



# Clinical characteristics of patients with difficult-to-treat ulcerative colitis: a nested case-control study using a Japanese claims database

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**Background/Aims:** Despite the advent of advanced therapies, cases of so-called “difficult-to-treat” (D2T) ulcerative colitis (UC) persist. This study aims to clarify the epidemiological and clinical characteristics of patients with D2T UC. **Methods:** We conducted a nested case-control study using the Medical Data Vision Claims Database in patients with UC who began an advanced therapy (biologics, advanced small molecules, calcineurin inhibitors) from January 2018 through April 2023. D2T UC patients were defined as having 2 or more switches of advanced therapies, or as undergoing surgery for UC, within 2 years after the first advanced therapy. **Results:** Four hundred and one (16.7%) and 1,996 patients (83.3%) met the definitions of patients with D2T UC and non-D2T UC, respectively. After 1:1 matching by index year, 355 patients per group were included in the analysis. Multivariate logistic regression analyses, including sensitivity analyses based on follow-up period after the first advanced therapy, showed that a prescribed corticosteroid dose of  $\geq 30$  mg/day during the 6-month baseline period was associated with D2T UC. In D2T UC patients, median duration of the first advanced therapy was 99 days, and median number of advanced therapies per year was 1.7. The first advanced therapy was continued for 2 years in 78% of patients with non-D2T UC. **Conclusions:** The proportion of D2T UC patients among UC patients starting advanced therapy was 16.7%. The factor most associated with D2T UC was the need for a corticosteroid dose  $\geq 30$  mg/day during the 6 months before initiation of advanced therapy. (Intest Res 2026;24:103-116)

**Key Words:** Ulcerative colitis; Difficult-to-treat; Claims database

## INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disorder of the colonic mucosa which is characterized by repeated cycles of relapse and remission.<sup>1,2</sup> First-line therapy for UC is 5-aminosalicylates (5-ASA). Treatment progresses to corticosteroids,

thiopurines, and advanced therapies depending on disease severity and patient response.<sup>2,3</sup> In recent years, the number of advanced therapies (biologics, advanced small molecules, calcineurin inhibitors) for patients with UC has increased,<sup>2,3</sup> and the goal of treatment has changed from symptom control to mucosal healing and histological remission.<sup>4,5</sup> A treat-to-target approach has been proposed, in which regular monitoring is performed using objective indices such as biomarkers and endoscopic findings, and optimization or switching of therapy is considered depending on target achievement.<sup>6</sup> However, the

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pathogenesis of UC is complex,<sup>7</sup> and selection of an appropriate advanced therapy for individual patients is difficult. Even when switching to another advanced therapy, an inadequate or unsustainable response to previous advanced therapies is reportedly associated with a decreased response to subsequent treatment.<sup>8</sup> Thus, despite the advent of multiple advanced therapies, so-called difficult-to-treat (D2T) UC persists: patients with this form of UC cannot achieve or maintain remission.<sup>9</sup>

The development of effective therapeutic drugs and treatment strategies for D2T UC patients is vital. To achieve this, we considered that a standard definition of D2T UC and a clear understanding of the clinical characteristics of D2T UC patients were needed. The International Organization for the Study of Inflammatory Bowel Disease (IOIBD) proposed a standard definition of D2T IBD through a qualitative survey<sup>10</sup> and a consensus meeting.<sup>11</sup> This approach is similar to that used for rheumatoid arthritis,<sup>12</sup> which already includes the concept of D2T. A consensus meeting of the IOIBD defined D2T UC as the failure of biologics and advanced small molecules with 2 or more different modes of action (MOA).<sup>11</sup> Nevertheless, the precise clinical characteristics of D2T UC patients remain undefined.

Here, using a claims database, we aimed to evaluate epidemiological and clinical characteristics of D2T UC patients in the real world, defined according to real-world clinical practice and with reference to the results of a qualitative survey by the IOIBD.<sup>10</sup>

## METHODS

### 1. Data Source

Data were extracted from a claims database owned by Medical Data Vision (MDV) Co., Ltd. The data were derived from acute care hospitals using the Diagnosis Procedure Combination system.<sup>13</sup> As of September 2021, MDV had accumulated data from more than 38 million patients, and accounting for 23% of acute care hospitals in Japan.<sup>13</sup> Because all patient data in the MDV claims database are anonymized, informed consent and ethical review as stipulated in the Ethical Guidelines for Medical and Health Research Involving Human Subjects were not required. Nevertheless, the study protocol was approved by the Ethical Review Committee for Human Tissue Research of Mitsubishi Chemical Group Corporation (H-23-002).

### 2. Study Design and Study Population

This was a nested case-control study of patients diagnosed

with UC and prescribed advanced therapies. The study population was identified with reference to a validated claims-based algorithm for UC in Japan.<sup>14</sup> Inclusion criteria were as follows: patients who (1) had International Classification of Diseases, 10th Revision (ICD-10) diagnosis codes of UC between April 1, 2008 and April 30, 2023; (2) were started on their first advanced therapy on or after the first day of the month of the initial diagnosis of UC and on or after January 1, 2018, because biologics or advanced small molecules other than anti-tumor necrosis factor (TNF)- $\alpha$  antibodies became available in 2018 (with the start date of the first advanced therapy defined as the “index date”); and (3) could be observed for at least 6 months before the index date (baseline period). Advanced therapies included infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, tofacitinib, filgotinib, upadacitinib, tacrolimus, and cyclosporine, which are therapeutic drugs for corticosteroid-refractory UC listed in the Japanese treatment guidelines.<sup>3</sup> Oral tacrolimus is used more frequently in Japan than in other countries in patients with moderate UC who are refractory to biologics. This also explains why calcineurin inhibitors were included as advanced therapies. Exclusion criteria were as follows: patients who (1) had ICD-10 diagnosis codes including the diagnosis of Crohn's disease, Behçet's disease, or colorectal cancer during the baseline period; (2) underwent surgery for UC during the baseline period and within 30 days after the index date; or (3) had ICD-10 diagnosis codes of colorectal cancer in the month in which surgery for UC was performed after the index date (to exclude colorectal cancer surgery in UC surgery patients).

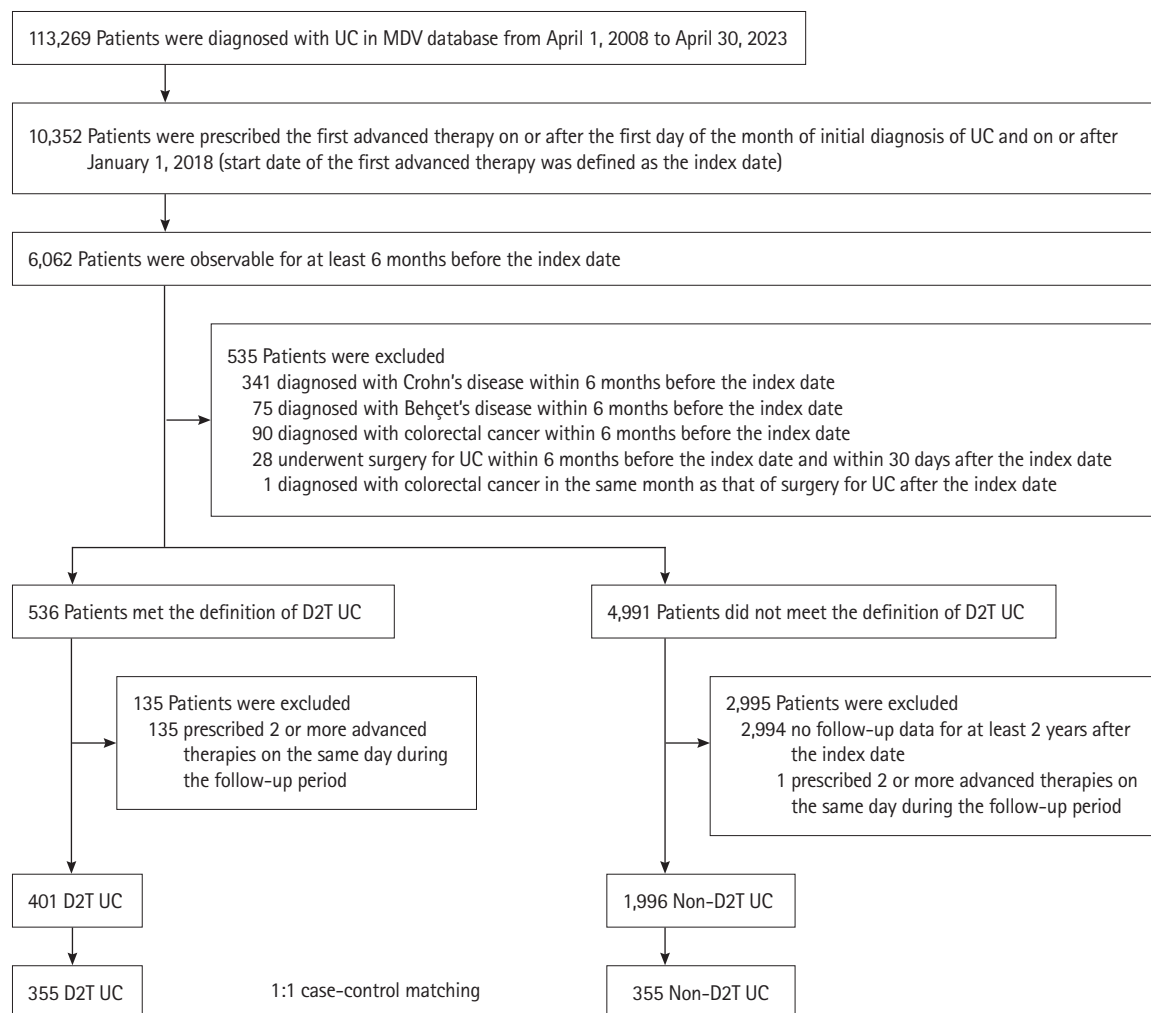
D2T UC patients were defined as those who met any of the following criteria: 2 or more switches of advanced therapies within 2 years after the index date (including patients who were returned to the same advanced therapy as that on the index date at the time of the second switch); or surgery for UC within 2 years after the index date, as supported as a criterion for D2T UC by 83% of physicians in a qualitative survey of the IOIBD<sup>10</sup> and classified as a treatment option for acute severe UC and medically refractory UC.<sup>15</sup> D2T UC patients were followed until the day before 2 years after the index date, the date of the first surgery for UC, or the last date when any medical practice was confirmed in the database, whichever came first. The maximum follow-up period was set at 2 years to exclude secondary non-responders who were thought to have factors different from those in patients with D2T UC (e.g., subtherapeutic drug level or development of anti-drug antibodies) as much as possible. In addition, to confirm the robustness of the

results, analyses were also performed by changing the maximum follow-up period from 2 years to 1 or 3 years. Patients with non-D2T UC were defined as those who did not meet any of the criteria for D2T UC patients, and who could be followed for 2 or more years after the index date. Patients who were recorded as receiving 2 or more advanced therapies on the same day were excluded from each group as (1) it is uncommon to use 2 or more advanced therapies on the same day in Japan and (2) the order of multiple advanced therapies recorded on the same day was unknown, resulting in some cases where it was impossible to determine whether the case fits the D2T UC criteria. The 2 groups were matched at a 1:1 ratio using the index year as a variable, since the number of available advanced therapies for UC has increased over several years. A schematic representation of the study design is shown in Supplementary Fig. 1. Names of diseases, drugs, procedures analyzed, and corresponding codes are shown in Supplementary Tables 1-3.

### 3. Endpoints

Primary endpoints were the epidemiological and clinical characteristics of patients with D2T UC and non-D2T UC during the baseline period and on the index date. The following factors were evaluated: age; sex; age at diagnosis of UC; duration of UC; extent of disease; extraintestinal manifestation(s); prescription of 5-ASA, corticosteroids (including prednisolone and prednisolone sodium succinate, given that corticosteroids other than prednisolone are rarely used for UC in Japan, and that corticosteroid doses were calculated as the prednisolone-equivalent), thiopurines, and proton pump inhibitors (PPIs) during the baseline period and on the index date; and size of the medical institution.

Secondary endpoints were the switching of advanced therapies in patients with D2T UC and non-D2T UC and the time of surgery in patients with D2T UC during the follow-up period. The distribution of the following variables was calculated: the



**Fig. 1.** Flowchart of the study population. UC, ulcerative colitis; MDV, Medical Data Vision; D2T, difficult-to-treat.

number of prescribed advanced therapies and MOAs, and the proportion of patients receiving each regimen; the number of advanced therapies per year and per person-year; advanced therapies and MOA by prescription order; the duration of advanced therapy; and the timing of the first surgery for UC.

#### 4. Statistical Analysis

Epidemiological and clinical characteristics were summarised using frequencies and percentages for categorical variables and median and interquartile range (IQR) for continuous variables. For the primary endpoints, multiple logistic regression analysis was performed with D2T UC or non-D2T UC as an outcome variable. The explanatory variables in multiple logistic regression analysis were selected based on the clinical perspective with reference to the results of univariate logistic regression analysis. As sensitivity analyses, we confirmed whether the following changes would alter the results of the primary endpoints: if the follow-up period to determine D2T UC was changed to within 1 and 3 years after the index date; and if missing values for extent of disease were imputed and included in the explanatory variables. Missing values for extent of disease were imputed using multiple imputation methods.

The variables used to predict the missing data were outcome and explanatory variables in multiple logistic regression analysis. The number of imputations was 100. The results of logistic regression are expressed as odds ratios (ORs) and 95% confidence intervals (CIs).

For the secondary endpoints, differences in the number of advanced therapies, the number of MOAs, and the duration of use between patients with D2T UC and non-D2T UC were confirmed with the Wilcoxon rank-sum test. Differences in the number of advanced therapies per person-year were confirmed by univariate generalized linear regression analysis assuming the Poisson distribution. Switching of drugs and timing of surgeries were visualized using Sankey diagrams and heat maps. All statistical analyses were performed using R (version 4.1.3; R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### 1. Patients with D2T UC and Non-D2T UC

Of 10,352 patients who were diagnosed with UC for the first time between April 1, 2008 and April 30, 2023, and subsequently prescribed the first advanced therapy after January 1,

**Table 1.** Demographic and Clinical Characteristics after Matching

| Characteristics                            |                   | Case-control matched   |                        |
|--------------------------------------------|-------------------|------------------------|------------------------|
|                                            |                   | Non-D2T UC (n = 355)   | D2T UC (n = 355)       |
| Age (yr)                                   | Median (IQR)      | 46 (34.5–57)           | 44 (29–57)             |
|                                            | ≥ 65 yr           | 57 (16.1)              | 56 (15.8)              |
| Sex                                        | Male              | 204 (57.5)             | 218 (61.4)             |
|                                            | Female            | 151 (42.5)             | 137 (38.6)             |
| Age at diagnosis of UC (yr)                | Median (IQR)      | 43 (32–55)             | 42 (27–55)             |
|                                            | ≥ 65 yr           | 41 (11.5)              | 39 (11.0)              |
| Duration of disease (day)                  | Median (IQR)      | 768 (331–1,546)        | 661 (261–1,340)        |
|                                            | ≥ 2 yr            | 186 (52.4)             | 166 (46.8)             |
| Extent of disease                          | Extensive         | 106 (29.9)             | 145 (40.8)             |
|                                            | Left-sided        | 35 (9.9)               | 43 (12.1)              |
|                                            | Proctosigmoiditis | 9 (2.5)                | 6 (1.7)                |
|                                            | Proctitis         | 13 (3.7)               | 15 (4.2)               |
|                                            | Unknown           | 192 (54.1)             | 146 (41.1)             |
| Extraintestinal manifestations             | Yes               | 64 <sup>a</sup> (18.0) | 49 <sup>a</sup> (13.8) |
| Treatment for 6 mo prior to the index date |                   |                        |                        |
| 5-ASA                                      | Yes               | 305 (85.9)             | 302 (85.1)             |
|                                            | No                | 50 (14.1)              | 53 (14.9)              |
| Duration of 5-ASA (day)                    | Median (IQR)      | 158 (76.5–178)         | 141 (26–175)           |
|                                            | < 1 mo            | 73 (20.6)              | 94 (26.5)              |
|                                            | ≥ 1 mo            | 282 (79.4)             | 261 (73.5)             |

(Continued to the next page)

Table 1. Continued

| Characteristics                                |              | Case-control matched |                  |
|------------------------------------------------|--------------|----------------------|------------------|
|                                                |              | Non-D2T UC (n = 355) | D2T UC (n = 355) |
| Corticosteroids                                | Yes          | 210 (59.2)           | 258 (72.7)       |
| Duration of corticosteroids (day)              | Median (IQR) | 15 (0-81)            | 28 (0-92)        |
|                                                | < 1 mo       | 214 (60.3)           | 181 (51.0)       |
|                                                | 1 to < 3 mo  | 60 (16.9)            | 80 (22.5)        |
|                                                | ≥ 3 mo       | 81 (22.8)            | 94 (26.5)        |
| Cumulative dose of corticosteroids (mg)        | Median (IQR) | 290 (0-1,231)        | 760 (0-1,571)    |
|                                                | < 1,800      | 307 (86.5)           | 285 (80.3)       |
|                                                | ≥ 1,800      | 48 (13.5)            | 70 (19.7)        |
| Maximum daily dose of corticosteroids (mg/day) | Median (IQR) | 12.5 (0-40)          | 30 (0-55)        |
|                                                | 0            | 145 (40.8)           | 97 (27.3)        |
|                                                | > 0 to < 10  | 25 (7.0)             | 20 (5.6)         |
|                                                | 10 to < 20   | 19 (5.4)             | 10 (2.8)         |
|                                                | 20 to < 30   | 25 (7.0)             | 19 (5.4)         |
|                                                | ≥ 30         | 141 (39.7)           | 209 (58.9)       |
| Thiopurines                                    | Yes          | 135 (38.0)           | 176 (49.6)       |
| Duration of thiopurines (day)                  | Median (IQR) | 0 (0-121)            | 0 (0-135)        |
|                                                | 0            | 220 (62.0)           | 179 (50.4)       |
|                                                | 1 to < 90    | 39 (11.0)            | 54 (15.2)        |
|                                                | ≥ 90         | 96 (27.0)            | 122 (34.4)       |
| PPIs                                           | Yes          | 167 (47.0)           | 180 (50.7)       |
| Duration of PPIs (day)                         | Median (IQR) | 0 (0-126)            | 3 (0-84)         |
|                                                | 0            | 188 (53.0)           | 175 (49.3)       |
|                                                | 1 to < 90    | 66 (18.6)            | 95 (26.8)        |
|                                                | ≥ 90         | 101 (28.5)           | 85 (23.9)        |
| Treatment on the index date                    |              |                      |                  |
| 5-ASA                                          | Yes          | 194 (54.6)           | 198 (55.8)       |
| Corticosteroids                                | Yes          | 122 (34.4)           | 168 (47.3)       |
| Thiopurines                                    | Yes          | 76 (21.4)            | 86 (24.2)        |
| PPIs                                           | Yes          | 95 (26.8)            | 107 (30.1)       |
| Medical institution (bed)                      | < 200        | 28 (7.9)             | 15 (4.2)         |
|                                                | 200 to < 500 | 152 (42.8)           | 127 (35.8)       |
|                                                | ≥ 500        | 175 (49.3)           | 213 (60.0)       |
| Index year                                     | 2018         | 53 (14.9)            | 53 (14.9)        |
|                                                | 2019         | 99 (27.9)            | 99 (27.9)        |
|                                                | 2020         | 115 (32.4)           | 115 (32.4)       |
|                                                | 2021         | 88 (24.8)            | 88 (24.8)        |
|                                                | 2022         | 0                    | 0                |
|                                                | 2023         | 0                    | 0                |

Values are presented as number (%) unless otherwise indicated.

<sup>a</sup>Number of patients with D2T UC and non-D2T UC by extraintestinal manifestations (including patients with 2 or more extraintestinal complications): scleritis in 0 and 1, iridocyclitis in 0 and 0, deep venous thrombosis in 16 and 25, primary sclerosing cholangitis in 2 and 3, autoimmune pancreatitis in 5 and 1, linear IgA dermatosis in 0 and 0, psoriatic arthritis in 0 and 3, erythema nodosum in 2 and 0, pyoderma gangrenosum in 1 and 3, rheumatoid arthritis in 23 and 32, ankylosing spondylitis in 1 and 2, and sacroiliitis in 0 and 0.

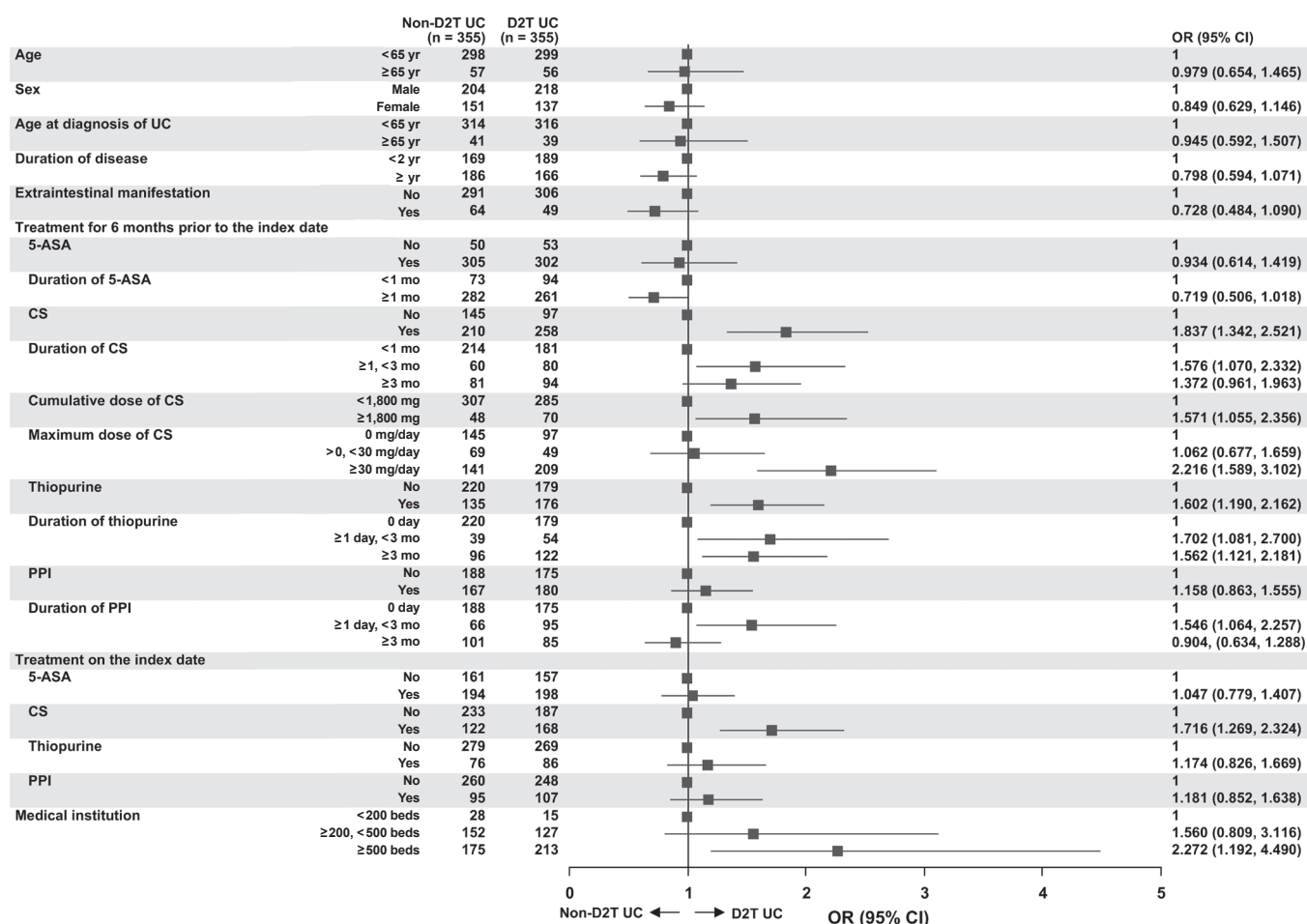
D2T, difficult-to-treat; UC, ulcerative colitis; IQR, interquartile range; 5-ASA, 5-aminosalicylates; PPI, proton pump inhibitor.

2018, 6,062 patients could be observed for 6 months or longer before the index date (Fig. 1). Of these 6,062 patients, 401 with D2T UC (cases) and 1,996 with non-D2T UC (controls) were identified. D2T UC patients accounted for 16.7%. After matching by index year, 355 patients each in the D2T UC group (matched cases) and non-D2T UC group (matched controls) were included in the analysis. Among the patients with D2T UC, 333 (93.8%) experienced 2 or more switches of advanced therapies within 2 years after the index date while 22 (6.2%) were included because they underwent surgery for UC. Epidemiological and clinical characteristics of the D2T UC and non-D2T UC groups during the baseline period and on the index date (Table 1) did not change greatly from those before matching (Supplementary Table 4).

## 2. Factors Associated with D2T UC and Non-D2T UC

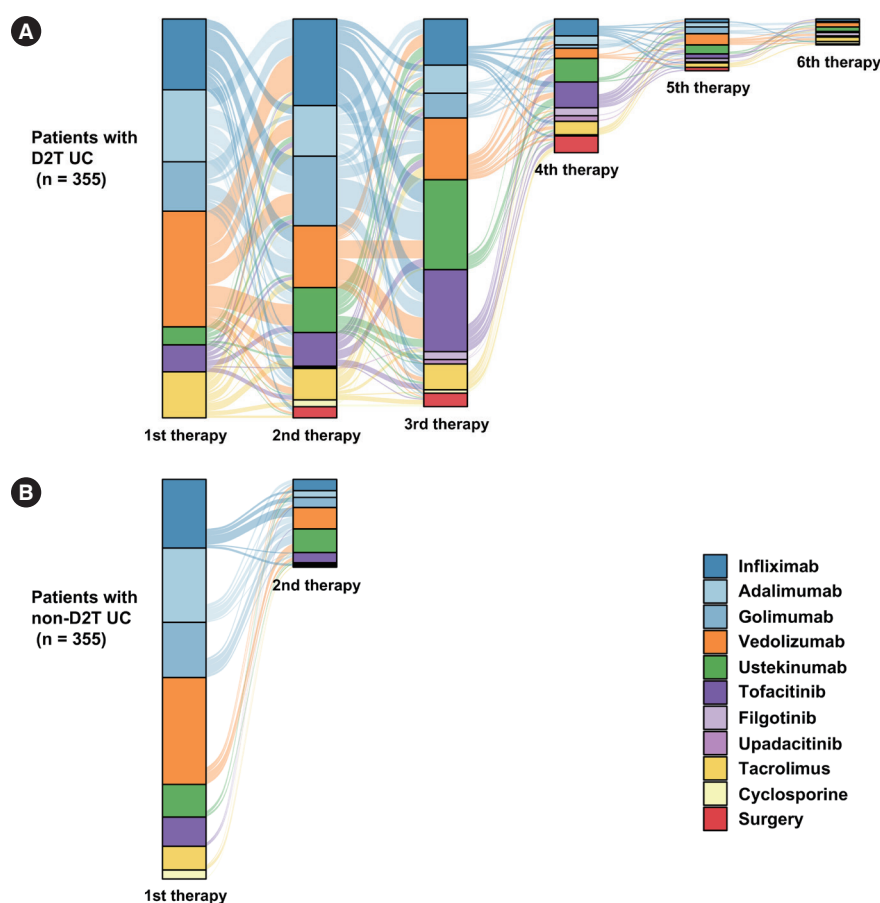
Factors associated with D2T UC and non-D2T UC were evalu-

ated by univariate logistic regression analysis. The following variables had an OR > 1 and a 95% CI not including 1: prescription of corticosteroids (OR, 1.837; 95% CI, 1.342–2.521); duration of corticosteroid treatment of at least 1 month to less than 3 months (OR, 1.576; 95% CI, 1.070–2.332); cumulative dose of prescribed corticosteroid of  $\geq 1,800$  mg (OR, 1.571; 95% CI, 1.055–2.356); prescribed corticosteroid dose of  $\geq 30$  mg/day (OR, 2.216; 95% CI, 1.589–3.102); prescription of thiopurine (OR, 1.602; 95% CI, 1.190–2.162); duration of thiopurine treatment of 1 day to less than 3 months (OR, 1.702; 95% CI, 1.081–2.700) or 3 months or longer (OR, 1.562; 95% CI, 1.121–2.181); duration of PPI treatment of 1 day to less than 3 months (OR, 1.546; 95% CI, 1.064–2.257) during the baseline period; treatment with corticosteroids on the index date (OR, 1.716; 95% CI, 1.269–2.324); and a medical institution with  $\geq 500$  beds (OR, 2.272; 95% CI, 1.192–4.490) (Fig. 2). There was no variable that had an OR < 1 and a 95% CI not including 1.

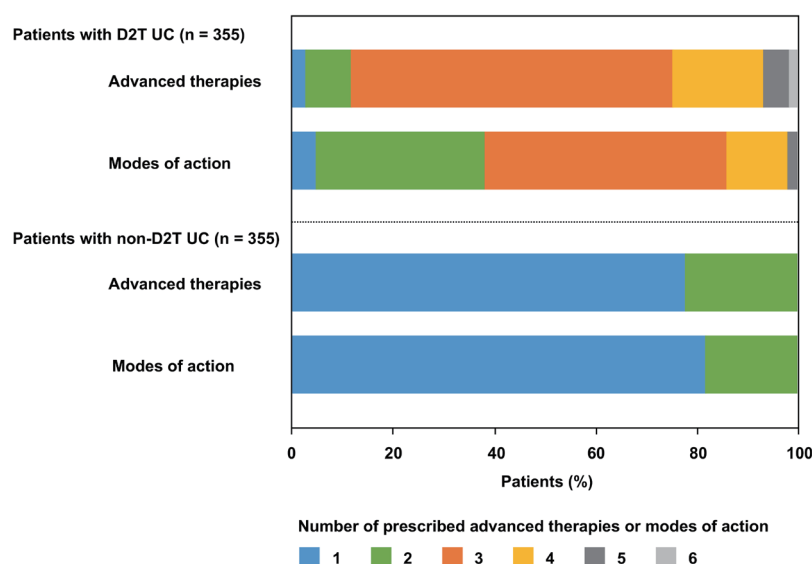


**Fig. 2.** Factors associated with D2T UC and non-D2T UC using univariate logistic regression by covariates. D2T, difficult-to-treat; UC, ulcerative colitis; OR, odds ratio; CI, confidence interval; 5-ASA, 5-aminosalicylates; CS, corticosteroids; PPI, proton pump inhibitor.





**Fig. 4.** Flow of advanced therapy use: switching and surgery during the follow-up period in patients with D2T UC and non-D2T UC depicted by a Sankey diagram. (A) Patients with D2T UC. (B) Patients with non-D2T UC. D2T, difficult-to-treat; UC, ulcerative colitis.



**Fig. 5.** Number of prescribed advanced therapies and modes of action during the follow-up period in patients with D2T UC and non-D2T UC. Advanced therapies included anti-tumor necrosis factor- $\alpha$  antibodies infliximab, adalimumab, and golimumab; anti- $\alpha 4\beta 7$  integrin antibody vedolizumab; anti-interleukin-12/23 antibody ustekinumab; Janus kinase inhibitors tofacitinib, filgotinib, and upadacitinib; calcineurin inhibitors tacrolimus and cyclosporine. D2T, difficult-to-treat; UC, ulcerative colitis.

**Table 2.** Summary of Advanced Therapies during the Follow-up Period

| Variable                                         | Non-D2T UC (n = 355)             |                         | D2T UC (n = 355)            |                           |
|--------------------------------------------------|----------------------------------|-------------------------|-----------------------------|---------------------------|
|                                                  | First advanced therapy           | Second advanced therapy | First advanced therapy      | Second advanced therapy   |
| Any advanced therapy                             | 355 (100)                        | 78 (22.0)               | 355 (100)                   | 345 (97.2)                |
| Anti-TNF- $\alpha$ antibodies                    | 176 (49.6)                       | 25 (7.0)                | 171 (48.2)                  | 184 (51.8)                |
| Infliximab                                       | 61 (17.2)                        | 10 (2.8)                | 63 (17.7)                   | 77 (21.7)                 |
| Adalimumab                                       | 66 (18.6)                        | 6 (1.7)                 | 64 (18.0)                   | 45 (12.7)                 |
| Golimumab                                        | 49 (13.8)                        | 9 (2.5)                 | 44 (12.4)                   | 62 (17.5)                 |
| Anti- $\alpha 4\beta 7$ integrin antibody        | 95 (26.8)                        | 19 (5.4)                | 103 (29.0)                  | 55 (15.5)                 |
| Vedolizumab                                      | 95 (26.8)                        | 19 (5.4)                | 103 (29.0)                  | 55 (15.5)                 |
| Anti-IL-12/23 antibody                           | 29 (8.2)                         | 21 (5.9)                | 16 (4.5)                    | 40 (11.3)                 |
| Ustekinumab                                      | 29 (8.2)                         | 21 (5.9)                | 16 (4.5)                    | 40 (11.3)                 |
| JAK inhibitors                                   | 26 (7.3)                         | 11 (3.1)                | 24 (6.8)                    | 32 (9.0)                  |
| Tofacitinib                                      | 26 (7.3)                         | 9 (2.5)                 | 24 (6.8)                    | 30 (8.5)                  |
| Filgotinib                                       | 0                                | 1 (0.3)                 | 0                           | 1 (0.3)                   |
| Upadacitinib                                     | 0                                | 1 (0.3)                 | 0                           | 1 (0.3)                   |
| Calcineurin inhibitors                           | 29 (8.2)                         | 2 (0.6)                 | 41 (11.5)                   | 34 (9.6)                  |
| Tacrolimus                                       | 21 (5.9)                         | 1 (0.3)                 | 41 (11.5)                   | 28 (7.9)                  |
| Cyclosporine                                     | 8 (2.3)                          | 1 (0.3)                 | 0                           | 6 (1.7)                   |
| Duration of advanced therapy use (day)           | 681 (208.5–714.5)                | NC                      | 99 (42–197) <sup>a</sup>    | 111 (49–216) <sup>b</sup> |
| Median (IQR)                                     | 239.5 (111.8–381.5) <sup>c</sup> |                         | 152 (67–272) <sup>a,c</sup> |                           |
| No. of advanced therapies per year, median (IQR) | 0.5 (0.5–0.5)                    |                         | 1.7 (1.5–2.5) <sup>a</sup>  |                           |
| No. of advanced therapies per person-year        | 0.61                             |                         | 2.03 <sup>d</sup>           |                           |

Values are presented as number (%) unless otherwise indicated.

<sup>a</sup> $P < 0.0001$  (vs. non-D2T UC group, Wilcoxon rank-sum test).

<sup>b</sup>Data from patients who switched to 3rd advanced therapy (n = 333).

<sup>c</sup>Data from non-D2T UC (n = 78) or D2T UC (n = 345) patients who switched to 2nd advanced therapy.

<sup>d</sup> $P < 0.0001$  (vs. non-D2T UC group, univariate generalized linear regression analysis: Poisson modeling).

D2T, difficult-to-treat; UC, ulcerative colitis; TNF, tumor necrosis factor; IL, interleukin; JAK, Janus kinase; NC, not calculated; IQR, interquartile range.

advanced therapy was vedolizumab (29.0%). All MOAs were used as first advanced therapy, with anti-TNF- $\alpha$  antibodies being the most prescribed MOA (48.2%). Median duration of the first advanced therapy treatment was 99 days. Switching to a second advanced therapy occurred in 345 D2T UC patients (97.2%), following a median duration of the first advanced therapy of 152 days. The most prescribed second advanced therapy was infliximab (21.7%), while the most commonly used second MOA was anti-TNF- $\alpha$  antibody (51.8%). During the follow-up period, 43 D2T UC patients (12.1%) underwent surgery for UC. Median time to surgery (IQR) was 190 (73, 346) days. The timing of surgery was after the first advanced therapy treatment in 10 patients (2.8%), after the second advanced therapy treatment in 12 patients (3.4%), and after the third or later advanced therapy treatment in 21 patients (5.9%).

Treatment with 1 advanced therapy and with 1 MOA was continued in the follow-up period (median, 730 days; IQR, 730–731 days) in 277 (78.0%) and 291 (82.0%) patients with non-D2T UC, respectively (Fig. 5). In patients with non-D2T UC, the median number of advanced therapies per year was 0.5 and the number of advanced therapies per person-year was 0.61 (Table 2). Similarly to the D2T UC group, the most prescribed first advanced therapy was vedolizumab (26.8%). All 5 MOAs were included in the first advanced therapies, with anti-TNF- $\alpha$  antibodies being the most frequently prescribed MOA (49.6%). Median duration of the first advanced therapy treatment was 681 days. Switching to a second advanced therapy occurred in 78 (22.0%) patients with non-D2T UC; median duration of the first advanced therapy treatment was 239.5 days, which was longer than that in D2T UC patients (152

days,  $P < 0.0001$ ). The most prescribed second advanced therapies were ustekinumab (5.9%) and vedolizumab (5.4%), and the most commonly prescribed second MOAs were anti-TNF- $\alpha$  antibodies (7.0%).

## DISCUSSION

This claims database study, which defined D2T UC patients as those with 2 or more switches of advanced therapies or surgery for UC within 2 years, is the first study to reveal the epidemiological and clinical characteristics of D2T UC patients in real-world clinical practice. We found that 16.7% of patients with UC who started advanced therapies met the criteria of D2T UC. A prescription of corticosteroid dose of  $\geq 30$  mg/day during the 6-month baseline period had the highest OR (1.896) for D2T UC, among various baseline factors. Median duration of first advanced therapy use in patients with D2T UC was 99 days and the median number of advanced therapies per year was 1.7. The first advanced therapy was continued for 2 years in 78% of patients with non-D2T UC.

After the initiation of this study, a consensus meeting of the IOIBD defined D2T UC as treatment failure with biologics and advanced small molecules with 2 or more different MOAs.<sup>11</sup> In contrast, our present study defined D2T UC according to real-world clinical practice, with reference to the results of a qualitative survey by the IOIBD,<sup>10</sup> which included several other conditions in addition to the above IOIBD definition.<sup>11</sup> Accordingly, we defined D2T UC slightly differently to the IOIBD definition.<sup>11</sup> First, we defined it by the number of switches without taking account of MOA, because the positioning of 3 anti-TNF drugs in terms of the treatment of severe patients differs depending on the route of administration.<sup>3</sup> Of the D2T UC patients in this study, 62% were prescribed 3 or more different MOAs. Second, we included surgery for UC in the definition of D2T UC, which was supported by 83% of physicians in a qualitative survey of the IOIBD10 and which is a treatment option for acute severe UC and medically refractory UC.<sup>15</sup> Third, we included calcineurin inhibitors, which the Japanese treatment guidelines list as advanced therapies, together with biologics and advanced small molecules. Even if these differences are taken into account, the present results are considered to acceptably represent the epidemiological and clinical characteristics of patients with D2T UC.

The proportion of patients with a history of at least 3 biologics or advanced therapies (included in our definition of D2T UC) can be identified in randomized controlled trials<sup>16</sup> and

prospective or retrospective cohort studies<sup>17-19</sup> of advanced therapies. However, the proportion of D2T UC patients among those who were prescribed advanced therapies was previously unknown, because some patients continued their first advanced therapy and were not included in the studies described above. Our present study found that  $> 15\%$  of patients with UC who started advanced therapies met our definition of D2T UC (2 or more switches of advanced therapies or surgery for UC within 2 years).

Multivariate logistic regression showed that a prescribed corticosteroid dose of  $\geq 30$  mg/day occurring in the 6 months before the start of advanced therapy had the highest impact on the D2T UC. Taking into account the results of sensitivity analyses that changed the follow-up period from 2 years to 1 or 3 years, this prescribed corticosteroid dose of  $\geq 30$  mg/day in the 6 months before the start advanced therapy should be considered to be a robust factor associated with D2T UC. It has been reported that a history of corticosteroid use or excessive use of corticosteroids negatively affects clinical outcomes in patients with UC.<sup>20-22</sup> In the present study, a corticosteroid dose of  $\geq 30$  mg/day—the recommended starting dose for patients with moderate to severe UC<sup>3,23</sup>—but not the duration of corticosteroid treatment, was highly associated with D2T UC. It was recently reported that the use of PPI decreased the effect of infliximab against IBD<sup>24</sup> and was associated with a poor prognosis.<sup>25,26</sup> In our present study, univariate analysis suggested a relationship between D2T UC and treatment with PPI for 1 day to less than 3 months over the 6 months before advanced therapy was started. However, PPI treatment was not extracted as related to D2T UC in multivariate analysis. Regarding the extent of disease, an association with the effect of biologics has not been generally reported.<sup>8</sup> The present study also showed no association between the extent of disease and D2T UC. These results suggest that patients who experience the first attack or exacerbation with severe inflammation or other advanced symptoms and who start corticosteroid therapy with a sufficiently high dose but show a poor response and require advanced therapy soon (within 6 months) after the start of corticosteroid therapy are likely to subsequently switch advanced therapies repeatedly. Thus, patients with a course of D2T UC may have characteristics of resistance to multiple drugs from the start of UC treatment. For these patients, shared decision-making (SDM) between the physician and patient is required with regard to enhanced monitoring, timely referral to specialists, and intensification of treatment, with the possibility of difficulty in subsequent treat-

ment kept in mind.

In this study, most patients (78%) with non-D2T UC continued treatment with the first advanced therapy alone for 2 years. In patients with D2T UC, in contrast, the treatment period of the first advanced therapy was short (median treatment period of about 100 days). These patients were then switched to a second advanced therapy or underwent surgery. These results suggest that D2T UC patients may be primary non-responders to the first advanced therapy. During the 2-year follow-up period, 43 patients in the D2T UC group underwent surgery for UC. The number of patients who transitioned to surgery increased in the following order: after use of the first (10 patients), second (12 patients), and third or later (21 patients) advanced therapy. This result is similar to that of a retrospective cohort study in the United States.<sup>27</sup>

In the present study, all MOAs of advanced therapies were prescribed as the first advanced therapy in both the D2T UC and non-D2T UC groups, and the most frequently prescribed initial therapy MOAs were the same in both groups. Based on our descriptive results, no characteristic sequence of advanced therapies was observed in patients with D2T UC or non-D2T UC. We considered 3 possible reasons for this: (1) the treatment guidelines for UC do not set any prioritization for advanced therapies<sup>3,23,28</sup> and the choice of advanced therapy is therefore made using SDM between physician and patient, which is influenced by not only efficacy and safety but also convenience and patient preference; (2) the complex pathology of UC may induce differences in response to treatment depending on disease stage and patient characteristics<sup>7</sup>; and (3) prior authorization from insurers is not required to prescribe advanced therapies in Japan. It should be noted that ustekinumab, filgotinib, and upadacitinib were approved for use in UC after 2018, the date set in this study as the first year in which the first advanced therapy was started. Prescription periods for these advanced therapies were limited to approximately 3 years, 1 year, and 6 months, respectively. It is therefore possible that the proportion of patients prescribed these advanced therapies may have been underestimated. A treatment algorithm with prioritization for UC was recently proposed on the basis of the results of clinical studies, real-world studies, network meta-analysis, and others.<sup>29</sup> Further accumulation of sequence data for advanced therapies and the development of effective biomarkers for treatment algorithms should aid in the identification of appropriate sequences of advanced therapies and improve treatment outcomes in the future.

The present study has some limitations. First, disease activity scores were not available in the MDV claims database, and the number of patients who had laboratory data for inflammatory markers was limited. Accordingly, the relationship between the severity of UC and D2T UC could not be analyzed. Second, since the MDV claims database does not track patients before they are transferred to a hospital, we set a baseline period of 6 months before advanced therapy was initiated. We considered that 6 months was sufficient to define a first-line advanced therapy, but cannot rule out the possibility that some patients received advanced therapy more than 6 months before the index date. In addition, the year of UC diagnosis and treatment data of therapeutic drugs from UC diagnosis to the start of advanced therapy could not be used for analysis. Therefore, use of the MDV claims database did not allow us to determine whether D2T UC patients could be identified at the time of UC diagnosis. To date, several research articles have utilized the MDV claims database to report the clinical characteristics of patients with UC receiving biologics, thiopurines, and corticosteroids.<sup>30-33</sup> In addition, the age distribution of patients diagnosed with UC in the MDV claims database from 2018 to 2022 showed distribution across all ages, with a particularly high proportion of patients in their 40s (18.3%–20.9%) and 50s (17.8%–19.7%). This is closely similar to the distribution reported for patients registered in the Japan Intractable Diseases System, which covers approximately 70% of UC patients nationwide (40s, 21.5%–23.5% and 50s, 19.3%–21.4%).<sup>34-39</sup> Further, the male-to-female ratio (1.2–1.3:1) of patients in the MDV claims database in those years was comparable to that reported in the nationwide survey (1.24) (Supplementary Table 5).<sup>40</sup> We therefore believe that the UC patient population in the MDV claims database is adequately representative of the wider Japanese UC patient population, despite the limitations mentioned above. Third, the definition of D2T UC was not validated, limiting the generalizability of the results of this study. A future validation study of the definition of D2T UC and subsequent analysis using the validated definition in several databases of UC patients is desirable.

In conclusion, this claims database study reveals for the first time the epidemiological and clinical characteristics of D2T UC patients in real-world clinical practice. We defined D2T UC patients by a high number of switches of advanced therapy or surgery for UC within 2 years, and found that 16.7% of patients had D2T UC. A prescribed corticosteroid dose of  $\geq 30$  mg/day during the 6-month baseline period had the highest OR for D2T UC, among various baseline factors. This result

suggests that patients who respond poorly to corticosteroids despite an appropriate starting dose and require advanced therapy soon (within 6 months) after the initiation of corticosteroid therapy are likely to subsequently switch advanced therapies repeatedly. Thus, patients with a course of D2T UC may have characteristics of resistance to multiple drugs from the start of UC treatment. These findings are expected to aid physicians and patients in SDM for UC which takes account of the anticipated clinical course of each patient.

## ADDITIONAL INFORMATION

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### Conflict of Interest

Matsuoka K has received speaking fees from Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd, Janssen Pharmaceutical K.K., AbbVie GK, Pfizer Japan Inc., EA Pharma Co., Ltd, Mochida Pharmaceutical Co., Ltd, Kyorin Pharmaceutical Co., Ltd, Zeria Pharmaceutical Co., Ltd, Kissei Pharmaceutical Co., Ltd, Nippon Kayaku Co., Ltd, Gilead Sciences K.K., Celltrion Healthcare Japan. K.K., and Eli Lilly Japan K.K.; research grants from AbbVie GK, EA Pharma Co., Ltd, Mochida Pharmaceutical Co., Ltd, Zeria Pharmaceutical Co., Ltd, Nippon Kayaku Co., Ltd, and JIMRO Co., Ltd. Igarashi A has received consulting fees from Mitsubishi Tanabe Pharma Corporation, AbbVie GK, Astellas Pharma Inc., Chugai Pharmaceutical Co., Ltd, Eli Lilly Japan K.K., Illumina, Inc., Janssen Pharmaceutical K.K., Moderna, Inc., Ono Pharmaceutical Co., Ltd, Takeda Pharmaceutical Co., Ltd, Pfizer Japan Inc., and Celltrion Healthcare Japan. K.K.; research grants from Takeda Pharmaceutical Co., Ltd, Otsuka Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd, Asahi Kasei Pharma Corporation, Edwards Lifesciences Corporation, Intuitive Surgical G.K., and Philips Japan, Ltd. Sato N, Mizuno N, Ishii M, Iizuka M are employees of Mitsubishi Tanabe Pharma Corporation. Iwasaki K and Shoji A are employees of Healthcare Consulting, Inc., which was commissioned to perform this work by Mitsubishi Tanabe Pharma Corporation. Hisamatsu T has received research grants from Mitsubishi Tanabe Pharma Corporation, EA Pharma Co., Ltd, AbbVie GK, JIMRO Co., Ltd, Zeria Pharmaceutical Co., Ltd, Kissei Pharmaceutical Co., Ltd, Kyorin Pharmaceutical Co., Ltd, Nippon Kayaku Co., Ltd, Takeda Pharmaceutical Co., Ltd, Pfizer Japan Inc., Mochida Pharma-

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### Data Availability Statement

The datasets generated and/or analyzed during the present study are not publicly available because the data were obtained from Medical Data Vision Co., Ltd. However, they are available from the corresponding author with the permission of Medical Data Vision Co., Ltd, on reasonable request.

### Author Contributions

Conceptualization: all authors. Data curation: Ishii M, Iizuka M, Iwasaki K, Shoji A. Formal analysis: Iizuka M, Iwasaki K, Shoji A. Investigation: all authors. Methodology: all authors. Project administration: Sato N. Visualization: all authors. Validation: Ishii M, Iizuka M, Iwasaki K, Shoji A. Resources: Iwasaki K, Shoji A. Software: Iwasaki K, Shoji A. Writing-original draft: Matsuoka K, Sato N. Writing-review and editing: all authors. Approval of final manuscript: all authors.

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## Supplementary Material

Supplementary materials are available at the Intestinal Research website (<https://www.irjournal.org>).

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