INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In Japan, the first case was identified in January 2020, and the COVID-19 pandemic has substantially worsened since. A state of emergency was declared in both metropolitan and provincial areas. Our hospital is located in Tochigi and a state of emergency was declared between 14 January and 7 February 2021. Based on the published information from Japan Broadcasting Corporation, the number of infected patients was 432,792 in Japan from January 2020 to February 2021, and 4,093 in Tochigi. The global COVID-19 pandemic is ongoing, and has affected both daily life and medical care around the world.

Inflammatory skin diseases, such as psoriasis, palmoplantar pustulosis (PPP), atopic dermatitis (AD), and hidradenitis suppurativa (HS), are characterized by the activation of the innate and adaptive immune system via the production of pro-inflammatory cytokines. Over the last decade, biologics have been developed and approved for the treatment of inflammatory skin diseases. The use of biologics seemed safe for use amidst COVID-19 infection during the observation period; however, further observation on a larger number of patients is required to confirm the risks and benefits of biologic use in the COVID-19 era.
diseases. Recent therapeutic developments have been remarkable; as of February 2021, 10 biologics were available for the treatment of psoriasis in Japan: three tumor necrosis factor (TNF) inhibitors, adalimumab (ADA), certolizumab pegol (CTZ), and infliximab (IFX); one interleukin (IL)-12/23 inhibitor, ustekinumab (UST); three IL-23 inhibitors, guselkumab (GUS), risankizumab (RIS), and tildrakizumab (TIL); and three IL-17 inhibitors, secukinumab (SEC), ixekizumab (IXE), and brodalumab (BRO). GUS has been used for the treatment of PPP, while dupilumab (DUP), which inhibits IL-4 and IL-13, has been used for AD, and ADA for HS. Biologics can provide significant symptomatic improvement that cannot be obtained with other types of therapies; however, it is unclear whether they suppress the severity of the disease, patients might discontinue their treatment, as well as hesitate to start biologic therapy or visit our hospital during the COVID-19 pandemic, for fear of infection. In this study, we analyzed the trend of biologic use for psoriasis, PPP, AD, and HS during the COVID-19 pandemic at the Jichi Medical University, Japan.

2 | METHODS

This study was approved by the Ethical Committee of Jichi Medical University.

2.1 | Patients

Patients with psoriasis, PPP, AD, or HS who received biologic therapy between 1 January 2020 and 28 February 2021 at the Jichi Medical University were enrolled in this study; the data were retrospectively collected from the electronic medical records. A survey was designed to acquire information regarding patients’ characteristics, prior medical history and comorbidities, the incidence of COVID-19, discontinuation and introduction of biologics, and use of telephone consultations. In patients with psoriasis, bioswitch was also analyzed for each drug and each type of psoriasis; the types of psoriasis included psoriasis vulgaris (PsO), psoriatic arthritis (PsA), generalized pustular psoriasis (GPP), and erythrodermic psoriasis (EP).

2.2 | Assessments

For psoriasis, the severity of skin lesions was evaluated using the Psoriasis Area and Severity Index (PASI). For PPP, the severity was evaluated using the PPP Area and Severity Index (PPPASI). The severity of AD was evaluated via the Investigators’ Global Assessment (IGA) and Eczema Area and Severity Index (EASI), while that of HS was evaluated by the Hurley clinical grading system.

3 | RESULTS

A total of 227 patients with psoriasis were enrolled in this study, of which 159 (70.0%) were male and 68 (30.0%) were female (Table 1); the average (mean ± standard deviation [SD]) age of the patients was 54.4 ± 14.4 years. A total of 58 patients (male: 38 cases, 25.6%; female: 20 cases) were aged 65 years and older. The most prevalent type of inflammatory skin disease was PsO (131 cases [57.7%]), followed by PsA (84 cases [37.0%]), GPP (nine cases [4.0%]), and EP (three cases [1.3%]) (data not shown). Medical history and comorbidities included obesity (body mass index [BMI] >30) (25 cases [11.0%]); male: 16 cases; female: nine cases), type 2 diabetes mellitus (DM) (46 cases [20.3%]; male: 36 cases; female: 10 cases), chronic kidney disease (CKD) (13 cases [5.7%]; male: 10 cases; female: three cases), chronic obstructive pulmonary disease (COPD) (eight cases [3.5%]; male: five cases; female: three cases), cancer (14 cases [6.2%]; male: 10 cases; female: four cases), cardiovascular disease (15 cases [6.6%]; male: 10 cases; female: five cases), and pregnancy (one case [0.4%]); a history of smoking was observed in 124 patients (54.6%; male: 103 cases; female: 21 cases). COVID-19 was confirmed in one male patient with PsA, who was hospitalized and fully recovered. The average duration of current therapy was 33.7 ± 28.8 months, and included ADA (36 cases [15.9%]), CTZ (five cases [2.2%]), IFX (18 cases [7.9%]), UST (22 cases [9.7%]), GUS (30 cases [13.2%]), RIS (30 cases [13.2%]), TIL (two cases [0.9%]), BRO (23 cases [10.1%]), IXE (31 cases [13.7%]), and SEC (30 cases [13.2%]).

A total of six patients with PPP were enrolled in this study (one [16.7%] male and five [83.3%] females; Table 1). The average age of the patients was 55.7 ± 11.1 years; one female patient (16.7%) was 65 years and older. The patients did not exhibit obesity, type 2 DM, CKD, COPD, cancer, cardiovascular disease, or pregnancy, while a history of smoking was observed in three cases (50.0%; male: one case; female: two cases). The average duration of therapy was 12.3 ± 2.4 months.

For AD, a total of 69 patients were enrolled in this study; 50 (72.5%) were male and 19 (27.5%) were female (Table 1). The average age of the patients was 35.6 ± 12.7 years; three patients (4.3%; male: one case; female: two cases) were aged 65 years and older. Medical history and comorbidities included obesity (five patients [7.2%]; male: two cases; female: three cases) and cancer (one female case [1.4%]); a history of smoking was observed in 13 patients (18.8%; male: 11 cases; female: two cases). The average duration of therapy was 13.6 ± 8.0 months.

For HS, a total of five male patients were enrolled in this study (Table 1); the average age of the patients was 37.4 ± 12.7 years. Medical history and comorbidities included cardiovascular disease (one case [20.0%]) and CKD (one case [20.0%]), while a history of smoking was observed in three patients (60.0%). The average duration of therapy was 11.4 ± 6.2 months.
Bioswitch for psoriasis

Bioswitch was performed in 25 patients with psoriasis (11.0%) during the observation period (18 males and seven females; Table 2) due to the insufficient therapeutic effects; the average age of the patients was 54.0 ± 14.8 years. The number of switches from a TNF inhibitor to another TNF inhibitor or IL-17 inhibitor were one and four cases, respectively. The number of switches from an IL-12/23 inhibitor to either an IL-23 inhibitor or IL-17 inhibitor were three and one case, respectively. The number of switches from an IL-23 inhibitor to another IL-23 inhibitor or IL-17 inhibitor were five and two cases, respectively. The number of switches from an IL-17 inhibitor to a TNF inhibitor or another IL-17 inhibitor were five and four cases, respectively. Focusing on each type of psoriasis, bioswitch was performed in 12 patients with PsO, 10 patients with PsA, two patients with GPP, and one patient with EP (Table S1).
Table 2: Bioswitch in patients with psoriasis

| Target before bioswitch | Target after bioswitch |
|-------------------------|------------------------|
| TNF                     | TNF                    |
| IL-23                   | 0                      |
| IL-17                   | 4                      |
| IL-12/23                | TNF                    |
| IL-23                   | 0                      |
| IL-17                   | 3                      |
| IL-23                   | 5                      |
| IL-17                   | 1                      |
| IL-17                   | 2                      |
| IL-23                   | 5                      |
| IL-17                   | 0                      |
| IL-17                   | 4                      |

Abbreviations: IL, interleukin; SD, standard deviation; TNF, tumor necrosis factor.

3.3 | Discontinuation and introduction of biologics

Biologics were discontinued in 14 patients with psoriasis (6.2%; eight males and six females) (Table 3); the average age of the patients was 55.9 ± 15.3 years, including ADA (two cases), IFX (three cases), UST (one case), GUS (two cases), RIS (one case), BRO (one case), IXE (two cases), and SEC (two cases) (Table S2). Of the 14 patients who discontinued biologic therapy, three were due to fear of COVID-19 infection (one patient with PsO treated with BRO, one patient with PsA treated with IFX, and one patient with PsA treated with SEC). Two patients discontinued their therapy autonomously (one patient with PsO treated with RIS and one patient with PsO treated with IXE), and four discontinued therapy due to comorbid malignancies (one patient with PsO treated with GUS, two patients with PsA treated with IFX, and one PsA treated with ADA). By contrast, the introduction of biologics was observed in 27 patients with psoriasis (11.9%; 15 males and 12 females; Table 3); the average age was 51.6 ± 15.1 years, and the average PASI was 7.8 ± 2.3 (n = 23). The introduction of biologics included patients with ADA (two cases), GUS (two cases), RIS (12 cases), TIL (two cases), IXE (two cases), and SEC (seven cases) (Table S3).

For PPP, GUS was not discontinued during the observation period (Table 3); by contrast, the introduction of GUS was observed in four patients (66.7%; one male and three females). The average age of the patients was 52.3 ± 5.9 years, and the average PPPASI was 10.2 ± 7.4. Arthritis was observed in three female cases.

For AD, DUP was discontinued in 10 patients (14.5%; six males and four females; Table 3); the average age of the patients was 30.4 ± 8.1 years. Of the 10 patients who discontinued biologic therapy, one was due to fear of COVID-19 infection. By contrast, the introduction of DUP was observed in in 33 patients (47.8%; 24 males and nine females). The average age of the patients was 35.4 ± 13.7 years, and the average IGA and EASI were 3.3 ± 0.4 and 25.8 ± 9.5, respectively.

For HS, ADA was discontinued in four male patients (80.0%; Table 3); the average age of the patients was 36.5 ± 14.0 years. Of the four patients who discontinued biologic therapy, one was due to fear of COVID-19 infection. By contrast, the introduction of ADA was observed in two male patients (40.0%); the average age of the patients was 31.5 ± 9.5 years. Hurley stage III was observed in both cases.

3.4 | Use of telephone consultations

In this study, a total of 307 patients with inflammatory skin diseases were enrolled; the use of telephone consultations was observed in six patients (0.2%; psoriasis: four cases; AD: two cases; Table S4). The number of use was 1–3 times. There were no patients who continuously used telephone consultations.

4 | DISCUSSION

A recent epidemiological study demonstrated that skin conditions, including psoriasis and AD, increased the risk of COVID-19, but decreased the risk of a severe course. In a nationwide Korean cohort, allergic rhinitis and asthma, but not AD, were associated with an increased susceptibility to SARS-CoV-2 infection and severe clinical outcomes for COVID-19. By contrast, no epidemiological studies have analyzed the association between PPP or HS and COVID-19. Biologics used for treatment of psoriasis may be beneficial against COVID-19, and DUP is not considered to increase the risk of viral infections. The Centers for Disease Control and Prevention classified the following comorbidities as established risk factors for severe COVID-19: cancer, CKD, COPD, Down syndrome, heart conditions, immunocompromised state, obesity, pregnancy, sickle cell disease, smoking, and type 2 DM.

In our study, one male patient who received ADA for the treatment of PsA suffered from COVID-19 during the observation period; he had a history of smoking, as well as type 2 DM and cardiovascular disease. His clinical course was mild, and he exhibited no noticeable symptoms other than a high fever, fully recovering after 7 days of hospitalization. His PsA symptoms were successfully treated with ADA (40 mg; every 2–3 months), and COVID-19 was confirmed 2 months after the last administration; thus, the association between COVID-19 and ADA was unclear.

At the beginning of the COVID-19 pandemic, it was unknown whether biologics should be discontinued due to their immunosuppressive effects. The rate of discontinuation varied within different areas during the pandemic, possibly due to the regional status.
TABLE 3 Discontinuation and introduction of biologics in patients with psoriasis, palmoplantar pustulosis, atopic dermatitis, and hidradenitis suppurativa

|                  | Psoriasis | Palmoplantar pustulosis | Atopic dermatitis | Hidradenitis suppurativa |
|------------------|-----------|-------------------------|-------------------|-------------------------|
| **Discontinuation** |           |                         |                   |                         |
| Number of patients | 14        | 0                       | 10                | 4                       |
| Male : female     | 8:6       | 0:0                     | 6:4               | 4:0                     |
| Age (year), mean ± SD | 55.9 ± 15.3 | -                      | 30.4 ± 8.1        | 36.5 ± 14.0             |
| **Due to fear of COVID-19** | 3         | 0                       | 1                 | 1                       |
| **Introduction**   |           |                         |                   |                         |
| Number of patients | 27        | 4                       | 33                | 2                       |
| Male : female     | 15:12     | 1:3                     | 24:9              | 2:0                     |
| Age (years), mean ± SD | 51.6 ± 15.1 | 52.3 ± 5.9              | 35.4 ± 13.7       | 31.5 ± 9.5              |
| Severity           | PASI 7.8 ± 2.3 (n = 23) | PPPASI, mean ± SD 10.2 ± 7.4 | IGA, mean ± SD 3.3 ± 0.4 | Hurley III |
|                   | Arthritis Female, 3 | EASI, mean ± SD 25.8 ± 9.5 |                   |                         |

Abbreviations: COVID-19, Coronavirus disease 2019; EASI, Eczema Area and Severity Index; IGA, Investigators’ Global Assessment; PASI, Psoriasis Area and Severity Index; PPPASI, palmoplantar pustulosis area and severity index; SD, standard deviation.

of COVID-19 and quality of information that patients acquired.26 In this study, the number of patients with psoriasis who discontinued their biologic drug treatment was 14 (6.2%), while the number of patients with PPP, AD, and HS was zero, 10 (14.5%), and four (80.0%), respectively. Fear of COVID-19 resulted in the discontinuation of biologics in three patients with psoriasis (1.3%), one patient with AD (1.4%), and one patient with HS (20.0%).

Patients with severe inflammatory skin diseases require biologics to control the disease severity, despite the COVID-19 pandemic. For psoriasis, bioswitch was performed in 25 patients (11.0%) during the observation period. Biologic drugs were introduced in 27 (11.9%), four (66.7%), 33 (47.8%), and two (40.0%) patients with psoriasis, PPP, AD, and HS, respectively. A national, multicenter, cross-sectional study showed that the incidence of severe COVID-19 in patients with psoriasis receiving biologics did not increase during the treatment initiation period when compared with those during the maintenance period;27 fortunately, no cases of COVID-19 were observed in our study after bioswitch or treatment initiation. As the region most affected by the infection, a state of emergency was declared in the Tochigi region between 14 January and 7 February 2021; however, this did not seem to affect the use of biologics in our hospital.

As a result of the COVID-19 pandemic, many restrictions have been put in place. In our study, two patients with psoriasis autonomously canceled scheduled visits and discontinued their therapy, possibly due to fear of COVID-19. Telemedicine is therefore one of the most effective strategies to ensure adherence to treatment. The limitations of personal dermatological care of patients with skin diseases during the COVID-19 pandemic can be partially compensated by the extension of telemedicine as a convenient and safe method;28 however, only six patients made use of telephone consultations in our hospital. The number of use was 1–3 times, and there were no patients who continuously used telephone consultations. Additionally, although telephone consultations were performed on the day of the scheduled visits, the patients’ condition could not be visually assessed due to the lack of remote monitoring systems. An established system for telemedicine is thus required during the COVID-19 pandemic, which may change the provision of medical care in the post-COVID-19 era.

The limitations of this study include its nature as a single-center study, the small sample size, limited data from the medical records, retrospective analysis, and the absence of statistical analysis. Nevertheless, the aim of our study was not to investigate the incidence of COVID-19 infection, but to report the use of biologics for inflammatory skin diseases during the COVID-19 pandemic.

In conclusion, we report our experience regarding the use of biologics for psoriasis, PPP, AD, and HS during the COVID-19 pandemic. To our knowledge, this is the first epidemiological study to examine the use of biologics for inflammatory skin diseases during the COVID-19 pandemic in Japan. Confirming the efficacy and safety of biologic use would require more evidence-based data.

CONFLICT OF INTEREST
None declared.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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