Psoriatic arthritis in Japan: difference in clinical features and approach to precision medicine

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Received and accepted on June 29, 2016

Clin Exp Rheumatol 2016; 34 (Suppl. 98): SXX-SXX.

Key words: psoriatic arthritis, biological DMARD, cytokine, treatment

Funding: This work was supported in part by a Grant-In-Aid for Scientific Research from the Ministry of Health, Labor and Welfare of Japan, the Ministry of Education, Culture, Sports, Science and Technology of Japan, Japan Agency for Medical Research and Development, and the University of Occupational and Environmental Health, Japan, through UOEH Grant for Advanced Research.

Competing interests: Y. Tanaka, has received consulting fees, speaking fees, and/or honoraria from Abbvie, Chugai, Daiichi-Sankyo, Bristol-Myers, Mitsubishi-Tanabe, Astellas, Takeda, Pfizer, Teijin, Asahi-kasei, YL Biologics, Sanofi, Janssen, Eli Lilly, GlaxoSmithKline and has received research grants from Mitsubishi-Tanabe, Takeda, Daiichi-Sankyo, Chugai, Bristol-Myers, MSD, Astellas, Abbvie, Eisai.

ABSTRACT

Psoriatic arthritis (PsA) is a chronic and progressive inflammatory arthritis that is common among patients with psoriasis, often resulting in permanent damage of joints and spines. Recent report indicates that the prevalence of PsA among Japanese patients with psoriasis is 14.3%, which is similar or slightly less than that of PsA in Caucasian, 6-42%. Skin disorders precede arthritis in 60-80% of Japanese patients with PsA and oligoarthritis or polyarthritis is the dominant pattern of them. The genotypic backgrounds appear different among Japanese and Caucasians. Biological DMARDs (bDMARDs) targeting cytokines IL-12/IL-23, TNF and IL-17 involved in the pathogenesis of PsA, have been emerging for the treatment. Although background characteristics are various among studies, anti-IL-17 seemed to be slightly better in Japanese than in global, whereas anti-IL-12/23 and anti-TNF tended to be better in global than in Japanese. Because PsA is a clinically heterogeneous disorder, we have tried to classify PsA by phenotypic differences of peripheral lymphocyte using 8-color flow cytometry and found that PsA can be divided to four types, activated Th17-dominant, Th1-dominant, both of them and neither of them. We currently try to treat patients with different bDMARDs based on the difference of lymphocyte phenotype, which may lead to precision medicine of PsA.

Introduction

Psoriasis is a chronic inflammatory and immune-mediated skin disorder often with systemic manifestation including spondylarthritis (SpA). Psoriatic arthritis (PsA) is a representative SpA and the chronic and progressive inflammatory arthritis often results in permanent joint damage and disability (1-4). It has been well known that the incidence of psoriasis and PsA is lower in Japan than in the Western countries; it might however be a wrong knowledge, based on the historically biased information in Japan.

A nationwide study using the Japanese national claims database reported that 565,903 patients with psoriasis were identified in 2010 and that the prevalence of psoriasis was 0.44% in Japan which was lower than the 1-4% observed in the Western countries (Table I) (5, 6). Male to female ratio was 1.44 and average age was 57 years, which contrasted with the almost equal distribution of males and females in the Western countries. The family accumulation of psoriasis was 4-5% in Japanese, whereas it was 20-40% in Caucasians. On the other hand, the 0.12% prevalence of palmoplantar pustulosis (PPP) was observed in Japan and it was higher than the 0.01– 0.05% found in Western countries. About 20% of these patients have psoriasis.

However, in the database, the incidence of PsA and pustulotic arthro-osteitis (PAO) was only 1.9% and 0.1% of psoriasis, respectively. Moreover, the prevalence of diabetes mellitus, hyperlipidemia and hypertension was 3.1%, 3.2% and 5.1%, respectively, although body weight and body mass index of patients with PsA are usually higher than gender- and age-matched healthy population (5). Thus, we realize that the incident ratio of PsA and systemic comorbidities appears to be much lower than our experience as well as that in the Western countries (7). It can be assumed that the presence of arthritis and comorbidities might be underestimated. The systemic comorbidities including arthritis in patients with psoriasis may have been missed, because the almost all patients with not only psoriasis but also PsA have historically been under the care of dermatologists, but not rheumatologists, in Japan.

Clinical features of PsA in Japan

A Japanese group of rheumatologists and dermatologists has recently reported epidemiological data of PsA (8). A total of 3021 patients with psoriasis were enrolled in the cohort and 431 patients were diagnosed by rheumatologists, based on clinical findings, with a mean prevalence of 14.3% (ranged 8.8 to 20.4%). It is different from that shown in the Japanese national database as above (1.9%), but it is similar to that of PsA in Caucasian, 6-42%. The prevalence of comorbidities was also similar to those in the Western countries, but is completely different from that in the national database; hyperlipidemia (43.9%), diabetes (15.1%), hyperuricemia (20.9%), hypertension (23.2%) and liver dysfunction (29.2%). Hyperlipidemia was numerically more prevalent in the PsA population than in the general population. Additionally, compared to patients without hyperlipidemia, patients with hyperlipidemia had higher body mass index (BMI), higher rate of hyperuricemia, hypertension and liver dysfunction. Thus, judging from data of rheumatologists, the epidemiological data regarding PsA in Japan is similar to that in the Western countries, which was different from our conventional knowledge.

In the Japanese epidemiological data, the median age at onset of psoriasis and arthritis was 37.0 and 45.0 years, respectively, and psoriasis proceeded arthritis in 72.9% of them and 11.0% was vice versa (8). Arthritis type was polyarthritis (60.4%), oligoarthritis (28.6%) and distal interphalangeal arthritis (8.9%). Among PsA 34.6% revealed axial symptoms and imaging findings regarding peripheral arthritis (66.4%) and axial joints (40.9%) were observed. It is note worthy that 89.7% of patients fulfilled CASPAR criteria for PsA, 98.2% fulfilled ASAS criteria for peripheral SpA and 63% fulfilled ASAS criteria for axial joint SpA. Skin lesion was psoriasis vulgaris (91.9%) and pustular psoriasis (6.2%). Thus, no large difference in age, age at onset, distribution of arthritis and skin disease type was observed between these Japanese data and reports from the Western countries.

Table I. Epidemiological differences in PsA between Japanese and Caucasians.

Factors	Japanese	Caucasians
Prevalence of psoriasis	0.44%	1-4%
Prevalence of PPP	0.12%	0.01-0.05%
Gender	Male 1.44 (1.2-1.6)	Almost equal
Family accumulation	4-5%	20-40%
Major HLA	HLA-A2, B27, B46, DR8	HLA-B16, B17, B27, Cw6
TNF polymorphism	Nothing	TNF-α-238G/A
Arthritis / psoriasis	14.3%	8-20%

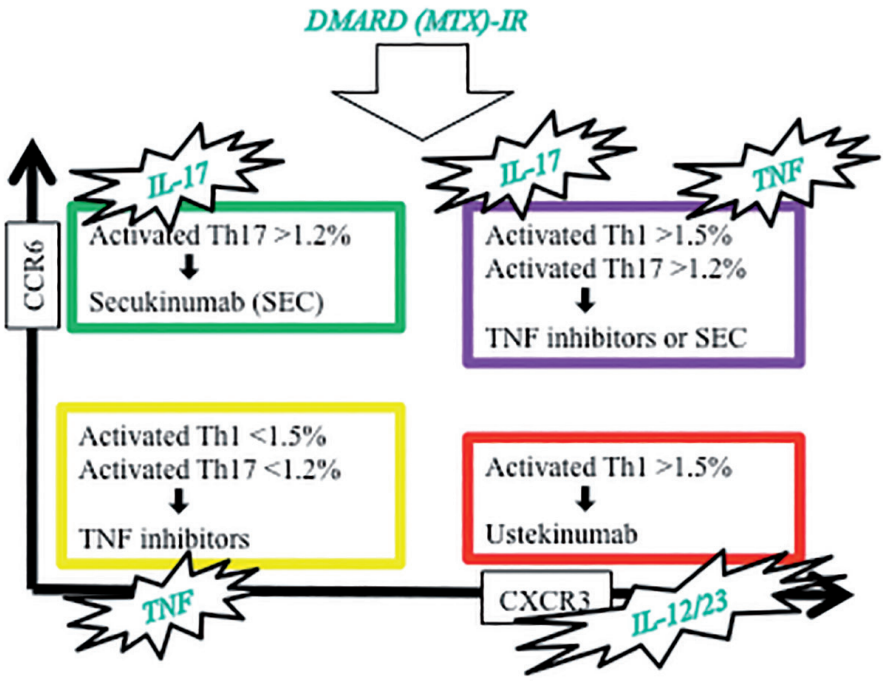

Fig. 1. Precision medicine using bDMADS based on lymphocyte phenotype in patients with PsA (FLOW study).
Based on lymphocyte phenotype, bDMARDs can be differential selected as the following; ustekinumab for patients with activated Th1-dominant, secukinumab for patients with activated Th17-dominant, adalimumab for patients with both-high and with major joint complaint, secukinumab for patients with both-high and with major skin complaint and adalimumab for patients with both-low.

However, male to female ratio is ranged 1.2 to 1.6 in multiple reports and 1.44 in the national database above, which contrasted with the almost equal distribution of males and females in the Western countries (9). Also, familiar accumulation of PsA is 4-5% in Japanese, whereas it is 20-40% in the Caucasians. Significant increase is noted in HLA-A2, -B27, -B46 and -DR8 in patients with PsA in Japan (10), whereas HLA-B16, -B17, -B27 and -Cw6 are known to be associated with PsA in Caucasians. One report indicates that the vast majority of PsA patients in Japan possess HLA-A2 (11). The association with HLA is various among Asian people, but HLA-B27 is not associated with PsA in Israel, Korea and Taiwan (12). There is marked difference in TNF gene polymorphism between Japanese and Caucasians. TNF is one of the most important cytokines during pathological processes of PsA and rheumatoid arthritis and gene loci of TNF-α locate within the HLA region. However, studies from Japan did not find any association between TNF gene polymorphism and PsA (13), whereas polymorphism of TNF-α is associated with PsA, especially joint erosion in early PsA in Caucasians. The association of gene polymorphism of HLA-Cw0602 and class I MHC chain-related gene A with PsA was also reported in Caucasians. Thus, the genotypic back-

grounds appear different among Japanese and Caucasians and differences in some clinical features may be due to such genetic differences and/or environmental exposures (14).

Table II. Characteristics of 44 patients with PsA at the initiation with bDAMRDs.

Base line characteristics	Means ± SD
Age	47.7 ± 12.8
Gender	Male 27 (61.3%)
Disease duration	139 ± 109 months
On set	Skin ahead 28, arthritis ahead 5, simultaneous 11
Treatment history of skin	Topical therapy (GC, PUVA) 19, nothing 21
Treatment history of arthritis	MTX 38, CsA 9, TAC 3, GC 6, SASP 8, IFX 11, ADA 2, UST 3
Concomitant drugs	MTX38, others 2, nothing 4
Comorbidities	Diabetes mellitus 8, hypertension 7, chronic kidney disease 2, hyperlipidemia 2
DAS28(ESR)	4.38 ± 1.22
SDAI	17.7 ± 11.0
PASI score	8.8 ± 12.3
Used biological DMARD	IFX 15, ADA 17, UST 7, SEC4

Response to biological DMARDs in PsA

Various cytokines such as IFN-γ, IL-12, IL-23, IL-17, IL-6 and TNF-α play a pivotal role in the pathogenesis of psoriasis and PsA by recruiting pro-inflammatory cells and biological DMARDs (bDMARDs) targeting these cytokines have been emerging for the treatment (3). The recommendations address conventional synthetic DMARDs (csDMARDs) as an initial therapy after failure of NSAIDs, followed, if necessary, by a bDMARD, including anti-TNF antibodies adalimumab or infliximab, an anti-IL-12/23 antibody ustekinumab and an anti-IL-17 antibody secukinumab (15). However, based on the Japan national claims database in which almost all patients with psoriasis visit dermatologist, only 0.8% of them were treated with bDMARD, whereas 81.4% and 59.6% were treated with topical corticosteroid and topical vitamin D, respectively (5).

The clinical trials of bDMARDs for psoriasis were also performed by dermatologists in Japan. A phase 2/3 study of adalimumab in patients with moderate to severe chronic plaque psoriasis was done by an adalimumab M04-688 study group (16). Patients were randomized to receive adalimumab 40 mg every other week (eow) monotherapy, adalimumab 40 mg with loading by 80 mg at week 0, 80 mg eow or placebo. At week 16, a 75% or greater improvement in psoriasis area and severity index (PASI 75) response rates of adalimumab 40mg were 57.9%, which are significantly greater than those of placebo (4.3%). In global phase 3 REVEAL trial, 1212 patients with moderate to severe psoriasis were randomized to adalimumab 40 mg eow or placebo (17). PASI 75 response rates of adalimumab and placebo were 82.6% and 16.3%, respectively at week 16. Efficacy of ustekinumab in Japanese patients with moderate to severe plaque psoriasis was assessed in a phase 2/3 study (18). PASI 75 response rates to ustekinumab 45 or 90 mg and placebo were 59.4%, 67.7% and 6.5%, respectively at week 12. In a global phase 3 POENIX 2 study, PASI 75 response rates to ustekinumab 45 or 90 mg and placebo were 66.7%, 75.7% and 3.7%, respectively at week 12 (19). Thus, responses to adalimumab or ustekinumab seem to be lower in the Japanese study than the global study, although patients' characteristics at baseline were different between these two studies.

In contrast, Japanese patients were also enrolled in a global phase 3 ERASURE study of secukinumab in patients with moderate to severe plaque psoriasis (20). PASI 75 response rates to secukinumab 150 mg every 4 weeks (q4w), 300 mg q4w and placebo were 4.5%, 71.6% and 81.6%, respectively at week 12 in the global study. PASI 75 response rates to 150mg and 300mg at week 52 were 60.1% and 74.3%. Thus, each dose of secukinumab was significantly efficacious than placebo. In the ERASURE study 87 patients were enrolled from Japan (21). PASI 75 at week 12 of secukinumab 150mg and 300mg was 86.2 and 82.8%, respectively, which was significantly greater than placebo (6.9%). PASI 75 response rates to 150mg and 300mg at week 52 were 75.9% and 88.2%. Thus, secukinumab appears to reveal slightly better in the Japanese group than the global one.

However, arthritis was not assessed at all in any of Japanese studies and prevalence of PsA among psoriasis enrolled in the studies was not reported. We, therefore, assessed the efficacy of bDMARDs in patients with PsA who were enrolled in the FIRST registry in our Department. All the patients with rheumatoid arthritis who initialized or switched bDMARDs were hospitalized and enrolled in the FIRST registry in order to check indication/contraindication and inclusion/exclusion criteria or to select appropriate bDMARDs. Patients with PsA treated with bDMARDs have been also registered since 2011 and 44 patients are on the list (Table II). Mean age was 48 years old, male-female ratio was 1.3, mean disease duration was 140 months, mean DAS28 (ESR) was 4.4, mean SDAI was 17.7 and mean PASI score was 8.8. Skin lesion proceeded to arthritis in 64% of them and 86% of them concomitantly used methotrexate. PASI score was significantly decreased from 8.8 to 3.4 and PASI 75 response ratio was 52% at month 6. DAS28 (ESR) and simplified disease activity index (SDAI) were significantly reduced from 4.4 to 2.8 and from 17.7 to 8.6 at month 6, respectively, by bDMARDs. At month 6, 50% and 48% reached DAS28 (ESR)-remission and SDAI-remission, 66% and 66% reached DAS28-low disease activity (LDA) and SDAI-LDA, respectively. Although the difference among bDMARDs was not found with the limited number, it is confirmed that bDMARDs efficiently improved arthritis as well as skin lesion in Japanese PsA patients.

Is precision medicine possible for PsA?

Although head-to-head comparison was not performed, all the bDMARDs targeting TNF, IL-17 or IL-12/IL-23 are almost similarly effective for patients with PsA from results of multiple global clinical phase 3 studies (22). However, it remains unclear how we can distinguish responders to each bDMARD before the intervention.

We have recently assessed phenotype of peripheral lymphocyte in patients with PsA using 8-color flow cytometry according to a human immunology project of NIH/FOCIS (FLOW study) (23). Lymphocyte phenotypic analyses are often useful to distinguish immunological characteristics of each patient because they reveal the followings; 1) differentiation stage such as naïve T cells or memory T cells, 2) lineage or functional difference such as Th1, Th2 or Th17, 3) activation status or cellular signaling pathways of lymphocytes. However, there were no significant differences in proportion of $CD3^+CD4^+CD45RA^-CXCR3^+CCR6^-$ Th1 cells, Th17 cells, Treg cells and other subsets among $CD4^+$ T cells between healthy volunteers and patients with PsA.

On the other hand, we have also realized that outliers of lymphocytic phenotypes were observed in some patients with PsA. For instance, some patients possessed high ratio of $CD3^+CD4^+CD45RA^-CXCR3^+CCR6^-CD38^+HLA\text{-}DR^+$ activated Th1 cells among $CD4^+$ T cells. Some patients beard activated Th17 cell-dominancy in their peripheral $CD4^+$ T cells. Furthermore, both activated Th1 cells and activated Th17 cells increased in some patients, whereas in some patients both of them are comparable to those in healthy volunteers. Thus, patients with PsA can be divided into 4 patterns in the phenotypes of peripheral $CD4^+$ T cells: 1) activated Th1-dominant, 2) activated Th17-dominant, 3) activated Th1/Th17-high or 4) activated Th1/Th17-low. Based on lymphocyte phenotype, bDMARDs can be differentially and strategically selected as the followings; ustekinumab for patients with activated Th1-dominant, secukinumab for patients with activated Th17-dominant, adalimumab for patients with both-high and with major joint complaint, secukinumab for patients with both-high and with major skin complaint and adalimumab for patients with both-low. This study has just started, but preliminary results appear successful. For instance, secukinumab was selected in a PsA patient with both activated Th1/Th17 high and with severe psoriasis and these phenotypes markedly reduced from peripheral $CD4^+$ T cells and SDAI-remission and PASI=0.0 were successfully obtained at month 6 after the treatment. The accumulation of data in multiple patients is prerequisite to get good evidence, but it can be expected that this strategic trial will lead to precision medicine of PsA.

Acknowledgements

The authors thank all medical staff in all institutions for providing the data.

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