Title

A cross-sectional multicenter observational study of psoriatic arthritis in Japanese patients: relationship between skin and joint symptoms and results of treatment with TNF-α inhibitors.

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Running title: Factors affecting PsA and biologic treatment

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ABSTRACT

Psoriatic arthritis (PsA) is an inflammatory arthritis with as yet unclear pathophysiology. This retrospective, multicenter, cross-sectional study was conducted in 19 facilities in western Japan and aimed to identify patients' characteristics and factors that affect the results of treatment with biologic agents. Of 2,116 patients with psoriasis, 285 (13.5%) had PsA. Skin manifestations preceded joint manifestations in 69.8%, the onset was simultaneous in 17.2%, whereas PsA preceded skin manifestations in 2.5%. Peripheral arthritis was most common, occurring in 73.7%, compared with axial disease in 21.8%, enthesitis in 23.5%, and dactylitis in 35.4%. Patients with severe skin manifestations were significantly younger at onset (OR 1.96, P=0.02) and more frequently had axial disease (OR 2.38, P<0.01). Biologic agents were used in 206 patients (72.3%), anti-tumor necrosis factor (TNF)-α antibodies being prescribed first to 157 of them. Anti-TNF-α antibodies were continued by 105 participants and discontinued in 47; the remaining five patients being lost to follow-up. Patients who discontinued anti-TNF-α antibodies were significantly older than those who continued them (55 years vs. 51 years, P=0.04) and significantly older at onset of joint manifestations (50 years vs. 44 years, P=0.01). Multivariate analysis revealed that patients over 50 years significantly more frequently terminated anti-TNF-α antibodies (OR=3.65, p<0.01). In conclusion, patients with PsA and severe skin manifestations have earlier onset and axial disease, which seriously impacts quality of life. Anti-TNF-α antibodies were generally effective enough to continue but less so in patients aged over 50 years. Further detailed research is needed.

Key words:

Psoriasis, psoriatic arthritis, osteoarthritis, epidemiology, multicenter study, Japan.

INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory arthropathy that often affects patients with psoriasis.[1,2] A typical feature of PsA is enthesitis, whereas rheumatoid arthritis is characterized by synovitis[3]. Arthralgia restricts patients' activities of daily living and reduces quality of life[4]. Furthermore, progressive arthritis causes permanent joint destruction in some patients[5]; thus, early diagnosis and preventive interventions are important.

The prevalence of psoriasis is 2%–4% worldwide[6] and 0.10%–0.34% in Japan[7]. It has been reported that only 1% of Japanese patients with psoriasis develop PsA[7]; however, a recent combined rheumatology, orthopedic surgery, and dermatology study revealed that PsA occurs in as many as 14.3% Japanese individuals with psoriasis.[8] Likewise, the most recent survey of the Japanese Society for Psoriasis Research also reported a prevalence of PsA of 15.3% (95% CI, 11.3–19.2).[9] This apparent sharp increase may be attributable to improvements in diagnostic tools and the resultant diagnosis of previously undiagnosed PsA, as well as to the emergence of more effective treatments.

Skin manifestations are present in 70% of patients with PsA, 15% reportedly having joint manifestations prior to skin manifestations and 15% with simultaneous onset[10]. Hence, dermatologists are likely to be the first physicians to encounter arthritis in individuals with psoriasis. We conducted a cross-sectional, multicenter investigation of patients with PsA to determine the current prevalence, severity, and treatment provided at dermatology clinics, and to investigate the factors that influence disease severity and the results of treatment with biologic agents.

MATERIALS AND METHODS

This was a retrospective, multicenter, cross-sectional, observational study in which 19 faculties participated, comprising university hospitals and dermatology departments of general hospitals in western Japan (Kyushu, Okinawa and Chugoku regions). First, the number of individuals with clinically or histopathologically diagnosed psoriasis seen at the participating centers between January 2010 and March 2016 was determined. Next, the medical records of patients diagnosed as having psoriatic arthritis were extracted. Patients with psoriasis and joint manifestations were classified according to the Classification Criteria for Psoriatic Arthritis[11] and further assessed by rheumatologists or orthopedic surgeons specializing in rheumatic disease in 18/19 (95%) of the participating facilities. Data extracted from the medical records included age, sex, height, weight, familial psoriasis, smoking history, age at onset of skin manifestations, age at onset of arthritis, severity of skin and joint manifestations, presence/absence of nail psoriasis, and treatment (immunosuppressants, systemic steroids or biologic agents). The severity of skin manifestations was classified by physicians' global assessment (PGA) as none, almost none, mild, moderate, or severe. For statistical analyses, continuous variables were assessed by Student's *t*-test and categorical data by Fisher's exact test. Logistic regression analysis was employed to exclude confounding factors. All statistical analyses were performed using JMP® Pro 12.2.0 software. Statistical significance was set at $P<0.05$. All comparisons were performed on untransformed data. This research was approved by the Ethics Committee of each facility.

RESULTS

Patient characteristics

The study cohort comprised 2,116 individuals (1,452 men, 664 women) with psoriasis (Table 1). Psoriatic arthritis was diagnosed in 285 of these patients (13.5%; 204 men [14.0%] and 81 women [12.2%]). Data for these 285 patients were analyzed further.

The current median age of the cohort was 54 years; the median age at onset of skin manifestations 35 years; and the median age at onset of arthritis 47 years. The median time from skin manifestations to onset of arthritis was 7 years. Skin manifestations preceded joint manifestations in 70% of the patients, onset was concurrent in 17%, arthritis was diagnosed first in 2%, and skin/joint precedence was unknown in 11%. The median body mass index (BMI) was 24.9 kg/m^2. Psoriasis among second-degree family members was reported by 7.6% of patients. Ninety-six patients (37.1%) were currently smoking (82 men [44.8%], 14 women [18.4%]); whereas 158 patients (61.0%) (131 men [71.6%] and 27 women [5.5%)] had smoked at some time.

Skin manifestations were ≤mild, moderate, and severe in 45.4%, 35.8%, and 18.8% of cases, respectively. Patients with nail manifestations comprised 53.3% of the cohort. Peripheral arthritis was present in 73.7%, axial arthritis in 21.8%, enthesitis in 23.5%, and dactylitis in 35.4%. C-reactive protein (CRP) concentrations were high in 201 patients (76.4%) without infection and 76 (38.6%) had high matrix metalloprotease-3 (MMP-3) concentrations measured at first visit.

With respect to systemic therapy, 102 patients (35.8%) received cyclosporine, 57 (20.0%) systemic steroids, 135 (48.4%) methotrexate, and 207 (72.6%) biologic agents.

Methotrexate was used in 46.9% of the patients receiving biological agents. As of March 2016, when the survey was conducted, four biologic agents were freely available in Japan, namely tumor necrosis factor (TNF)-α inhibitors, (infliximab [IFX] and adalimumab [ADA]), the anti-IL12/23p40 antibody, ustekinumab (UST), and the anti-IL17-A antibody, secukinumab (SEC). The most common first-line biologic agent prescribed was IFX (92 patients, 44.7%) followed by ADA (65, 31.6%), UST (23, 11.2%), SEC (12, 5.8%), and others 14 (6.8%), including clinical trials. TNF-α inhibitors (IFX or ADA) accounted for 157 (76.2%) of all first-line biologic agents. The next most frequently prescribed first-line biologic agents were IFX in nine patients (11.8%), ADA in 31 (40.8%), UST in 22 (28.9%), SEC in 13 (17.1%), and others in one (1.3%, a clinical trial).

Clinical characteristics of PsA and severity of skin manifestations (Tables 2, 3)

When patients were stratified by the severity of skin manifestations (no/mild or moderate/severe), those in the moderate/severe category (n=154) had younger onset of skin manifestations (P=0.01), higher BMI (P=0.02), more frequent nail lesions (P=0.04), more frequent axial disease (P=0.03), and higher serum CRP concentrations (P=0.02) on initial testing than those in the ≤mild category. Multivariate analysis revealed that patients with PsA and moderate/severe skin manifestations were significantly younger (<40 years old) at onset of psoriasis (OR 1.96, P=0.02) and had more frequent axial disease (OR 2.38, P=0.01) than patients with no/mild skin manifestations.

Factors affecting termination of anti-TNF-α antibodies (Tables 4, 5)

Biologic agents were used in 206 patients (72.3%), anti-TNF-α antibodies being the most frequently prescribed first- line biologic agent (157 participants). Anti-TNF-α antibodies

were continued in 105 individuals and discontinued in 47 because of ineffectiveness. The remaining five patients were lost to follow-up and could not be evaluated (Fig. 1).

Patients who discontinued anti-TNF-α antibodies were significantly older than those who continued taking them (55 years vs. 51 years, P=0.04), and also significantly older at onset of joint manifestations (50 years vs 44 years, p=0.01). Multivariate analysis revealed that patients aged over 50 years terminated anti-TNF-α antibodies significantly more frequently (OR=3.65, p<0.01). Gender, BMI, smoking habit, and severity of psoriasis (PGA≧moderate) did not influence the termination of anti-TNF-α.

DISCUSSION

Patients characteristics

We analyzed 285 patients diagnosed as having PsA among 2,116 individuals with psoriasis attending 19 dermatological facilities in the Kyushu, Okinawa and Chugoku regions. The frequency of PsA in this cohort was 13.5%. According to a survey by Yamamoto et al.[12], 10.5% of the 2,581 patients with psoriasis newly attending their dermatology facilities had PsA. Ohara et al.[13] reported that 431 (14.3%) of 3,021 patients with psoriasis had PsA in a joint survey of dermatology, rheumatology and orthopedic surgery institutes. Our results are compatible with these findings, confirming that a high proportion of individuals with psoriasis visiting dermatology clinics have PsA. To the best of our knowledge, our study is the largest multicenter, joint-observation survey including the results of blood tests and treatment modalities of patients attending dermatology departments.

In our patient cohort, skin manifestations preceded arthritis in 69.8%, the onset was

simultaneous in 17.2%, and joint manifestation preceded in only 2.5%. These findings are largely consistent with recent reports, [13,14] however, we found fewer patients with joint precedence. One possible explanation of this discrepancy is that some patients (10.5%) did not know which manifestations arose first; it can be difficult for patients to remember the exact time of onset of joint symptoms.

In the present survey, as many as 53.3% of patients with PsA had nail manifestations. It has previously been reported that risk factors for the onset of PsA include having psoriatic plaques on the scalp, nails, and buttocks[15]. In particular, nail lesions are an important reflection of enthesitis of the extensor tendon attached to the distal phalanx, which is located immediately under the nail matrix[16]. We previously reported that nail psoriasis is an independent risk factor for PsA in a cross-sectional study of the Fukuoka University Psoriasis Registry (OR, 5.05; 95% confidence interval [CI] 2.63–9.96)[17]. Also, Zenke et al. reported that the presence of transverse grooves is significantly associated with PsA possibly reflecting distal interphalangeal arthritis and enthesitis.[18]

Body mass index

The median BMI was 24.9 kg/m^2. Obese patients reportedly are at greater risk of developing PsA in Europe and the United States[19]. However, in our previous research on Japanese patients, we did not find a positive relationship between BMI and the incidence of PsA; however, individuals with psoriasis had a larger BMI than controls. In PSOLAR[20], a worldwide longitudinal psoriasis registry in North America, Europe and Latin America, individuals with psoriasis have a mean BMI of 30.9 kg/m^2. In contrast, the BMI of such individuals is lower in Japan.[21,22] The correlation between BMI and incidence of PsA may

depend on the degree of obesity and/or on race.

Smoking history

Participants with a current smoking habit comprised 44.8% of men and 18.4% of women, whereas 71.6% of men and 35.5% of women had a smoking history. These smoking rates are clearly higher than the Japanese national average (30.2% of men and 8.2% of women, http://www.mhlw.go.jp/bunya/kenkou/eiyou/dl/h28-houkoku-06.pdf). There have been several reports on the relationship between smoking and the onset and severity of psoriasis.[23,24] Whether people with a smoking habit have a greater incidence of PsA than those who do not smoke has not been established; in our previous study we found no differences in smoking rates. In the present study, smoking history did not influence the efficacy of TNF inhibitors. Although smoking seems to be related to the onset of psoriasis itself, it may be irrelevant to the onset or severity of PsA.

Type of arthritis

Of the types of PsA, peripheral arthritis was most common, occurring in 73.7% of patients, whereas 21.8% had axial disease, 23.5% enthesitis, and 35.4% dactylitis. We found a lower incidence of axial disease and enthesitis than did Ohara et al.[13] This may be attributable to the sample population. Subjects in our study include patients who visited dermatology at first, and patients with severe joint symptoms without significant skin lesions may not be included. Close co-operation between rheumatologists and orthopedic surgeons may help to standardize the diagnosis.

Laboratory data

High CRP concentrations were found in 76.4% of patients and high MMP-3 concentrations in 38.6%. Moderate/severe skin manifestations were associated with high CRP (P=0.02) according to univariate analysis (Table 2). Asahina et al.[25] reported that individuals with high CRP are more likely to have PsA, a greater body surface area, higher severity index scores. CRP concentrations may reflect both the severity of skin manifestations and presence of the complication of PsA in individuals with psoriasis.

Severity of skin manifestations and arthritis

In multivariate analysis, we found that patients with PsA and moderate/severe skin manifestations were significantly younger (<40 years) at onset of psoriasis (OR 1.96 P=0.02), and had more axial disease (OR2.38, P=0.01) than those with no/mild skin manifestations. Axial disease is a more severe form of PsA; thus, dermatologists should particularly check for this condition when seeing patients with younger onset severe psoriasis.

Treatment

In our survey, a large proportion of PsA patients (72.3%) were treated by biologics. This may partly be because methotrexate is not yet labeled for psoriasis and PsA in Japan. Originally, TNF-α inhibitors were recommended as the first-line biologic agents against PsA[26]; however, more recently other classes of biologic agents have also been recommended[27]. As expected, in our study TNF-α inhibitors (IFX/ADA) were the most frequently employed biologic agent for first-line treatment (76.2% of patients), 52.6% of participants receiving them as a second-line treatment. TNF inhibitors were continued in 105 individuals, and discontinued in 47. They were terminated significantly more

frequently in patients aged over 50 years than in younger patients (OR=3.65, P<0.01). Although the effect was modest, the older age may suggest coexistence of other refractory conditions. Distal interphalangeal joints are the most typically involved joints in PsA, but are also frequently affected by osteoarthritis (OA). Moreover, these two arthritis types affect many joints in common, including the proximal interphalangeal joints, knee, and cervical vertebrae. Marco et al.[28] reported that 56.3% of individuals with psoriasis vulgaris had OA and 11.2% had a combination of OA and PsA. Chronic OA can often be distinguished from PsA by X-radiography, but this is not always possible for OA with bone erosion. MacGonagle et al.[29] have discussed the possibility of an overlapping OA–PsA category that is susceptible to failure of TNF-α or IL23/17 inhibitors. Our results are consistent with the hypothesis that patients with late onset joint manifestations may also have OA. Acute inflammation may resolve with biologic agents in such patients; however, pain caused by OA may not be mitigated, leading to the secondary failure of biologics. Further investigation of the pathophysiology of PsA and OA is needed to determine the optimal treatment for patients of all ages.

In conclusion, in our large survey 13.5% of individuals with psoriasis had PsA. Our finding that axial disease is present more frequently in patients with moderate/severe manifestations is new, as is the finding that TNF inhibitors are less effective in older patients with PsA, suggesting the presence of other overlapping conditions. Our study's limitations include that the cohort included only Japanese individuals and that the study design was cross-sectional and lacked longitudinal observation. A further cohort study is needed.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Table 1. Patient characteristics

Clinical characteristics

Sex, Male	204 (71.6%)
Age, years [IQR]	54.0 [43.0-64.0]
BMI, kg/m^2	24.9 [22.3-27.6]
Familial psoriasis	20 (7.6%)
Smoking (current or past)	158 (61.0%)
Age at psoriasis onset, years	35.0 [26.0-49.0]
Age at arthritis onset, years	47.0 [36.0-57.0]
Latency time to onset of arthritis, years	7.0 [1.0-15.0]
Timing of onset	
Psoriasis first	199 (69.8%)
Simultaneous	49 (17.2%)
Arthritis first	7 (2.5%)
Unclear	30 (10.5%)
PGA (skin symptoms)	
none or mild / moderate / severe	128 (45.4%)/ 101 (35.8%)/ 53 (18.8%)
Nail lesions	152 (53.3%)
Joint symptom	
Peripheral arthritis	210 (73.7%)
Axial disease	62 (21.8%)
Enthesitis	67 (23.5%)
Dactylitis	101 (35.4%)

Blood tests	
Elevated C-reactive protein	201 (76.4%)
Elevated matrix metalloprotease-3	76 (38.6%)
Treatment history	
Cyclosporine	102 (35.8%)
Systemic steroids	57 (20.0%)
Methotrexate	135 (48.4%)
Biological treatment	206 (72.3%)
First biologics	
Infliximab	92 (44.7%)
Adalimumab	65 (31.6%)
Ustekinumab	23 (11.2%)
Secukinumab	12 (5.8%)
Others including clinical trial	14 (6.8%)
Second biologics	
Infliximab	9 (11.8%)
Adalimumab	31 (40.8%)
Ustekinumab	22 (28.9%)
Secukinumab	13 (17.1%)
Others including clinical trial	1 (1.3%)

Sample size, n=285. Data are presented as median with interquartile range (IQR) or n (%).BMI, body mass index; PGA, physician's global assessment.

Table 2. Clinical characteristics in individuals with psoriasis according to severity of skin manifestations

	none/mild (n=128)	moderate/severe (n=154)	P value
Male, n (%)	86 (67)	115 (75)	0.19
Age, mean, n (SD), years	55 (14)	53 (13)	0.19
Age at psoriasis onset, mean (SD), years	40 (16)	35 (15)	0.01*
Age at arthritis onset, mean (SD), years	48 (14)	45 (14)	0.08
Latency time to onset of arthritis, years	8 (9)	10 (10)	0.06
BMI, mean (SD), kg/m^2	24.6 (4)	26.0 (5)	0.02*
Family history, n (%)	9 (8)	11 (7)	1.00
Smoking (current or past), n (%)	68 (59)	89 (63)	0.52
Nail lesions, n (%)	60 (47)	92 (60)	0.04*
Peripheral arthritis, n (%)	95 (74)	114 (74)	1.00
Axial disease, n (%)	20 (16)	41 (27)	0.03*
Enthesitis, n (%)	28 (22)	38 (25)	0.67
Dactylitis, n (%)	42 (33)	56 (36)	0.61
Elevated CRP, n (%)	83 (69)	116 (82)	0.02*

Sample size, n=282. Results are expressed as odds ratio with 95% confidence interval (CI) in parentheses. BMI, body mass index; CRP, C-reactive protein. P-values with an asterisk (*) are statistically significant.

Table 3. Associations between clinical characteristics of PsA and severity of skin manifestations according to multivariate analysis

	Odds ratio (95% Cl)	P value
Male	1.14 (0.61-2.12)	0.68
Age at psoriasis onset<40, years	1.96 (1.11-3.47)	0.02*
BMI≥25, kg/m^2	1.71 (0.97-3.02)	0.06
Nail lesions	1.54 (0.87-2.72)	0.14
Axial disease	2.38 (1.19-4.75)	0.01*
Elevated CRP	1.95 (1.00-3.78)	0.05

Sample size, n=225. Results are expressed as odds ratio with 95% confidence interval (CI) in parentheses. BMI, body mass index; CRP, C-reactive protein. P-values with an asterisk (*) are statistically significant.

Table 4. Factors affecting termination of anti-TNF-α antibodies

	continuing (n=105)	discontinued (n=47)	P value
Male, n (%)	78 (74)	31 (66)	0.33
Age, mean, n (SD), years	51 (13)	55 (11)	0.04*
Age at psoriasis onset, mean (SD), years	35 (15)	37 (16)	0.43
Age at arthritis onset, mean (SD), years	44 (13)	50 (12)	0.01*
Latency time to onset of arthritis, years	8 (10)	12 (11)	0.06
BMI, mean (SD), kg/m^2	26.2 (5)	26.0 (5)	0.88
Family history, n (%)	8 (9)	3 (7)	1.00
Smoking (current or past), n (%)	62 (65)	26 (56)	0.36
Psoriasis, PGA≥moderate, n (%)	58 (56)	30 (64)	0.38
Peripheral arthritis, n (%)	81 (77)	35 (74)	0.84
Axial disease, n (%)	20 (19)	11 (23)	0.52
Enthesitis, n (%)	30 (29)	16 (34)	0.57
Dactylitis, n (%)	41 (39)	17 (36)	0.86
Elevated CRP, n (%)	74 (76)	38 (84)	0.38

Data are presented as means with standard deviations (SD) or percentages (%). Differences were tested by the unpaired Fisher's exact probability test. TNF, tumor necrosis factor; BMI, body mass index; CRP, C-reactive protein; P-values with an asterisk (*) are statistically significant.

Table 5. Factors affecting termination of anti-TNF-α antibodies according to multivariate analysis

	Odds ratio (95% Cl)	P value
Male	0.93 (0.39-2.17)	0.86
Age≥50, years	3.65 (1.62-8.23)	<0.01*
BMI≥25, kg/m2	2.04 (0.94-4.47)	0.07
Smoking	0.70 (0.31-1.58)	0.39
Psoriasis, PGA≥moderate	1.25 (0.58-2.69)	0.57

Sample size, n=136. Results are expressed as odds ratio with 95% confidence interval (CI) in parentheses. TNF, tumor necrosis factor; BMI, body mass index; PGA, physician's global assessment. P-values with an asterisk (*) are statistically significant.

Figure 1. Flowchart showing the flow of studies