (2.2)	112 (13.4)	< 0.0001
5-ASA + biologic + IM + steroid	21 (1.6)	3 (0.6)	18 (2.2)	0.0254
5-ASA + biologic + steroid	52 (3.9)	15 (3.0)	37 (4.4)	0.1771
5-ASA + enteral nutrition	14 (1.0)	12 (2.4)	2 (0.2)	0.0002
5-ASA + IM	49 (3.6)	17 (3.4)	32 (3.8)	0.6539
5-ASA + steroid	33 (2.5)	27 (5.3)	6 (0.7)	< 0.0001
Biologic	173 (12.9)	27 (5.3)	146 (17.4)	< 0.0001
Biologic + IM	28 (2.1)	2 (0.4)	26 (3.1)	0.0007
Biologic + steroid	20 (1.5)	2 (0.4)	18 (2.2)	0.0099
IM	15 (1.1)	7 (1.4)	8 (1.0)	0.4733
Steroid	18 (1.3)	15 (3.0)	3 (0.4)	< 0.0001
Other combination[c]	86 (6.4)	31 (6.1)	55 (6.6)	0.7375
First-line treatment groups (3 categories)				
Biologics alone	173 (12.9)	27 (5.3)	146 (17.4)	< 0.001
Biologics in combination	649 (48.2)	101 (19.9)	548 (65.4)	
No biologics	524 (38.9)	380 (74.8)	144 (17.2)	
First-line treatment groups (2 categories)				
Biologics (alone or in combination)	822 (61.1)	128 (25.2)	694 (82.8)	< 0.001
No biologics	524 (38.9)	380 (74.8)	144 (17.2)	

[a] Patients with an intestinal inspection procedure code within 12 months prior to biologic introduction

[b] For each first-line treatment, Wald's test of equality of proportions was used (2-sided *P* value); for first-line treatment groups, chi-square tests were used

[c] Combinations of 5-ASA, biologics (adalimumab, infliximab, or ustekinumab), IM (azathioprine or 6-mercaptopurine), other immunosuppressants (ciclosporin, tacrolimus, or methotrexate), steroids, antimicrobials, enteral nutrition, and CAP or GCAP

5-ASA 5-aminosalicylates, *CAP* cytapheresis, *GCAP* granulocytapheresis, *IM* immunomodulatory

Table 3 Summary of outcomes

Outcome	All patients	By intestinal inspection		*P* value
		Yes[a]	No	
	($N = 1346$)	($n = 508$)	($n = 838$)	
Time from first CD diagnosis to biologic introduction, months				
Mean (SD)	4.1 (11.0)	9.4 (15.5)	0.9 (4.7)	< 0.001
Median (IQR)	0.5 (0–1.7)	2.5 (0.8–9.9)	0 (0–0.5)	
First biologic drug prescribed, *n* (%)				
Adalimumab	434 (32.2)	206 (40.6)	228 (27.2)	< 0.001
Infliximab	892 (66.3)	285 (56.1)	607 (72.4)	
Ustekinumab	20 (1.5)	17 (3.4)	3 (0.4)	
Time from last intestinal inspection to biologic introduction, months[b]				
Mean (SD)	53.7 (139.4)	38.0 (52.0)	848.9 (496.9)	< 0.001
Median (IQR)	21.0 (8.0–46.0)	20.5 (7.0–44.0)	826.0 (386.0–1142.0)	
Switch after biologic introduction, *n* (%)				
No	1261 (93.7)	470 (92.5)	791 (94.4)	0.171
Yes	85 (6.3)	38 (7.5)	47 (5.6)	
Time from biologic introduction to switch, months				
Mean (SD)	14.8 (13.0)	15.4 (13.3)	14.3 (12.8)	0.704
Median (IQR)	11.1 (4.7–22.3)	12.9 (4.9–22.1)	10.4 (4.7–23.6)	
Discontinuation after biologic introduction, *n* (%)				
No	589 (43.8)	227 (44.7)	362 (43.2)	0.594
Yes	757 (56.2)	281 (55.3)	476 (56.8)	
Time from biologic introduction to discontinuation, months[c]				
Mean (SD)	14.0 (13.9)	13.0 (12.3)	14.6 (14.8)	0.816
Median (IQR)	8.4 (4.0–19.5)	8.7 (3.9–18.3)	8.1 (4.0–20.8)	
Biologic persistence, *n* (%)				
No	842 (62.6)	319 (62.8)	523 (62.4)	0.888
Yes	504 (37.4)	189 (37.2)	315 (37.6)	
Time from biologic introduction to loss of persistence, months[c]				
Mean (SD)	14.1 (13.8)	13.3 (12.4)	14.5 (14.7)	0.881
Median (IQR)	8.7 (4.0–20.1)	9.1 (4.0–19.1)	8.3 (4.0–20.8)	
Complications any time after biologic introduction, *n* (%)				
No	909 (67.5)	344 (67.7)	565 (67.4)	0.911
Yes	437 (32.5)	164 (32.3)	273 (32.6)	
Time from biologic introduction to first complication, months[c]				
Mean (SD)	9.9 (15.1)	9.7 (14.5)	9.9 (15.4)	0.887
Median (IQR)	2.0 (0.9–13.1)	1.7 (0.7–13.8)	2.0 (1.2–13.1)	
Surgery any time after biologic introduction, *n* (%)				
No	1054 (78.3)	392 (77.2)	662 (79.0)	0.429
Yes	292 (21.7)	116 (22.8)	176 (21.0)	
Time from biologic introduction to first surgery, months[c]				
Mean (SD)	21.8 (20.8)	19.5 (20.1)	23.3 (21.2)	0.132

Median (IQR)	15.8 (5.5–31.2)	11.9 (4.1–26.0)	16.1 (7.2–33.5)

See methods for definitions of biologic persistence and complications

[a] Patients with an intestinal inspection within 12 months prior to biologic introduction

[b] For patients with an intestinal inspection at any time prior to biologic introduction

[c] For patients with an event
CD Crohn's disease, *IQR* interquartile range, *SD* standard deviation

Table 4 Multivariate Cox proportional hazards analyses ($N = 1346$)

Covariate	Time to biologic introduction		Time to first complication after biologic introduction		Time to first surgery after biologic introduction		Time to loss of biologic persistence	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Intestinal inspection at any time prior to biologic introduction								
No (ref.)								
Yes	0.23 (0.19–0.28)	**< 0.0001**	1.21 (0.86–1.70)	0.279	1.50 (0.98–2.30)	0.064	1.11 (0.85–1.44)	0.463

Statistically significant covariates are shown in bold text

Figures

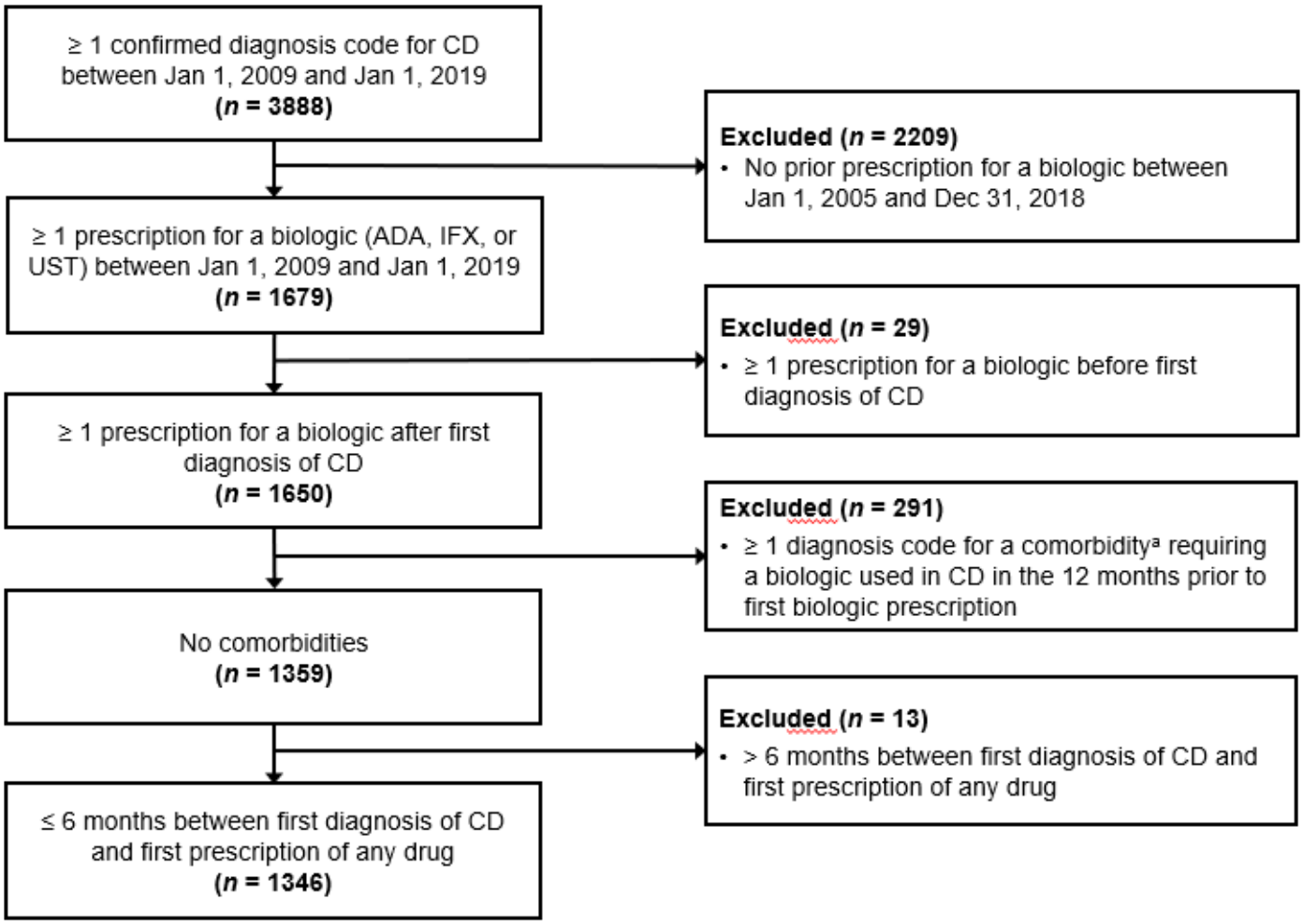

Figure 1

Patient flow. a Comorbidities could include rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, ulcerative colitis, intestinal Behçet's disease, ankylosing spondylitis, axial spondyloarthritis, and juvenile idiopathic arthritis. ADA, adalimumab; CD, Crohn’s disease; IFX, infliximab; UST, ustekinumab.

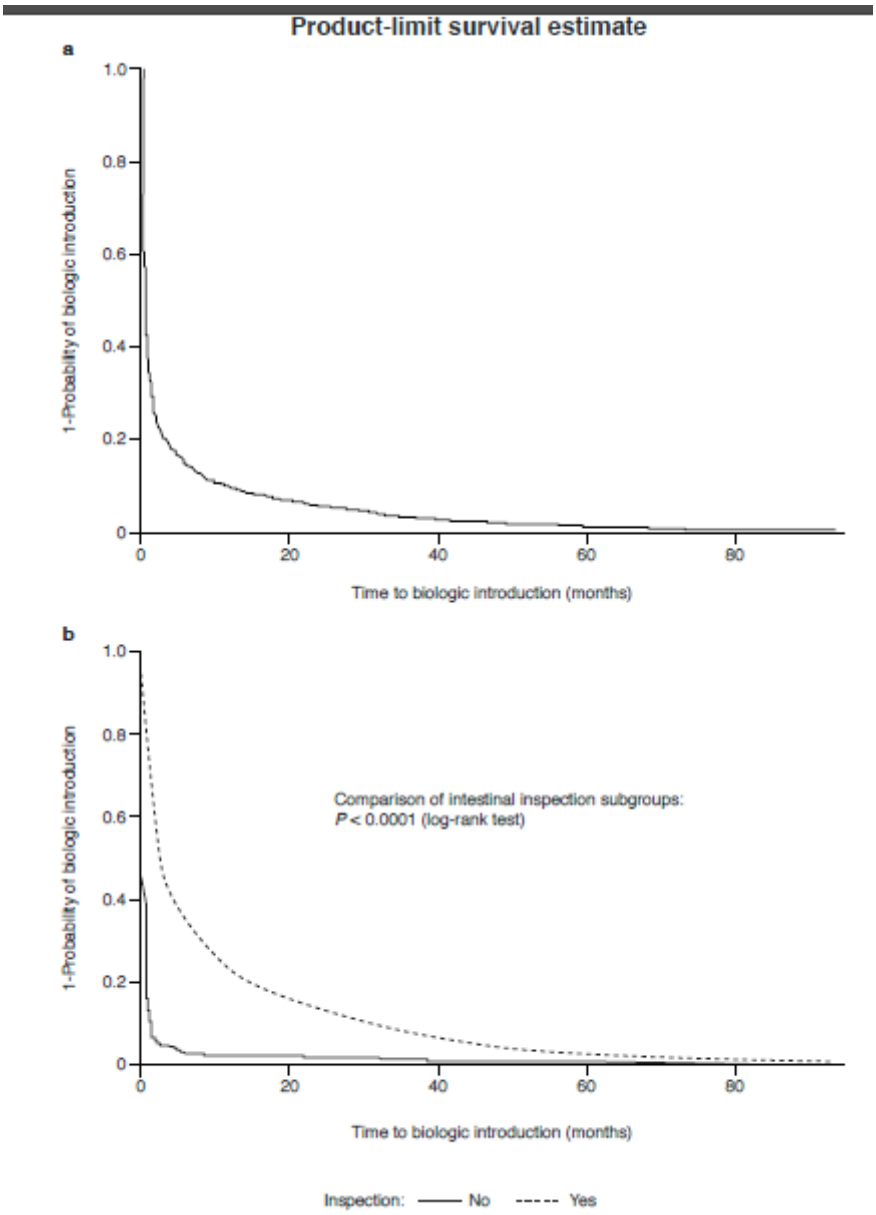

Figure 2

Kaplan–Meier survival curves for time from first Crohn's disease diagnosis to biologic (adalimumab, infliximab, or ustekinumab) introduction (N = 1346): a all patients and b by intestinal inspection in the 12 months prior to biologic introduction.

Supplementary Files

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