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# Factorial Analysis of *Clostridioides Difficile* Colitis and Pseudomembranous Colitis Using JADER

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***Clostridioides difficile* (*C. difficile*) colitis and pseudomembranous colitis are known as healthcare-associated intestinal infections. In this study, the incidence of *C. difficile* colitis and pseudomembranous colitis was investigated using the Japanese Adverse Drug Event Report (JADER). Using JADER data between April 2004 and September 2017, the patient who developed *C. difficile* colitis and pseudomembranous colitis were investigated. During the study period, 375 cases of *C. difficile* colitis and 903 cases of pseudomembranous colitis were reported. The numbers of reported cases of both *C. difficile* colitis and pseudomembranous colitis were largest in those in their 70s, accounting for 24.7% and 25.6%, respectively. Patients in their 60s-90s comprised the majority of all patients with both *C. difficile* colitis and pseudomembranous colitis. Both *C. difficile* colitis and pseudomembranous colitis were caused by antibiotics in many patients, and signals of all antibiotics were detected. In *C. difficile* colitis, signals of immunosuppressants, corticosteroids, and alkylating drugs were also detected among drugs other than antibiotics. For pseudomembranous colitis, the use of molecularly targeted drugs, antimetabolic drugs, and corticosteroids was reported other than antibiotics. Using JADER, we revealed risk factors for the development of *C. difficile* colitis and pseudomembranous colitis, and firstly revealed that molecularly targeted drugs other than antibiotics could also be potential risk factors. Our findings may be useful for the early detection of drug-induced *C. difficile* colitis and pseudomembranous colitis.**

**Key words** Japanese Adverse Drug Event Report, *Clostridioides difficile* colitis, pseudomembranous colitis

## INTRODUCTION

*Clostridioides difficile* colitis are known as healthcare-associated infections that are primarily due to the gram-positive obligate anaerobe *C. difficile*. Pseudomembranous colitis and antibiotics-associated diarrhea are also associated with *C. difficile* infection (CDI). These diseases are caused mostly by dysbiosis, which are disrupted state of the microbiome due to the use of antibiotics. In addition to dysbiosis, pseudomembranous colitis includes signs of raised yellow plaques as well as swelling in colon, therefore, pseudomembranous colitis is more sever state of CDI. The primary symptom of CDI is diarrhea, but it is occasionally accompanied by abdominal pain and fever. The disease may recur or become intractable and may even be fatal in severe cases. In addition, the disease is also known to be caused by the use of drugs other than antibiotics ($H_2$ blockers, proton pump inhibitors (PPI), sucralfate),[1] and there is a report that PPI, in particular, exacerbate CDI.[2] Therefore, CDI is frequently caused by drug therapy, and considered as adverse events of drugs.

In the United States, CDI was named the most important healthcare-associated infection,[3] and antibiotic stewardship programs have been reported to significantly control the incidence of antibiotic-associated diarrhea.[4] Its prevalence is 6.9/1000 hospitalized patients in the United States but is relatively low at 0.3-5.5/1000 in Japan.[5] This difference in prevalence may be ascribed to differences in the distribution of epidemic strains and methods for their detection,[5,6] but the details are unclear. Moreover, the incidence of CDI is considered to increase in older people, but that of community-acquired CDI has been reported to be high in younger people aged under 45 years in the United States.[7] Thus, surveillance of its etiological factors in each countries is thought to be necessary.

The Pharmaceutical and Medical Device Agency (PMDA) publishes the Japanese Adverse Drug Event Report database (JADER). Analysis of JADER may be useful to spread consciousness among medical care workers, in addition to aiding in the selection of appropriate drugs and prevention and early discovery of adverse events. As such, its contribution to the safety of medical care is strongly expected. Adverse events reported in 2004 and thereafter in Japan were accumulated in JADER. There are methods to calculate and quantify the safety signal to acquire beneficial information from JADER. Most of these are disequilibrium analyses relatively comparing the reporting frequency, and the reporting odds ratio (ROR) is the representative method with a high sensitivity capable of detecting signals at an early stage using few case reports. Furthermore, time information from drug administration to the development of adverse events is described in JADER.[8,9] Therefore, JADER is suitable for factorial analysis of CDI in Japan, however; there are no reports about it.

In this study, we investigated the factors, such as sex, age,

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drugs, and onset time that involved in incidence of *C. difficile* colitis or pseudomembranous colitis using JADER, and the ROR and 95% confidence interval (CI) were calculated.

## MATERIALS AND METHODS

**Data Source** In January 2018, we downloaded JADER from the PMDA website and conducted the study using the data between April 2004 and September 2017. The number of patients and cases were extracted from JADER.

**Definition of *C. Difficile* Colitis or Pseudomembranous colitis** Adverse events labeled with *Clostridium difficile*, *Clostridium difficile* infection, *Clostridium difficile* colitis, *Clostridium difficile* gastroenteritis, *Clostridium difficile* bacteremia, or *Clostridium difficile* toxin-positive were extracted as cases of *C. difficile* colitis. Adverse events described as pseudomembranous colitis were extracted as cases of pseudomembranous colitis. Overlapping data of the same outcome from drug with the same identification number were deleted.

**Data Extraction** The sex, age, drugs suspected to be responsible, and time of onset of the patients who developed *C. difficile* colitis or pseudomembranous colitis were investigated. The sex was recorded as "unknown" when it was not mentioned. When a drug was specified as suspected drug, and no other suspected drugs or concomitant medications were mentioned, concomitant medication was defined as absent. The time of onset was calculated by adding 1 to the number of days from the day of the beginning of administration to the day of the appearance of the adverse event. Patients lacking records of the day of the beginning of administration or the day of the appearance of the adverse event were excluded. Those for whom only the year and month were available were also excluded.

**Statistical Analysis** The safety signal index, ROR, was calculated from the 2×2 contingency table (Table 1). When the lower limit of the 95% CI exceeded 1, the drug was regarded as signal-positive.

## RESULTS

**Number and Characteristics of Reported Cases** The total numbers of patients and adverse events registered in JADER during the study period were 483,152 and 764,287, respectively. They included 373 cases of *C. difficile* colitis in 369 patients and 903 cases of pseudomembranous colitis in 899 patients (Table 2 and 3). Of the patients with *C. difficile* colitis, 47.2% (174/369) were males, 49.1% (181/369) were females (Table 2). Of the patients with pseudomembranous colitis, 44.4% (399/899) were males, 53.8% (484/899) were females (Table 2). Signals were detected in female patients with pseudomembranous colitis (ROR=1.30, 95% CI 1.14-1.49).

Of the patients with *C. difficile* colitis, 24.7% (91/369) were in their 70s, followed by those aged less than 10 years (15.7%, 58/369) and those in their 60s (15.7%, 58/369) (Table 3). Signals of *C. difficile* colitis were detected in those aged under 10 years (ROR=4.58, 95% CI 3.46-6.06) and those in their 90s (ROR=2.89, 95% CI 1.72-4.85) (Table 3). Of the patients with pseudomembranous colitis, 25.6% (230/899) were in their 70s, followed by 19.8% (178/899) in their 60s and 16.2% (146/899) in their 80s (Table 3). Signals of pseudomembranous colitis were detected in those in their 80s (ROR=1.54, 95% CI 1.29-1.84) and those in their 90s (ROR=2.44, 95% CI 1.70-3.49). Patients in their 60s-90s comprised the majority of both patients with *C. difficile* colitis and those with pseudomembranous colitis.

**Number of Cases According to the Drug** The drugs suspected to have caused the diseases were classified into categories. The top 10 drugs suspected to have caused *C. difficile* colitis or pseudomembranous colitis are shown in Tables 4 and 5. *C. difficile* colitis was most frequently ascribed to antimicrobial agents (cephalosporins (157 cases, ROR=31.61, 95% CI 25.69-38.89), new quinolones (66 cases, ROR=12.20, 95% CI 9.34-15.94), macrolides (62 cases, ROR=20.99, 95% CI 15.95-27.62), penicillins (57 cases, ROR=14.25, 95% CI 10.73-18.92), carbapenems (39 cases, ROR=16.42, 95% CI

**Table 1.** 2×2-Contingency Table

| | Target adverse events | Non-target adverse events | Total |
|---|---|---|---|
| Target drug | n11 | n12 | n1+ |
| Non-target drug | n21 | n22 | n2+ |
| Total | n+1 | n+2 | n++ |

ROR= (n11/n21)/(n12/n22).

**Table 2.** Number and ROR of *C. Difficile* Colitis or Pseudomembranous Colitis Cases by Sex

| | Sex | n (%) | ROR | 95% CI |
|---|---|---|---|---|
| *C. difficile* colitis | Male | 174 (47.2) | 0.93 | 0.76-1.14 |
| | Female | 181 (49.1) | 1.08 | 0.88-1.32 |
| | Unclear | 14 (3.8) | 0.99 | 0.58-1.68 |
| Pseudomembranous colitis | Male | 399 (44.4) | 0.83 | 0.73-0.95 |
| | Female | 484 (53.8) | 1.30 | 1.14-1.49 |
| | Unclear | 16 (1.8) | 0.45 | 0.28-0.74 |

**Table 3.** ROR of *C. Difficile* Colitis or Pseudomembranous Colitis Cases by Age

| | Age | n (%) | ROR | 95% CI |
|---|---|---|---|---|
| *C. difficile* colitis | <10 | 58 (15.7) | 4.58 | 3.46-6.06 |
| | 10s | 13 (3.5) | 1.25 | 0.72-2.17 |
| | 20s | 14 (3.8) | 1.16 | 0.68-1.98 |
| | 30s | 18 (4.9) | 0.87 | 0.54-1.39 |
| | 40s | 31 (8.4) | 1.17 | 0.81-1.69 |
| | 50s | 22 (6.0) | 0.46 | 0.30-0.70 |
| | 60s | 58 (15.7) | 0.69 | 0.52-0.91 |
| | 70s | 91 (24.7) | 1.11 | 0.88-1.41 |
| | 80s | 32 (8.7) | 0.75 | 0.53-1.08 |
| | 90s | 15 (4.1) | 2.89 | 1.72-4.85 |
| | Unclear | 9 (2.4) | 0.39 | 0.20-0.76 |
| | Others | 8 (2.2) | 1.21 | 0.60-2.42 |
| | Total | 369 (100) | - | - |
| Pseudomembranous colitis | <10 | 38 (4.2) | 1.08 | 0.78-1.50 |
| | 10s | 12 (1.3) | 0.46 | 0.26-0.82 |
| | 20s | 40 (4.4) | 1.37 | 1.00-1.88 |
| | 30s | 40 (4.4) | 0.79 | 0.57-1.08 |
| | 40s | 46 (5.1) | 0.69 | 0.51-0.93 |
| | 50s | 98 (10.9) | 0.88 | 0.71-1.09 |
| | 60s | 178 (19.8) | 0.91 | 0.77-1.07 |
| | 70s | 230 (25.6) | 1.17 | 1.00-1.35 |
| | 80s | 146 (16.2) | 1.54 | 1.29-1.84 |
| | 90s | 31 (3.4) | 2.44 | 1.70-3.49 |
| | Unclear | 30 (3.3) | 0.54 | 0.38-0.78 |
| | Others | 10 (1.1) | 0.62 | 0.33-1.15 |
| | Total | 899 (100) | - | - |

**Table 4.** Number and ROR of *C. Difficile* Colitis Cases Associated with Each Drug

| Drug | n | ROR | 95% CI |
|---|---|---|---|
| Cephalosporin | 157 | 31.61 | 25.69-38.89 |
| New quinolone | 66 | 12.20 | 9.34-15.94 |
| Macrolide | 62 | 20.99 | 15.95-27.62 |
| Penicillin | 57 | 14.25 | 10.73-18.92 |
| Carbapenem | 39 | 16.42 | 11.76-22.92 |
| Aminoglycoside | 38 | 16.96 | 12.10-23.76 |
| Immunosuppressants | 38 | 1.77 | 1.26-2.47 |
| Corticosteroid | 32 | 1.86 | 1.30-2.68 |
| Antimetabolic drug | 31 | 0.96 | 0.66-1.38 |
| Alkylating drug | 22 | 3.06 | 1.99-4.71 |

**Table 5.** Number and ROR of Pseudomembranous Colitis Cases Associated with Each Drug

| Drug | n | ROR | 95% CI |
|---|---|---|---|
| Cephalosporin | 336 | 25.87 | 22.57-29.66 |
| New quinolone | 168 | 13.10 | 11.07-15.52 |
| Penicillin | 166 | 17.97 | 15.16-21.31 |
| Carbapenem | 115 | 20.82 | 17.07-25.40 |
| Macrolide | 82 | 5.85 | 4.68-7.33 |
| Aminoglycoside | 74 | 13.38 | 10.52-17.02 |
| Antitubercular drug | 55 | 11.82 | 8.97-15.56 |
| Molecularly targeted drug | 57 | 0.52 | 0.40-0.68 |
| Antimetabolic drug | 51 | 0.63 | 0.47-0.83 |
| Corticosteroid | 49 | 1.13 | 0.85-1.51 |

11.76-22.92), and aminoglycosides (38 cases, ROR=16.96, 95% CI 12.10-23.76)) (Table 4). In *C. difficile* colitis cases, signals were also positive for immunosuppressants (38 cases, ROR=1.77, 95% CI 1.26-2.47), corticosteroids (32 cases, ROR=1.86, 95% CI 1.30-2.68), and alkylating drugs (22 cases, ROR=3.06, 95% CI 1.99-4.71) other than antibiotics.

Pseudomembranous colitis was most frequently ascribed to antimicrobial agents (cephalosporines (336 cases, ROR=25.87, 95% CI 22.57-29.66), new quinolones (168 cases, ROR=13.10, 95% CI 11.07-15.52), penicillins (166 cases, ROR=17.97, 95% CI 15.16-21.31), carbapenems (115 cases, ROR=20.82, 95% CI 17.07-25.40), macrolides (82 cases, ROR=5.85, 95% CI 4.68-7.33), aminoglycosides (74 cases, ROR=13.38, 95% CI 10.52-17.02), and antitubercular drugs (55 cases, ROR=11.82, 95% CI 8.97-15.56)) (Table 5). For pseudomembranous colitis, molecularly targeted drugs (57 cases), antimetabolic drugs (51 cases), and corticosteroids (49 cases) other than antibiotics were reported to be responsible, but no signals were detected for these drugs.

**Time of Onset According to the Drug** The time of onset of *C. difficile* colitis and pseudomembranous colitis is shown in Figs. 1 and 2. In most cases of *C. difficile* colitis and pseudomembranous colitis, the onset was within 21 d after the beginning of antibiotic administration (Fig. 1, 2). However, *C. difficile* colitis and pseudomembranous colitis due to antimetabolic drugs developed within 8 weeks after the beginning of administration (Fig. 1I, 2I). Pseudomembranous colitis due to molecularly targeted drugs developed within 1 year after the beginning of administration (Fig. 2H).

**Numbers of Reported Cases Ascribed to Different Molecularly Targeted Drugs** The numbers of cases of *C. difficile* colitis and pseudomembranous colitis ascribed to molecularly targeted drugs are shown in Table 6. Epidermal growth factor receptor (EGFR) targeting drugs (*C. difficile* colitis 3/17, pseudomembranous colitis 7/57), vascular endothelial growth factor (VEGF) or VEGF receptor (VEGFR) targeting drugs (*C. difficile* colitis 2/17, pseudomembranous colitis 10/57), multikinase inhibitors (*C. difficile* colitis 1/17, pseudomembranous colitis 6/57), Bcr-Abl inhibitors (*C. difficile* colitis 1/17, pseudomembranous colitis 11/57) were frequently reported.

## DISCUSSION

*C. difficile* colitis and pseudomembranous colitis are healthcare-associated infections of global concern, and there have been a number of meta-analyses and systematic reviews regarding their etiological and risk factors. However, as host and environmental factors are involved in the etiology of infections, the results of overseas surveillance may not be applied to Japan if there are differences in race, temperature, humidity, and epidemic strains. For example, the appearance of a highly virulent strain (NAP1/BI/027) is discussed in the United States and Europe,[10,11] but there have been few instances of its detection in Japan[12,13] and it has not been recognized as a problem. Furthermore, *C. difficile* is present in the natural environment. It also inhabits the intestines of healthy humans and mostly remains dormant, but causes symptoms if the intestinal microbiome is disturbed by stress such as hospitalization or medical treatments (e.g., use of antibiotics). Recently, the intestinal microbiome has been reported to differ between Japanese and non-Japanese. According to a report by Nishijima *et al*., not only diet but also environmental factors in living conditions play roles in the differences in intestinal microbiome among countries.[14] Therefore, etiological factors of CDI must be investigated in each country because CDI is caused by dysbiosis.

The patients with *C. difficile* colitis were mostly aged 70-79 years, followed by 0-9 years and 60-69 years, and those with pseudomembranous colitis were mostly aged 70-79 years, followed by 60-69 years and 80-89 years in descending order. Meta-analyses and systematic analyses have demonstrated that old age is a risk factor. A meta-analysis of the incidence of CDI in Japan also reported old age as a risk factor.[5] Regarding *C. difficile* colitis, signals were detected in patients under 10 years. The risk of CDI has been reported to be higher in those aged 0-3 years than in those aged 7 years and above,[15] but the risk of CDI compared with that in children aged 10 years and above and adults is unknown. In JADER, patients aged 0-9 years are grouped together as those under 10 years old, and details of their age distribution is unclear. The rate of asymptomatic colonization of *C. difficile* in neonates to infants has been reported to be 20-90%, but it is 2-15% in adults[16–18]; therefore, the colonization rate decreases with growth from the neonatal or infantile period.

In this study, immunosuppressants, corticosteroids, antimetabolic drugs, alkylating drugs, and molecularly targeted drugs in addition to antibiotics were suspected of causing *C. difficile* colitis and pseudomembranous colitis. Both immunosuppressants and corticosteroids have immunosuppressive effects, and have been reported as risk factors for CDI.[19,20] Similarly, vitamin D, which acts as an intrinsic immunomodulatory factor, was low in CDI patients, and the odds ratio of the incidence of severe CDI was 1.61 (95% CI: 1.02-2.53) in low 25(OH)

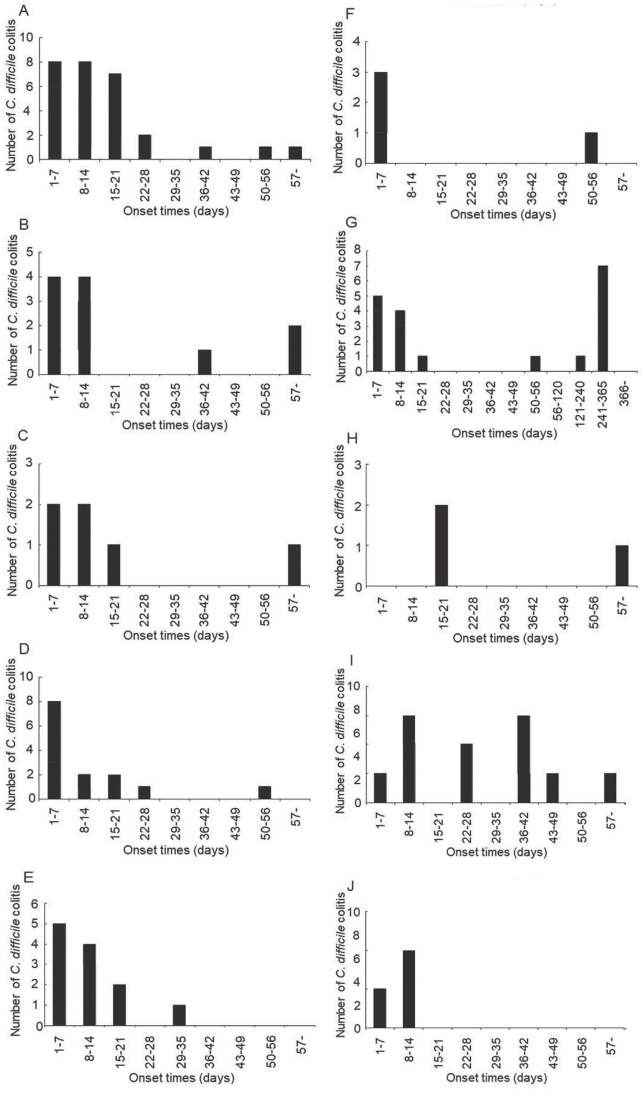


**Fig. 1.** Onset Time of *C. Difficile* Colitis After Administration of Each Drug

(A) Cephalosporin, (B) New quinolone, (C) Macrolide, (D) Penicillin, (E) Carbapenem, (F) Aminoglycoside, (G) Immunosuppressant, (H) Corticosteroid, (I) Antimetabolic drug, (J) Alkylating drug.

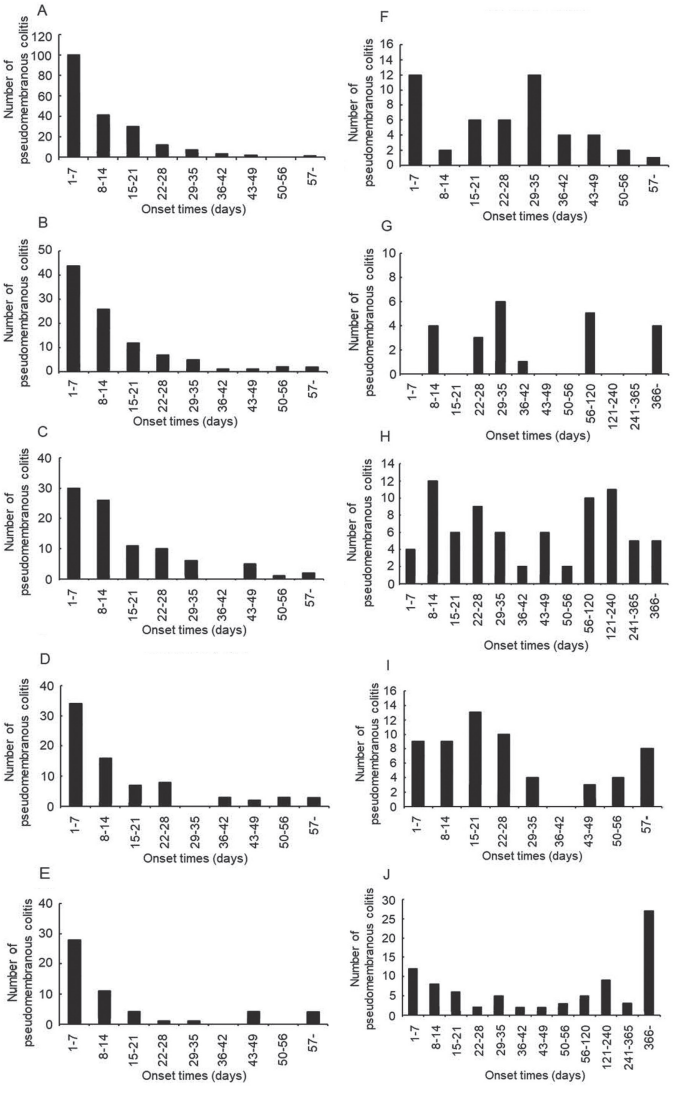


**Fig. 2.** Onset Time of Pseudomembranous Colitis After Administration of Each Drug

(A) Cephalosporin, (B) New quinolone, (C) Penicillin, (D) Carbapenem, (E) Macrolide, (F) Aminoglycoside, (G) Antitubercular drug, (H) Molecularly targeted drug, (I) Antimetabolic drug, (J) Corticosteroid.

D patients.[21] Immune imbalance may be a risk factor for the development of CDI. For example, immunocompromised patients with immunosuppressive medications associated with solid organ transplantation and allogenic hematopoietic stem cell transplantation or HIV/AIDS patients undergo diarrhea caused by *C. difficile*.[22,24,26] The innate immune system is important in defense mechanism against *C. difficile*.[28] Thus, disturbance of the normal immune system is considered to be a risk factor for the development of CDI. Antimetabolic drugs and alkylating drugs have immunosuppressive effects associated with bone marrow suppression. In this study, fluorouracil was reported frequently among antimetabolic drugs, and based on its dose and concomitant medications, it was considered to have been used in chemotherapy against colon cancer. Therefore, these patients may have had tumors or inflammation in the large intestine and may have undergone surgical resection. For example, inflammatory bowel disease and malignant neoplasm together with prolonged hospitalization before gastrointestinal surgery for these diseases have been reported as risk factors for the development of CDI.[23] In particular, a history of gastrointestinal surgery is associated with an increased risk for CDI compared with other surgeries, and the odds ratio after surgery of the lower gastrointestinal tract was reported to be 2.01 (95% CI 1.06-3.08).[25,27]

Drugs targeting VEGF-VEGFR signals were frequently reported because 1) colon cancer is one of their indications and there were other risk factors for the development of CDI, such as tumor, inflammation, history of gastrointestinal surgery, and prolonged preoperative hospitalization,[23] and because 2) VEGF induces ischemia due to suppression of angiogenesis. Patients with ischemic bowel disease have been reported to have a greater risk for developing CDI and exacerbation of CDI than other patients.[29] Of note, however, the induction of VEGF-A secretion by *C. difficile* toxin has been reported to play a role in intestinal damage by *C. difficile* and exacerbation of the condition, and there are reports that suggest the possibility of suppression of VEGF-A as an effective treatment.[30] According to a report by Huang *et al*., the VEGF-A level was higher in CDI patients than in healthy individuals and decreased after treatment.[30] These reports suggest that

**Table 6.** Number of *C. Difficile* Colitis or Pseudomembranous Colitis Cases Associated with Molecular Targeted Drugs

| Classification | Drugs | Target molecule | *C. difficile* colitis | Pseudomembranous colitis |
|---|---|---|---|---|
| EGFR targeting drug | Afatinib | EGFR | 1 | 1 |
| | Erlotinib | EGFR | 2 | 1 |
| | Gefitinib | EGFR | - | 2 |
| | Cetuximab | EGFR | - | 2 |
| | Panitumumab | EGFR | - | 1 |
| ALK targeting drug | Crizotinib | ALK, HGFR, ROS1 | - | 2 |
| | Alectinib | ALK, RET | 1 | - |
| HER2 targeting drug | Lapatinib | HER2, EGFR | - | 2 |
| | Trastuzumab | HER2 | - | 1 |
| VEGF/VEGFR targeting drug | Bevacizumab | VEGF | 2 | 7 |
| | Ramucirumab | VEGFR-2 | - | 1 |
| | Axitinib | VEGFR | - | 2 |
| Multikinase inhibitor | Sorafenib | VEGFR, PDGFR, Raf, FLT-3, KIT, RET | - | 4 |
| | Sunitinib | VEGFR, PDGFR, CSF-1R, FLT-3, KIT, RET | 1 | 2 |
| mTOR inhibitor | Everolimus | mTOR | - | 4 |
| | Temsirolimus | mTOR | - | 1 |
| Bcr-Abl inhibitor | Imatinib | Bcr-Abl, KIT, PDGFR | 1 | 3 |
| | Nilotinib | Bcr-Abl, KIT, PDGFR | - | 1 |
| | Dasatinib | Bcr-Abl, KIT, PDGFR | - | 7 |
| Anti-CD20 antibody | Rituximab | CD20 | 5 | 2 |
| | Ibritumomab tiuxetan | CD20 | | 2 |
| ADC drug | Gemtuzmab Ozogamicin | CD33 | - | 3 |
| | Brentuximab Vedotin | CD30 | 1 | - |
| Immune-checkpoint inhibitor | Pembrolizmab | PD-1 | 1 | - |
| JAK inhibitor | Ruxolitinib | JAK | - | 2 |
| Proteasome inhibitor | Bortezomib | UPP | 2 | 4 |
| Total | | | 17 | 57 |

EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; HGFR, c-Met/hepatocyte growth factor receptor; ROS1, c-ROS oncogene 1; RET, ret proto-oncogene; HER2, human epidermal growth factor receptor Type 2; VEGF, vascular endothelial growth factor; PDGFR, platelet-derived growth factor receptor; FLT-3, FMS-like tyrosine kinase 3; CSF-1R, colony stimulating factor 1 receptor; mTOR, mammalian target of rapamycin; PD-1, programmed cell death 1; JAK, Janus kinase; UPP, ubiquitin-proteasome pathway

increased VEGF secretion due to tumors is related to the etiology and exacerbation of *C. difficile* colitis, and that anti-VEGF agents suppress the development of CDI. However, whether the administration of anti-VEGF agents in cancer patients exerts suppressive effects on CDI is controversial, and further evaluation is necessary. There have been no reports evaluating the effects of the inclusion of bevacizumab in the regimen of anticancer chemotherapy (e.g. FOLFOX±Bev) on the incidence of CDI, and the effects of factors, such as differences in progression-free survival, due to such differences in regimen on the incidence of CDI cannot be excluded, which makes comparative evaluation difficult.

As Bcr-Abl is used for blood cancer patients, the immune function is considered to be reduced in administered patients. Moreover, the target molecules of the Bcr-Abl inhibitors reported in this study included both Bcr-Abl and PDGFR. PDGF is an angiogenic agent, similar to VEGF.[31] Therefore, PDGFR inhibitors are considered to suppress angiogenesis and induce ischemia. The rectal mucosal blood flow in pseudomembranous colitis patients measured using hydrogen gas clearance has been reported to decrease in the active period and increase with remission.[32] Whether this decrease in the mucosal blood flow in pseudomembranous colitis is an etiological factor or a result of pseudomembrane formation is unknown, but ischemic bowel disease is a risk factor for the development and exacerbation of CDI.[29] Furthermore, *C. difficile* colitis and pseudomembranous colitis were caused by molecularly targeted drugs until 1 year after the beginning of administration, unlike antibiotics. This suggests that the etiological mechanism of *C. difficile* colitis and pseudomembranous colitis due to molecularly targeted drugs is different from that due to antibiotics.

JADER used for analysis in this study is considered to be useful for safety evaluation in clinical practice and to aid in the prevention of adverse events; however, there are limitations in interpretation of the results of analysis using such a voluntary report system because of the absence of a control group and the presence of biases such as reporting bias and patient bias depending on the background of the patients such as the underlying disease.[8,33] Therefore, prospective epidemiological studies and evaluation with adjustment for background factors are necessary for genuine risk assessment. However, the analysis of *C. difficile* colitis and pseudomembranous colitis as adverse drug reactions will enable the discovery of common features among analogous drug effect groups, and may improve the consciousness and motivation for the early detection of these conditions in inpatient pharmaceutical service.

In this study, using JADER, we firstly investigated the risk factors of incidence of *C. difficile* colitis and pseudomembranous colitis, and clarified that molecularly targeted drugs other than antibiotics were suspected to be risk factors of them. This study is considered to aid in the early detection of drug-induced *C. difficile* colitis and pseudomembranous colitis.

**Conflict of interest** The authors declare no conflict of interest.

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