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Incidence rates for hospitalized infections, herpes zoster, and malignancies in patients with ulcerative colitis in Japan: an administrative health claims database analysis

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Background/Aims: Patients with ulcerative colitis (UC) are at an increased risk of certain infections and malignancies compared with the general population. Incidence rates (IRs) of hospitalized infections, herpes zoster (HZ), and malignancies in patients with UC, stratified by treatment, in Japan were estimated. **Methods:** This retrospective study identified patients with UC treated with corticosteroids, immunosuppressants, or tumor necrosis factor inhibitors (TNFi) from 2 administrative databases (Japan Medical Data Center [JMDC] and Medical Data Vision [MDV]). IRs (unique patients with events per 100 patient-years) were estimated for hospitalized infections, HZ, and malignancies, between June 2010 and May 2018. **Results:** Among 6,033 MDV patients with UC receiving corticosteroids, immunosuppressants, or TNFi, IRs (95% confidence intervals) were: hospitalized infections, 1.73 (1.52–1.93); HZ, 1.00 (0.85–1.16), and malignancies, 1.48 (1.29–1.66). Among 958 JMDC patients with UC receiving corticosteroids, immunosuppressants, or TNFi, IRs (95% confidence intervals) were: HZ, 1.82 (1.27–2.37) and malignancies, 1.35 (0.87–1.82). In both cohorts, IRs of malignancies were generally similar among patients receiving immunosuppressants, TNFi, or combination therapy (immunosuppressants and TNFi); this was also true for IRs of hospitalized infections and HZ in the MDV cohort. IRs of hospitalized infections, HZ, and malignancies were higher in patients receiving calcineurin inhibitors compared with immunosuppressants or TNFi, in both cohorts. **Conclusions:** IRs of hospitalized infections, HZ, and malignancies among patients with UC were generally similar regardless of UC treatment, except for calcineurin inhibitors. **(Intest Res 2023;21:88-99)**

Key Words: Colitis, ulcerative; Safety; Infections; Neoplasms

INTRODUCTION

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory disorder of the colon that generally begins in young adulthood and lasts throughout life.[1] Although the incidence and prevalence of UC has stabilized in Europe and North America,[2] the prevalence of UC in Japan has increased in recent years, rising from 18.1 per 100,000 population in 1991[3] to 172.9 per 100,000 population in 2014.[4]

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Patients with UC are at an increased risk of infection and malignancy, which is partly inherent to the disease itself[5] but also due to the therapies used in the management of UC, or a combination of these factors.[6,7] Therapies used for disease control, such as corticosteroids, immunosuppressants (azathioprine and 6-mercaptopurine [6-MP]), calcineurin inhibitors, and tumor necrosis factor inhibitors (TNFi; infliximab, adalimumab, and golimumab), have a primary function in the inhibition and control of immune system activity. Therefore, these therapies have the potential to reduce a patients' immunological response resulting in an increased risk of infection. Additionally, some infections have been associated with the use of certain therapies and may be due to the mechanism of action of individual therapies.[8]

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Herpes zoster, caused by the reactivation of latent varicella zoster virus, is a major public health issue and the incidence rate of herpes zoster in Japan has been previously estimated to be 0.49 per 100 patient-years (95% confidence interval [CI], 0.49–0.50) in the general population.[9] Inflammatory bowel disease (IBD) is associated with cellular and humoral immune dysfunctions, resulting in susceptibility to viral infection and reactivation; studies in Western countries and Japan have demonstrated that patients with IBD are at an increased risk for herpes zoster.[9-13] The use of corticosteroids, thiopurines, TNFi, and combination therapy have been reported to increase the risk of herpes zoster.[11,12,14] However, the association between herpes zoster and UC therapies in patients with UC in Japan is uncertain due to a lack of data from Asian patients with UC. In contrast to the previous Western studies, a nationwide, population-based study in Korea concluded that only corticosteroid-induced immunosuppression is an important risk factor for the development of herpes zoster in patients with IBD.[15]

Certain types of malignancies have been reported at an increased rate in patients with IBD,[16] and treatments such as thiopurines and TNFi have been associated with an increased risk of malignancy in patients with UC.[16-19] Although, the increased risk attributed to TNFi is thought to be driven by concomitant immunomodulatory therapy with no evidence to suggest an increased risk with TNFi alone.[16,20] Most estimates of the risk of cancer in patients with UC are from populations within Europe and North America, with few studies in Asian patients. Variations in disease progression as a result of differences in the genetic basis of UC,[21] available therapies for the control of inflammation, and differences in clinical practice[22] may result in a different risk in patients with UC in Japan, compared with Western populations. However, a recent systematic review and meta-analysis concluded that the risk of colorectal cancer in Asian patients with UC was similar to estimates within Europe and North America.[23]

In Japan, data relating to the incidence of hospitalized infections, herpes zoster, and malignancies with UC therapies are unclear. We therefore utilized data from 2 administrative health claims databases to evaluate the incidence of hospitalized infections, herpes zoster, and malignancies in patients with UC in Japan.

METHODS

1. Study Design

This was a retrospective, non-interventional analysis of data from patients with UC extracted from 2 administrative health claims databases in Japan: the Japan Medical Data Center (JMDC; Tokyo, Japan)[24] and Medical Data Vision (MDV; Tokyo, Japan), for the period between June 2010 and May 2018. The JMDC database has accumulated receipts (inpatient, outpatient, and dispensing) received from multiple employees' health insurance associations since 2005, and included a cumulative observed population of 5 million patients at the time of the study. Whilst in employment, JMDC can track individual patient claims data across clinics, hospitals, and dispensing pharmacies. However, Japanese employees commonly retire at 60–65 years of age, therefore the JMDC database does not include patients ≥75 years of age, and patients aged ≥65 to <75 only account for 3.5% of patients in this database, therefore, only limited data from elderly patients with UC are available from the JMDC database. The MDV database consists of healthcare insurance claims data provided by hospitals using the Japanese Diagnosis Procedure Combination/per-diem payment system for approximately 21 million patients of all generations from 333 (at the time of the study) participating hospitals in Japan. It is of note, that the MDV database does not capture any medical records other than hospital records, and the record is censored if the patient changed hospital. Both databases hold anonymized information about diagnoses, patient characteristics, drug prescriptions, medical procedures, features of medical facilities, and reimbursement costs.

2. Patient Analysis

Patients with UC were identified from administrative health claims databases using a validated claims-based algorithm.[25] Eligible patients were adults (≥18 years) with a diagnosis of UC, defined per the International Classification of Diseases, 10th Revision (ICD-10) code K51 (Supplementary Material), who had been prescribed at least 1 of the following: 5-aminosalicylates, corticosteroids (prednisolone, prednisolone sodium succinate, prednisolone sodium phosphate, budesonide, triamcinolone acetonide, betamethasone, betamethasone sodium phosphate, methylprednisolone, or methylprednisolone acetate), immunosuppressants (tacrolimus monohydrate, 6-MP, azathioprine, or cyclosporine), or TNFi (infliximab, adalimumab, or golimumab) in the month of, or the following month after, the first diagnosis of UC (Supplementary Table 1). While not approved for the treatment of UC in Japan, 6-MP and cyclosporine were included in the algorithm in order to account for the off-label use of these treatments. Patients were also required to have data available for at least 1 year from the

index date. The index date was defined as the date of the first treatment of corticosteroids, immunosuppressants, or TNFi.

Patients who had concurrent Crohn's disease (ICD-10:K50) or Behçet's disease (ICD-10:M35.2), or who had received immunosuppressants or TNFi in the 6 months prior to the index date, were excluded.

In this analysis, patients were assessed as 4 groups based on the initial prescription received for UC. Group 1 consisted of patients who had taken ≥1 corticosteroid, immunosuppressant, or TNFi. Group 2 consisted of patients who had taken immunosuppressant therapy only, and these patients were further divided into 2 subgroups–patients who had received calcineurin inhibitors (tacrolimus and cyclosporine; group 2-1) and patients who had received azathioprine and 6-MP (group 2-2). Group 3 consisted of patients who had taken TNFi only and group 4 consisted of patients who had taken a combination of an immunosuppressant and TNFi. Concomitant 5-aminosalicylates was permitted in all groups. Patients could be included in more than 1 group. Vedolizumab, ustekinumab, and tofacitinib were not included in this analysis as these were not approved for the treatment of UC in Japan during the study period.

3. Definition of Hospitalized Infections, Herpes Zoster, and Malignancy

Hospitalized infections were identified based on ICD-10 codes for bacterial and viral infections (Supplementary Material), and were analyzed using 2 separate definitions: an infection which results in hospitalization (hospitalized infection 1) and an infection which results in the most charged medical resources during hospitalization (hospitalized infection 2). The information required for the determination of hospitalized infections was not available in the JMDC database, therefore hospitalized infections were analyzed using data from the MDV database only.

Events of herpes zoster were defined as patients reporting an ICD-10 code for herpes zoster (B02) and a prescription for antiviral medication (acyclovir, valaciclovir hydrochloride, vidarabine, famciclovir, ganciclovir, or foscarnet sodium hydrate) within ±1 claim month of the herpes zoster diagnosis date.

Malignancy events were analyzed using 2 separate claims-based algorithms: an ICD-10 code of malignancy (C00–C97 malignant neoplasm or D00–D09 *in situ* neoplasms) with a procedure record of cancer management (B-001-00-03, B-001-00-18, B-001-00-22, B-001-00-23, B-001-00-24, B-005-06, H-007-02) within the same claim month (malignancy 1) and an ICD-10 code of malignancy in at least 2 consecutive claims months (malignancy 2).

4. Statistical Analyses

Descriptive statistics were used to analyze patients' demographic and baseline clinical characteristics. Incidence rates (unique patients with events per 100 patient-years) for hospitalized infections, herpes zoster, and malignancies were estimated with associated two-sided 95% CIs for each treatment group. For calculation of incidence rates, the first event that occurred during the exposure period of interested treatment were counted. The exposure period was calculated from the index date to the date of the first event for patients with events and was censored at the end of the follow-up period for patients without events. The follow-up period was defined from the index date to the earliest of either the date of lost medical or pharmacy coverage, discontinuation of treatment, or end of the study period. For groups 2–4, the study follow-up period ended if patients initiated or switched to a new medication.

Incidence rates within each treatment group were calculated by age category (<35, ≥35, <50, ≥50, <65, and ≥65 years of age) and gender. Given the descriptive nature of this study no formal statistical comparisons were made. Data derived from the JMDC and MDV databases were analyzed separately.

5. Ethical Considerations

This analysis used data extracted from the JMDC and MDV databases in an anonymized format and was therefore exempt from ethical review as Japanese ethical guidelines for medical and health research involving human subjects do not apply to studies that use anonymized secondary data.[26] The informed consent was waived.

RESULTS

1. Patients and Baseline Characteristics

Fig. 1 shows the selection of patients from the JMDC and MDV databases, and group allocation for analysis. Baseline characteristics for patients with UC in the JMDC cohort by treatment group are shown in Table 1, and for the MDV cohort in Table 2. In the JMDC cohort, 958 patients were included in group 1, of which 36.7% were female, 97.2% were <65 years of age with a mean age of 41.3 years, and a mean follow-up duration of 2.5 years. In the MDV cohort, 6,033 patients were included in group 1, of which 43.0% were female, 81.0% were <65 years of age with a mean age of 47.5 years, and a mean follow-up dura-

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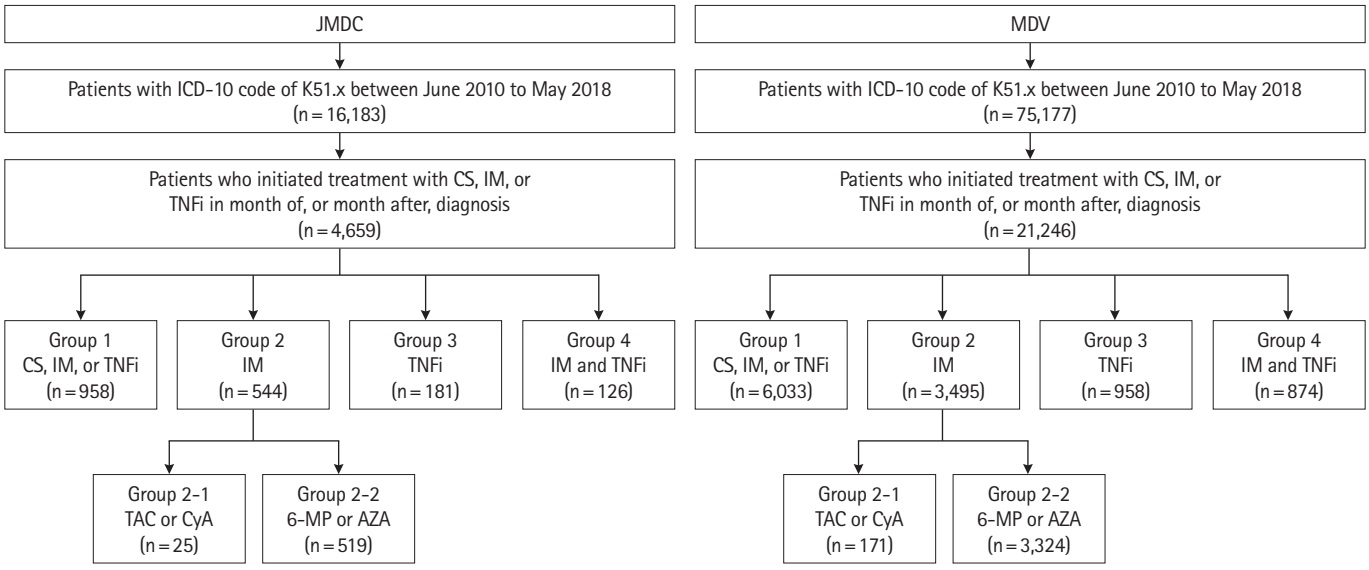

Fig. 1. Selection of patients with ulcerative colitis in the JMDC and MDV databases. CS included prednisolone, prednisolone sodium succinate, prednisolone sodium phosphate, budesonide, triamcinolone acetonide, betamethasone, betamethasone sodium phosphate, methylprednisolone, or methylprednisolone acetate. IM included TAC monohydrate, 6-MP, AZA, or CyA. TNFi included infliximab, adalimumab, or golimumab. Concomitant 5-aminosalicylates were permitted in all groups. Patients could be included in more than 1 group. JMDC, Japan Medical Data Center; MDV, Medical Data Vision; ICD-10, International Classification of Diseases, 10th Revision; CS, corticosteroid; IM, immunosuppressant; TNFi, tumor necrosis factor inhibitor; TAC, tacrolimus; CyA, cyclosporine; 6-MP, 6-mercaptopurine; AZA, azathioprine.

tion of 2.8 years. Baseline demographics were generally similar between treatment groups for both JMDC and MDV cohorts, with the exception of a higher proportion of females in group 2-1.

2. Hospitalized Infection

Incidence rates (unique patients with events per 100 patient-years) for hospitalized infections, using the 2 definitions, for the MDV cohort are shown in Fig. 2. Among the patients receiving corticosteroids, immunosuppressants, or TNFi (group 1), the incidence rates of hospitalized infections were similar between the 2 definitions. Using the hospitalized infection 1 definition (an infection which results in hospitalization), 278 hospitalized infections were identified with an incidence rate of 1.73 (95% CI, 1.52–1.93; 16,115.0 patient-years), and using the alternative definition, hospitalized infection 2 (an infection which results in the most charged medical resources during hospitalization), 258 hospitalized infections were identified with an incidence rate of 1.59 (95% CI, 1.40–1.79; 16,181.17 patient-years). The incidence rate of hospitalized infections was similar among patients receiving an immunosuppressant (group 2), TNFi (group 3), or both an immunosuppressant and TNFi (group 4). When stratified by immunosuppressant medication, the incidence rate of hospitalized infection, using both definitions, was numerically higher among patients receiving tacrolimus or cyclosporine (group 2-1) compared with patients receiving 6-MP or azathioprine (group 2-2). The incidence rate of hospitalized infections, using both definitions, increased with age for all treatment groups (Supplementary Table 2).

3. Herpes Zoster

Incidence rates (unique patients with events per 100 patient-years) of herpes zoster are shown in Fig. 3. In the JMDC cohort, among 958 patients receiving corticosteroids, immunosuppressants, or TNFi (group 1), 42 herpes zoster events were identified with an incidence rate of 1.82 (95% CI, 1.27–2.37; 2,310.67 patient-years). In the MDV cohort, among 6,033 patients receiving corticosteroids, immunosuppressants, or TNFi (group 1), 163 herpes zoster events were identified with an incidence rate of 1.00 (95% CI, 0.85–1.16; 16,285.00 patient-years).

Among the JMDC cohort, the incidence rate of herpes zoster was numerically higher in patients receiving TNFi (group 3), and in patients receiving both an immunosuppressant and TNFi (group 4), compared with patients receiving only an immunosuppressant (group 2). In contrast, in the MDV cohort, the incidence rate of herpes zoster was similar in patients receiving an immunosuppressant (group 2), patients receiving

Table 1. Baseline Characteristics of Patients with Ulcerative Colitis in the JMDC Database, by Treatment Group

Baseline characteristic	Group 1 (CS, IM, or TNFi)	Group 2 (IM)	Group 2-1 (TAC or CyA)	Group 2-2 (6-MP or AZA)	Group 3 (TNFi)	Group 4 (IM and TNFi)
Total No.	958	544	25	519	181	126
Female sex, No. (%)	352 (36.7)	201 (36.9)	14 (56.0)	187 (36.0)	63 (34.8)	37 (29.4)
Age (yr)						
Mean ± SD	41.3 ± 12.8	42.3 ± 12.6	48.3 ± 12.3	42.0 ± 12.5	39.6 ± 12.3	40.9 ± 11.6
Median (range)	41 (18–73)	42 (18–73)	49 (19–72)	42 (18–73)	39 (18–68)	41 (18–66)
Age category (yr), No (%)						
< 35	306 (31.9)	156 (28.7)	3 (12.0)	153 (29.5)	67 (37.0)	36 (28.6)
≥ 35	652 (68.1)	388 (71.3)	22 (88.0)	366 (70.5)	114 (63.0)	90 (71.4)
< 50	687 (71.7)	372 (68.4)	13 (52.0)	359 (69.2)	140 (77.3)	95 (75.4)
≥ 50	271 (28.3)	172 (31.6)	12 (48.0)	160 (30.8)	41 (22.7)	31 (24.6)
< 65	931 (97.2)	527 (96.9)	23 (92.0)	504 (97.1)	177 (97.8)	124 (98.4)
≥ 65 to < 75	27 (2.8)	17 (3.1)	2 (8.0)	15 (2.9)	4 (2.2)	2 (1.6)
Treatment at index date, No. (%)						
IM	562 (58.7)	544 (100.0)	25 (100.0)	519 (100.0)	0	126 (100.0)
TNFi	223 (23.3)	0	0	0	181 (100.0)	126 (100.0)
Corticosteroid	351 (36.6)	119 (21.9)	6 (24.0)	113 (21.8)	34 (18.8)	28 (22.2)
Corticosteroid dosage[a]						
Mean ± SD	19.6 ± 18.1	19.7 ± 17.5	13.7 ± 13.2	20.1 ± 17.7	18.6 ± 15.0	16.0 ± 10.9
Median (range)	15.0 (0.5–80.0)	16.3 (1.0–70.0)	7.5 (2.0–30.7)	16.3 (1.0–70.0)	17.9 (1.0–72.5)	15.3 (1.0–40.0)
Follow-up duration (yr)						
Mean ± SD	2.5 ± 1.5	2.3 ± 1.3	2.3 ± 1.2	2.3 ± 1.3	2.3 ± 1.4	2.3 ± 1.2
Median (range)	2.0 (1.0–8.0)	1.9 (1.0–7.7)	1.8 (1.0–5.1)	1.9 (1.0–7.7)	1.7 (1.0–7.8)	2.0 (1.0–5.7)

[a]Prednisolone equivalent at index date.
JMDC, Japan Medical Data Center; CS, corticosteroid; IM, immunosuppressant; TNFi, tumor necrosis factor inhibitor; TAC, tacrolimus; CyA, cyclosporine; 6-MP, 6-mercaptopurine; AZA, azathioprine; SD, standard deviation.

TNFi (group 3), and patients receiving both an immunosuppressant and TNFi (group 4). However, when stratified by immunosuppressant medication, the incidence rate of herpes zoster was numerically higher in patients receiving tacrolimus or cyclosporine (group 2-1) compared with patients receiving 6-MP or azathioprine (group 2-2).

Across all treatment groups, the incidence rate of herpes zoster was, in general, higher in females compared with males, and generally increased with age, in both the JMDC and MDV cohorts (Supplementary Table 3).

4. Malignancies

Incidence rates (unique patients with events per 100 patient-years) for malignancies are shown in Fig. 4. In both the JMDC and MDV cohorts, the incidence rate of malignancies differed depending upon the definition used. In the JMDC cohort, among patients receiving corticosteroids, immunosuppressants, or TNFi (group 1), 31 malignancies (incidence rate, 1.35; 95% CI, 0.87–1.82; 2,303.92 patient-years) were identified using malignancy definition 1, compared with 68 malignancies (incidence rate, 3.05; 95% CI, 2.33–3.78; 2,227.67 patient-years) using malignancy definition 2. This trend was also observed in the MDV cohort, 239 malignancies (incidence rate, 1.48; 95% CI, 1.29–1.66; 16,184.08 patient-years) were identified in group 1 using malignancy definition 1, compared with 464 malignancies (incidence rate, 2.97; 95% CI, 2.70–3.24; 15,648.08 patient-years) using malignancy definition 2. The trend for numerically higher incidence rates using malignancy definition 2 compared with malignancy definition 1 was also observed across treatment groups.

In the MDV cohort, the incidence rates for malignancies were numerically higher in patients receiving an immunosup-

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Table 2. Baseline Characteristics of Patients with Ulcerative Colitis in the MDV Database, by Treatment Group

Baseline characteristic	Group 1 (CS, IM, or TNFi)	Group 2 (IM)	Group 2-1 (TAC or CyA)	Group 2-2 (6-MP or AZA)	Group 3 (TNFi)	Group 4 (IM and TNFi)
Total No.	6,033	3,495	171	3,324	958	874
Female sex, No. (%)	2,594 (43.0)	1,461 (41.8)	107 (62.6)	1,354 (40.7)	470 (49.1)	304 (34.8)
Age (yr)						
Mean ± SD	47.5 ± 16.9	47.3 ± 16.4	54.4 ± 17.8	47.0 ± 16.2	46.2 ± 16.3	44.4 ± 15.6
Median (range)	47 (18–97)	47 (18–97)	57 (18–93)	47 (18–97)	45 (18–90)	44 (18–92)
Age category (yr), No. (%)						
< 35	1,562 (25.9)	872 (24.9)	26 (15.2)	846 (25.5)	271 (28.3)	265 (30.3)
≥ 35	4,471 (74.1)	2,623 (75.1)	145 (84.8)	2,478 (74.5)	687 (71.7)	609 (69.7)
< 50	3,351 (55.5)	1,937 (55.4)	66 (38.6)	1,871 (56.3)	577 (60.2)	553 (63.3)
≥ 50	2,682 (44.5)	1,558 (44.6)	105 (61.4)	1,453 (43.7)	381 (39.8)	321 (36.7)
< 65	4,884 (81.0)	2,889 (82.7)	108 (63.2)	2,781 (83.7)	786 (82.0)	762 (87.2)
≥ 65	1,149 (19.0)	606 (17.3)	63 (36.8)	543 (16.3)	172 (18.0)	112 (12.8)
Treatment at index date, No. (%)						
IM	3,727 (61.8)	3,494 (100.0)	171 (100.0)	3,324 (100.0)	0	874 (100.0)
TNFi	1,308 (21.7)	0	0	0	958 (100.0)	874 (100.0)
Corticosteroid	2,137 (35.4)	820 (23.5)	46 (26.9)	774 (23.3)	187 (19.5)	156 (17.8)
Corticosteroid dosage[a]						
Mean ± SD	22.9 ± 19.4	21.5 ± 17.2	10.6 ± 11.7	22.1 ± 17.3	20.9 ± 17.5	19.2 ± 16.3
Median (range)	20.0 (0.5–150.0)	19.4 (0.5–133.3)	4.5 (1.0–50.0)	20.0 (0.5–133.3)	20.0 (0.5–100.0)	17.9 (0.5–86.7)
Follow-up duration (yr)						
Mean ± SD	2.8 ± 1.7	2.5 ± 1.5	2.5 ± 1.5	2.5 ± 1.5	2.6 ± 1.5	2.6 ± 1.5
Median (range)	2.2 (1.0–9.8)	2.0 (1.0–9.7)	1.9 (1.0–8.7)	2.0 (1.0–9.7)	2.1 (1.0–8.9)	2.2 (1.0–9.4)

[a]Prednisolone equivalent at index date.
MDV, Medical Data Vision; CS, corticosteroid; IM, immunosuppressant; TNFi, tumor necrosis factor inhibitor; TAC, tacrolimus; CyA, cyclosporine; 6-MP, 6-mercaptopurine; AZA, azathioprine; SD, standard deviation.

pressant (group 2), compared with patients receiving TNFi (group 3) or an immunosuppressant and TNFi (group 4), with each malignancy definition. When stratified by immunosuppressant medication, the incidence rate of malignancies, when using both definitions, was numerically higher in patients receiving tacrolimus or cyclosporine (group 2-1) compared with patients receiving 6-MP or azathioprine (group 2-2).

Across all treatment groups, the incidence rates of malignancies were generally similar in females and males, and generally increased with age, in both the JMDC and MDV cohorts (Supplementary Tables 4 and 5).

DISCUSSION

To our knowledge, this is the first analysis to assess the incidence rates of hospitalized infections, herpes zoster, and malignancies among patients with UC, stratified by treatment, from administrative health claims databases in Japan. For this analysis, patients with UC were analyzed according to their treatment, which reflected the most common UC care pathways at the time of the study period in Japan. Patients with UC were identified from administrative health claims databases using a recently validated claims-based algorithm based on a combination of diagnostic codes and claims codes for systemic therapies prescribed for the treatment of UC.[25]

Serious infections are generally defined as infections that require hospitalization or intravenous antibiotics. Among patients with IBD, the incidence rate of serious infections has been reported to range between 1 and 10 per 100 patient-years.[27-30] This analysis assessed infection events that result in hospitalization, which were extracted from the MDV database using 2 separate definitions. Incidence rates of hospitalized in-

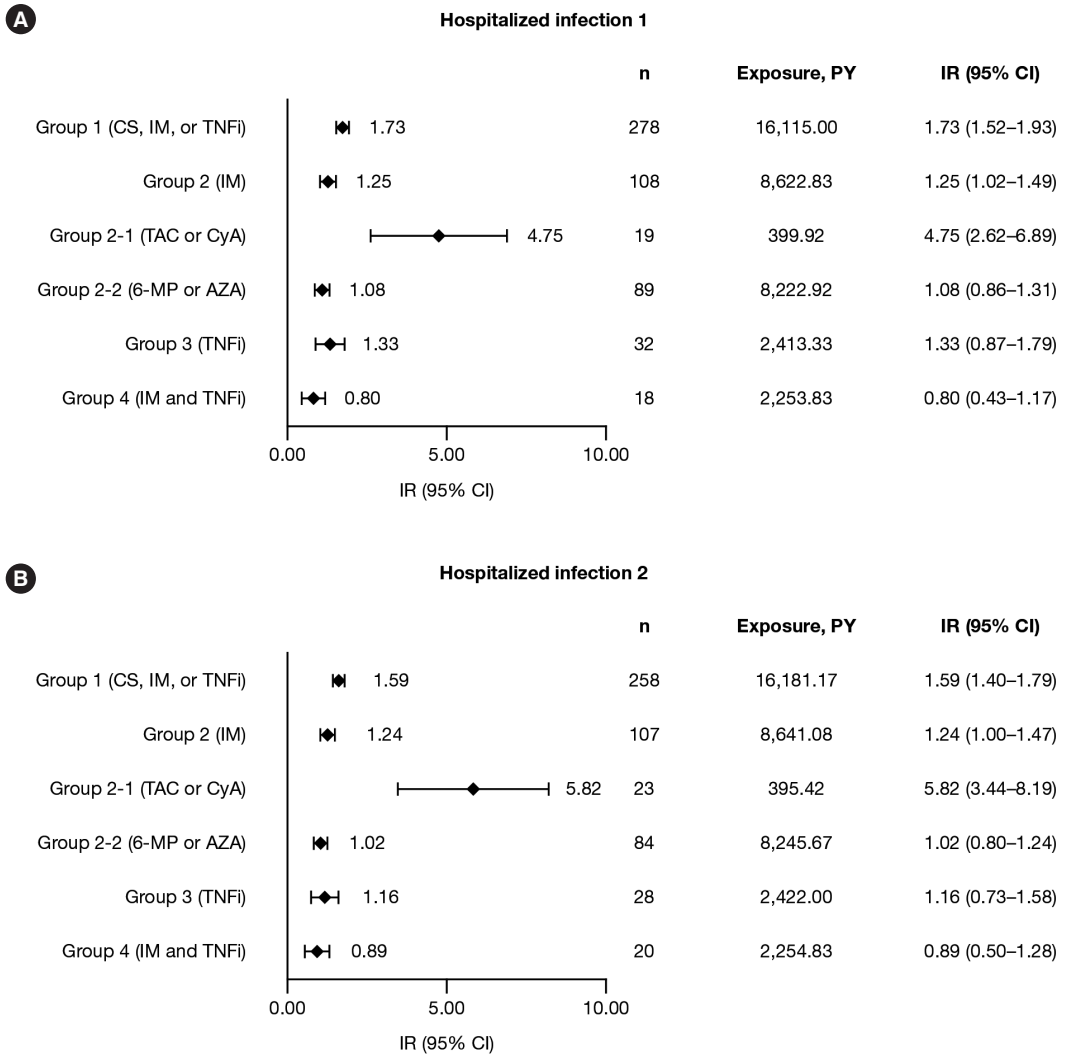

Fig. 2. Incidence rates (unique patients with events per 100 patient-years) for hospitalized infections in the MDV database. (A) Hospitalized infection 1 (defined as an infection which results in hospitalization). (B) Hospitalized infection 2 (defined as an infection which results in the most charged medical resource during hospitalization). MDV, Medical Data Vision; CS, corticosteroid; IM, immunosuppressant; TNFi, tumor necrosis factor inhibitor; TAC, tacrolimus; CyA, cyclosporine; 6-MP, 6-mercaptopurine; AZA, azathioprine; n, number of events; PY, patient-years; IR, incidence rate (unique patients with events per 100 PY); CI, confidence interval.

fections were similar for all treatment groups (with the exception of calcineurin inhibitors), when estimated using both definitions. The incidence rates of hospitalized infections (using either definition) in patients receiving TNFi reported here were lower than incidence rates of serious infection (defined as an infection requiring hospitalization) reported in a nationwide, population-based cohort study of patients with IBD in France,[27] in an analysis of pooled data from 2 large US and French nationwide, population-based cohorts of patients with IBD,[30] and in a population-based cohort of patients with UC in the United States.[31] The reason for the lower incidence rate of hospitalized infections in this study compared with the previous studies is unknown, but could be related to differences in exposure definitions and study populations. In our analysis, the incidence rates of hospitalized infections were generally similar between patients receiving immunosuppressants or TNFi alone and those receiving an immunosuppressant and TNFi (with the exception of the incidence rate estimated in patients receiving calcineurin inhibitors). This is in contrast to the data previously reported in the French nationwide, population-based cohort study in which the incidence rates of hospitalized infections with thiopurine and TNFi combination therapy were higher compared with either thiopurine or TNFi monotherapy.[27]

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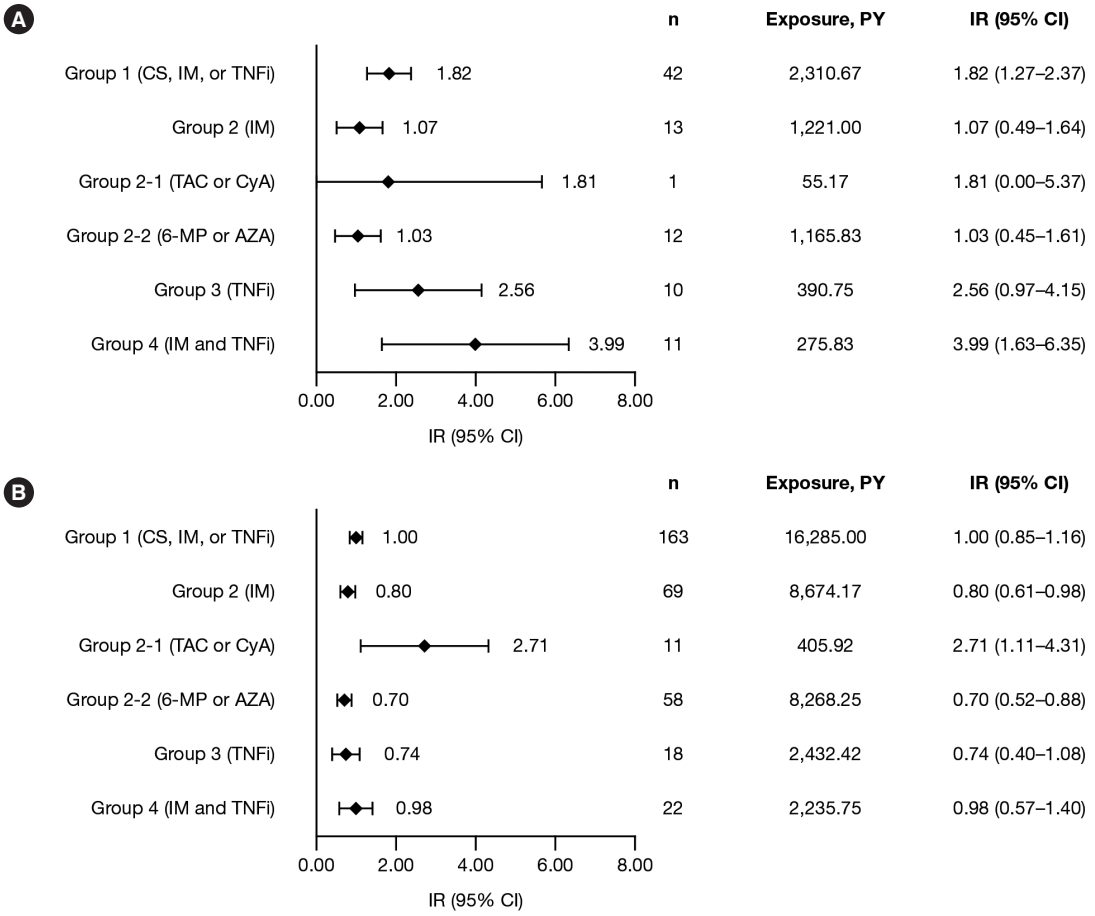

Fig. 3. Incidence rates (unique patients with events per 100 patient-years) for herpes zoster in the (A) JMDC database and the (B) MDV database. JMDC, Japan Medical Data Center; MDV, Medical Data Vision; CS, corticosteroid; IM, immunosuppressant; TNFi, tumor necrosis factor inhibitor; TAC, tacrolimus; CyA, cyclosporine; 6-MP, 6-mercaptopurine; AZA, azathioprine; n, number of events; PY, patient-years; IR, incidence rate (unique patients with events per 100 PY); CI, confidence interval.

The incidence rate of herpes zoster in Japan has been previously estimated to be 0.49 per 100 patient-years (95% CI, 0.49–0.50) in the general population and 0.74 per 100 patient-years (95% CI, 0.52–1.02) among patients with IBD.[9] The incidence rates estimated in this analysis in all treatment groups of the MDV cohort (with the exception of the incidence rate estimated in patients receiving calcineurin inhibitors) were comparable to the previous estimate among patients with IBD. In patients with IBD, previous studies have reported an association between the use of corticosteroids, thiopurines, and TNFi and the risk of herpes zoster,[11,14] and the herpes zoster risk has been shown to increase with thiopurine and TNFi combination therapy, compared with either thiopurine or TNFi monotherapy.[14] In a population-based cohort of patients with UC in the United States, Curtis et al.[31] reported numerically higher incidence rates of herpes zoster among patients receiving combination therapy with TNFi and immunosuppressants/immunomodulators, compared with patients receiving immunosuppressants/immunomodulators monotherapy. Similarly, in this analysis, the incidence rate of herpes zoster in the JMDC cohort was numerically higher in patients receiving combination therapy with an immunosuppressant and TNFi, compared with either immunosuppressant or TNFi monotherapy, whereas numerically similar incidence rates were reported across treatment groups in the MDV cohort. In Japan, the incidence rate of herpes zoster is known to be higher among females compared with males, and increased with age, both in adults with and without IBD,[9,32] and our findings from these UC patient populations were in general, consistent with this observation.

In this analysis, the incidence rate of malignancies were extracted from the 2 databases using 2 separate disease-identifying algorithms. Estimated incidence rates of malignancies extracted using the malignancy 2 definition (an ICD-10 code of

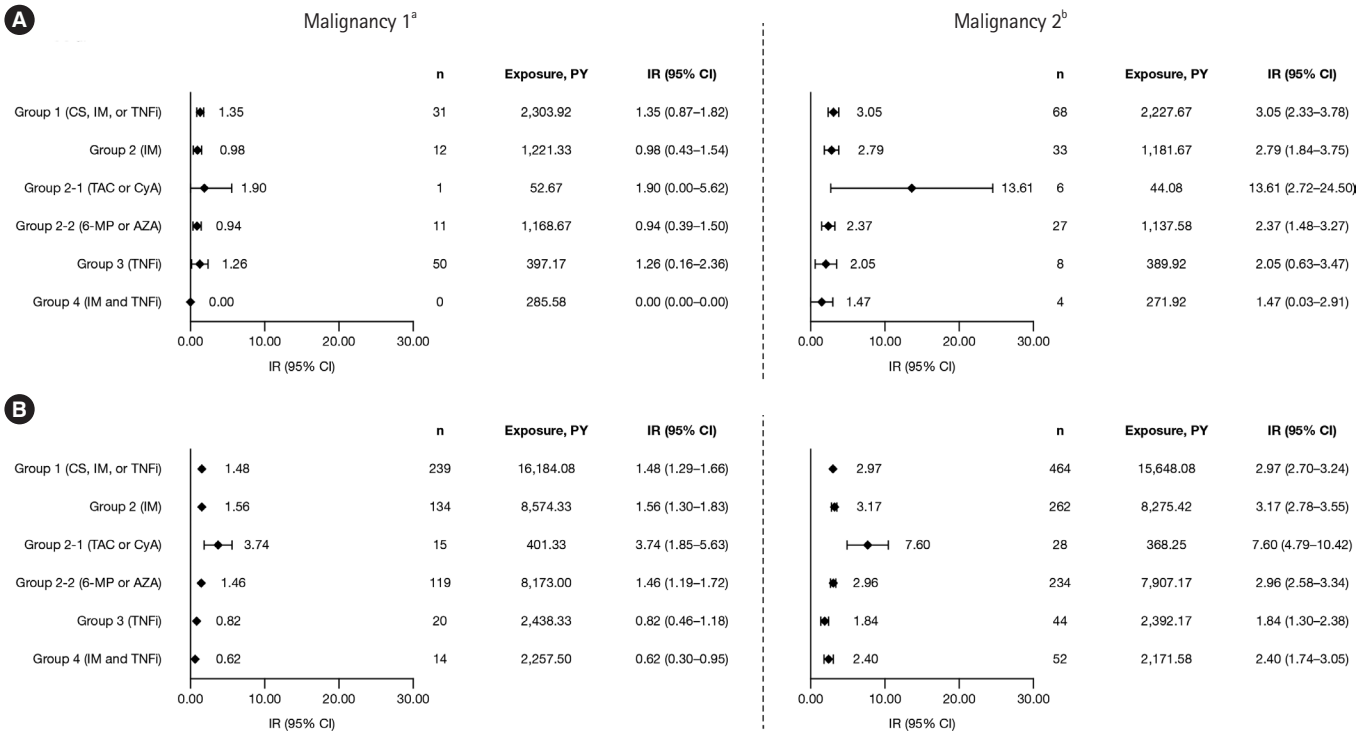

Fig. 4. Incidence rates (unique patients with events per 100 patient-years) for malignancies in the (A) JMDC database and the (B) MDV database. [a]Malignancy 1 was defined as an ICD-10 code of malignancy (C00–C97 malignant neoplasm or D00–D09 *in situ* neoplasms) along with a cancer management code (B-001-00-03, B-001-00-18, B-001-00-22, B-001-00-23, B-001-00-24, B-005-06, H-007-02) within the same claim month; [b]Malignancy 2 was defined as confirmed diagnosis within 2 consecutive claims months. JMDC, Japan Medical Data Center; MDV, Medical Data Vision; ICD-10, International Classification of Diseases, 10th Revision; CS, corticosteroid; IM, immunosuppressant; TNFi, tumor necrosis factor inhibitor; TAC, tacrolimus; CyA, cyclosporine; 6-MP, 6-mercaptopurine; AZA, azathioprine; n, number of events; PY, patient-years; IR, incidence rate (unique patients with events per 100 PY); CI, confidence interval.

malignancy within 2 consecutive claims months) were numerically higher than those extracted using the malignancy 1 definition (an ICD-10 code of malignancy along with a cancer management code within the same claim month). A key component in the use of claims data is the ability to demonstrate high validity of the algorithms used to identify study populations and outcomes of interest. The VALIDATE-J study investigated the validity of several predefined diseases-identifying algorithms using hospital claims data in Japan.[33] The claims-based algorithm in VALIDATE-J was based on diagnostic and procedural codes, which was the same as the algorithm for the malignancy 1 definition used here, which identified malignancies with a high specificity and modest to moderate sensitivity, suggesting that malignancies extracted using this algorithm may be underestimated,[33] and this is a limitation of a claims based analysis.

Previous studies in patients with UC have suggested that the increased malignancy risk attributed to TNFi therapy is driven by the concomitant immunosuppressant therapy,[20] with no evidence to suggest an increased risk in those treated with TNFi alone.[16] In our study, the incidence rate of malignancies extracted using the algorithm for the malignancy 2 definition (a malignancy diagnosis within 2 consecutive claims months) was numerically higher in patients receiving immunosuppressants compared with patients receiving TNFi, however, the incidence rate in patients receiving TNFi alone was comparable to those receiving combination therapy with an immunosuppressant and TNFi. Similar findings have been reported in a recent administrative database study of patients with UC in Japan, which demonstrated that thiopurines with or without a TNFi may be associated with an increased risk of non-melanoma skin cancer.[34]

In this analysis, when immunosuppressant medications were categorized by mode of action, the incidence rates for hospitalized infections, herpes zoster, and malignancies were higher in patients receiving calcineurin inhibitors (tacrolimus or cyclosporine) compared with all other treatment groups. It is unclear if this is an expected observation as safety data of

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the long-term administration of calcineurin inhibitors are limited, potentially due to current European Crohn's and Colitis Organisation guidelines which recommend discontinuation of calcineurin inhibitors within 6 months because of side effects, including infections and malignancies.[35]

This study has some limitations. Patients were grouped based on their initial prescription received for UC and patients could be included in more than 1 group, which limits the comparison of incidence rates between groups. This study did not consider treatment history more than 6 months prior to the index date, which may have an influence on the incidence rates calculated here, however, considering the half life of TNFi, the effect of prior TNFi treatment is thought to be minimal if more than 6 months have passed since the last administration of TNFi. The duration of treatment exposure was not captured in this study, however, due to the study inclusion criteria, the duration of exposure was at least 1 year for every patient. The MDV database only captures events from participating hospitals and does not include events treated in other clinical settings, potentially leading to an underestimation of the incidence of events of interest. Additionally, as the data in the MDV database are mostly based on hospitals with acute medical care, the incidence of hospitalized infections may have been overestimated, compared with the incidence of hospitalized infections in general hospitals (i.e., those without acute medical care). Due to the methodology used, hospitalized infections could only be extracted from the MDV database as the reason for hospitalization could not be identified from the JMDC database. Furthermore, hospitalization was defined by the disease name claimed under the Diagnosis Procedure Combination system and there may be a difference between patients who were recorded to have been hospitalized in actual clinical practice versus those hospitalized in the Diagnosis Procedure Combination data. Patients with herpes zoster were identified using an ICD-10 code and a prescription for antiviral medication and, therefore, herpes zoster cases where an antiviral medication was not prescribed would not have been included, and this might have led to an underestimation of incidence rates. Malignancies were extracted from the administrative health claims databases using 2 different algorithms, which may have led to an underestimation or overestimation of malignancies. Additionally, malignancy events were not analyzed by types of malignancies. The study populations included in this analysis were relatively young, with more than 80% aged <65 years, and this might have influenced incidence rates. Finally, the data from our analysis should be reviewed cautiously due to the limited patient numbers and events in some treatment groups.

In conclusion, this large-scale administrative health claims database study provides an indication of the real-world estimates of the incidence rates of hospitalized infections, herpes zoster, and malignancies in patients with UC in Japan. Despite the aforementioned limitations, the characterization of safety in this study demonstrated that observed incidence rates for safety events of interest varied depending on the specific definition used to identify them. The numerically higher incidence rates of hospitalized infections, herpes zoster, and malignancies in patients with UC receiving calcineurin inhibitors highlights the importance of close monitoring of patients during calcineurin inhibitor treatment. These population-based data will support the safety comparison of current and future therapeutic agents for the treatment of UC.

ADDITIONAL INFORMATION

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Conflict of Interest

Matsuoka K has served as a scientific adviser for EA Pharma; has served on advisory boards for Boehringer Ingelheim, Bristol-Meyers Squibb, and Eli Lilly; has received personal fees from AbbVie, EA Pharma, Janssen, JIMRO, Kissei Pharmaceutical, Kyorin Pharmaceutical, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Pfizer Inc, Takeda Pharmaceutical, and Zeria Pharmaceutical; and has received research grants from AbbVie, EA Pharma, JIMRO, Kissei Pharmaceutical, Kyorin Pharmaceutical, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Nippon Kayaku, and Takeda Pharmaceutical. Togo K, Hoshi M, and Arai S are employees and stockholders of Pfizer Japan Inc. Yoshii N was a former employee of Pfizer Japan Inc.

Matsuoka K is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Data Sharing Statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual anonymized participant data.

See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Author Contribution

Conceptualization: Matsuoka K, Togo K, Yoshii N, Arai S. Methodology: Togo K, Yoshii N, Arai S. Formal analysis: all authors. Funding acquisition: all authors. Project administration: Arai S. Visualization: all authors. Writing - original draft: all authors. Writing - review and editing: all authors. Approval of final manuscript: all authors.

Non-Author Contributions

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Supplementary Material

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

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