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SPONDYLOARTHRITIS (M KHAN, SECTION EDITOR)

Optimal Biologic Selection for Treatment of Psoriatic Arthritis: the Approach to Precision Medicine

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Abstract

Purpose of Review This review describes previously reported findings on optimal biologic agent selection for psoriatic arthritis (PsA) treatment and outlines our approach to developing precision medicine techniques for targeted treatment of this disease.

Recent Findings Clinical trials have reported the effectiveness of numerous biologics with different targets, such as tumor necrosis factor-α, interleukin (IL)-17A, IL-17 receptor, IL-12/23(p40), and IL-23(p19) for the treatment of PsA. Although several studies have suggested specific predictors of treatment responses to each biologic, how biologics are differentially chosen in each patient remains unclear. Recent reports indicate the possibility of treating PsA using precision medicine based on individual immunological phenotypes.

Summary Because PsA exhibits numerous symptoms, selecting an optimal biologic for each patient may be important. The establishment of appropriate selection guidelines will require further clinical trials.

Keywords Psoriatic arthritis · Biologics · Treatment · T cells · Precision medicine

Introduction

Psoriatic arthritis (PsA) is one of the most common comorbidities of psoriasis, affecting 0.3–1.0% of the global population [1]. While the primary pathological condition of PsA is enthesitis, various clinical symptoms are common, including skin lesions, peripheral arthritis, spondylarthritis, nail lesions, dactylitis, and uveitis. Although synovitis resembling rheumatoid arthritis (RA) may be present, RA and PsA result from different pathogenetic mechanisms. In RA, synovitis first occurs, leading to destruction of bone and cartilage. In contrast, PsA first manifests as enthesitis, which spreads throughout the enthesis organ and secondarily causes entheseal and periarticular abnormalities [2, 3]. PsA is associated with high rates of comorbid lifestyle-related diseases and an increased incidence of cardiovascular events associated with them. Thus, PsA may markedly impair the quality of life because of its various clinical symptoms and high rates of comorbid lifestyle-related diseases [4].

A variety of cytokines, including interferon (IFN)-γ, interleukin (IL)-12, IL-23, IL-17, IL-6, and tumor necrosis factor (TNF)-α, have been shown to play an important role in the pathogenesis of PsA [5]. Biologics targeting TNF-α, IL-17A, IL-17 receptor, IL-12/23(p40), and IL-23(p19) are already available [6].

After the efficacy of etanercept (ETN) was first reported [7], the efficacy of adalimumab (ADA) [8], infliximab (IFX) [9, 10], golimumab [11], and certolizumab pegol [12] was observed in large-scale clinical trials. The efficacy of biologics targeting T helper (Th) 17 cells or IL-17 has also been reported. The IL-12/23 inhibitor ustekinumab (UST) was shown to be effective in the Phase III PSUMMIT I and PSUMMIT II trials [13–15]. Further studies have demonstrated the efficacy of the IL-23 inhibitor guselkumab (GSL) [16], the IL-17A inhibitors secukinumab (SEC) [17–19] and ixekizumab (IXE) [20–23], and the anti-IL-17 receptor antibody brodalumab (BRO) [24]. All of these biologics except BRO have been shown to inhibit osteoclastic activity.

Despite the availability of these numerous biologics, some patients are resistant to treatment. While these biologics target different molecules, no protocols have been established for selecting the optimal biologics for a particular patient. This

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report reviews findings that may guide the selection of optimal biologic agents for the treatment of PsA and outlines an approach to using precision medicine to choose individualized treatment based on the PsA patient's immunological phenotype.

Biologics for the Treatment of Psoriatic Arthritis

The European League Against Rheumatism (EULAR) 2015 recommendations for the management of PsA [25] state that the treatment objective is to reach remission (the absence of symptoms and signs) or at least low (or minimal) disease activity. If this treatment objective is not achieved, transition to the next phase is recommended. Similarly, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2015 Treatment Recommendations for Psoriatic Arthritis [26] suggest implementation of the treat-to-target approach.

Accordingly, the Tight Control of Psoriatic Arthritis (TICOPA) study examined 105 patients in the standard care group every 4 weeks to determine whether they achieved the treatment objective [minimal disease activity (MDA)] and compared them with 101 patients in the tight control group, whose treatment was escalated if the objective was not achieved. The proportion of patients achieving the primary endpoint, which was 20% improvement at 48 weeks according to the American College of Rheumatology (ACR) response criteria (ACR20), was significantly higher in the tight control group (odds ratio, 1.91; 95% confidence interval, 1.03–3.55; $P = 0.0392$). Thus, this study demonstrated the usefulness of the tight control and treat-to-target approaches [27]. Based on these studies, present strategies for treating PsA aim to achieve MDA [28].

The EULAR treatment recommendations [25] indicate the use of biologics in Phase III and IV after Phase I use of nonsteroidal anti-inflammatory drugs and/or local steroid injection and Phase II use of methotrexate (MTX) (leflunomide/sulfasalazine or cyclosporine A if MTX is contraindicated). The GRAPPA treatment recommendations [26] indicate that peripheral arthritis, skin lesions, and dactylitis should be first treated with synthetic disease-modified anti-rheumatic drugs (DMARDs) and phosphodiesterase (PDE)-4 inhibitors, followed by biologics. In both treatment recommendations, the use of biologics without treatment with synthetic DMARDs or PDE4 inhibitors is recommended when spondylarthritis and enthesitis are the predominant symptoms. In other words, treatment tailored to the pathological conditions of each patient is recommended. Regarding biologics types, the early use of TNF-i is recommended for patients significantly affected by peripheral arthritis who show an insufficient response to synthetic DMARDs or for those significantly affected by spondylarthritis or enthesitis. IL-12/23(p40) and IL-17 inhibitors are recommended for patients with an insufficient response to MTX by EULAR 2015; however, TNF-i is regarded as a preferable first choice. GRAPPA 2015 treatment recommendations regard IL12/23 and IL-17 inhibitors as comparable to TNF-i [29].

As previously described, implementing the treat-to-target approach and the use of biologics are recommended for treating PsA, as with RA. However, as might be expected, neither the EULAR nor GRAPPA treatment recommendations indicate how to determine which biologics to use. Based on previous clinical trials, UST appears inferior to other biologics in treating joint symptoms. In contrast, IL-17 inhibitors have been demonstrated to be nearly as effective as TNF-i in terms of the rate of improvement in joint symptoms. In fact, the 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis [30] contains the following description: Treat with a TNF-i biologic over an IL-17-i biologic; treat with a TNF-i biologic over an IL-12/23i biologic; treat with an IL-17-i biologic over an IL-12/23-i biologic. However, the level of evidence underlying these guidelines is considered to be very low. Indeed, the efficacy of TNF-i and SEC is considered to be relatively comparable based on the results of the SPIRIT-P1 study [20], although the study did not directly compare the efficacy of these drugs. Many large-scale clinical trials vary in terms of inclusion criteria for patients, sample size, and other factors, making comparisons difficult. Thus, whether IL-17 inhibitors are actually as effective as other biologics is unclear. The possibility that they are more effective than other biologics such as TNF-i cannot be completely ruled out.

An indirect comparative study of ADA and SEC in TNF-i-naive PsA patients selected from the FUTURE II study (SEC vs. placebo; $n = 299$) and the ADEPT study (ADA vs. placebo; $n = 313$) with matching data [31] reports higher ACR response rates for SEC from 16 to 48 weeks. However, because this investigation is not a direct comparative study, determining which biologic is superior based on these results is not possible. The study also provides no clear evidence indicating differential use of biologics according to individual patients. A randomized, double-blind controlled study comparing ADA and SEC monotherapies for PsA is presently being conducted (A randomized double-blind, active control, multicenter study to evaluate the efficacy at week 52 of secukinumab monotherapy compared with adalimumab monotherapy in patients with active psoriatic arthritis [EXCEED]: ClinicalTrials.gov Identifier: NCT02745080). We expect new findings that will guide the differential use of biologics.

Optimal Biologic Selection for Treatment of Psoriatic Arthritis

No studies have directly compared biologics to determine their relative merits. The appropriate way to differentiate the use of these biologics according to individual patients remains unclear. Here, we review reports on predictors of treatment responses to each biologic, particularly TNF-i and IL-17A inhibitors.

Predictors for achieving MDA have been recently investigated using the results at 144 weeks in the ADEPT study, which included patients with moderate or severe PsA (ADA vs. placebo) [32]. This investigation identifies high Health Assessment Questionnaire-Disability Index (HAQ-DI) scores at baseline as a significant predictor for failing to achieve MDA. In contrast, low tender joint counts (TJCs) and low HAQ-DI scores at baseline are identified as predictors for achieving and maintaining MDA. A retrospective cohort study of TNF-i persistence has identified the female sex and the presence of comorbid lifestyle-related diseases among baseline patient characteristics as predictors for lower TNF-i persistence. Although TNF-i persistence was lower in patients switching from first-line to second-line TNF-i than in those treated with first-line TNF-i, the inhibitor was not excluded from options at the time of switching from biologics. This study supports the use of TNF-i as one option among various biologics [33].

A systematic literature review provides no consistent views on predictors of treatment responses of PsA patients to TNF-i [34]. In this review, 4034 PsA patients collected from 23 reports (22 studies) were analyzed. The results showed that demographic factors had been analyzed to identify predictors for treatment responses in eight studies. In five studies, data on age were available. Only one study observed an inverse correlation between age and achievement of MDA. Furthermore, the effect of sex was assessed in these eight studies, five of which reported that men responded better to treatment than women.

In addition, only one study revealed an inverse correlation between MDA achievement and body mass index. Clinical items were evaluated in 16 studies, and baseline HAQ scores were assessed in six. However, no consistent trends were revealed. Similarly, the results concerning baseline joint counts, visual analog scale (VAS) pain, VAS global, and 28-joint Disease Activity Score (DAS28) were inconsistent between the studies. The use of concomitant DMARDs was evaluated in 13 studies. Although one study reported better treatment responses with combination therapy with MTX than with monotherapy, none of the studies yielded any significant results determining whether the use of concomitant DMARDs (including concomitant MTX) is a predictor of any treatment response. Regarding large joint involvement, axial involvement, dactylitis, erosive arthritis, and disease duration, the studies showed inconsistent results or statistically insignificant results. The same holds for serum C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), matrix metalloproteinase-3, and human leukocyte antigen (HLA)-B27. This review indicates that age, sex, baseline Bath Ankylosing Spondylitis Disease Activity Index/Bath Ankylosing Spondylitis Functional Index, CRP, and HLA-B27 are predictors of treatment responses to TNF-i in patients with ankylosing spondylitis but concludes that no factors were identified that could predict treatment responses of PsA patients to biologics.

IL-17A inhibitors are reviewed in a meta-analysis of 1718 cases collected from seven randomized controlled trials [35]. Meta-regression analysis eliminated the following variables as significant predictors for achieving ACR20 response at 12 weeks: age, sex, baseline DAS28 (CRP), history of treatment with MTX, and baseline Psoriasis Area and Severity Index (PASI). Thus, the results of individual studies suggest several candidate predictors of treatment responses of PsA patients to biologics. However, no predictors have been indicated by meta-analysis.

The Approach to Precision Medicine

While several biologics were proven effective for the treatment of PsA, no studies have directly compared the efficacy of each biologic. Although several studies suggest potential predictors of treatment responses to TNF-i or IL-17A inhibitors, no meta-analysis supports these findings. Thus, no procedures have been established to guide the selection of biologics for a particular patient.

Many clinical trials have been conducted using the ACR response rate as the primary endpoint. However, because this measure does not include the assessment of skin lesions, spine lesions, dactylitis, and enthesitis, it cannot be used as an indicator of PsA manifestations. The ACR response rate was developed as an assessment indicator of RA, not PsA. Because PsA is a heterogeneous disease exhibiting various symptoms of differing frequency and severity, the development of a simple classification system to aid optimal biologic selection based on clinical symptoms and laboratory findings may be difficult.

However, simple classification of diseases with complex clinical manifestations has proven useful for planning therapeutic interventions in other diseases. For example, a randomized, double-blind, placebo-controlled, phase IIb study of anifrolumab, an anti-IFN-receptor antibody indicated for moderate to severe systemic lupus erythematosus, demonstrated that anifrolumab is efficacious and more effective in patients with high baseline levels of expression of four specific IFN signature genes [36]. Given the immunologic heterogeneity among PsA patients, we investigated the use of

precision medicine to treat PsA using biologics selected according to lymphocyte phenotypes [37••].

Phenotyping of peripheral lymphocytes is useful for classifying individual patients according to immunological profile because the phenotyping reveals (1) the differentiation stage; (2) different lineages and functions, such as those of Th1, Th2, and Th17 cells; and (3) the activation state and intracellular signals involved in pathogenesis [38, 39]. In our previous study of 64 PsA patients, we compared changes in disease activity over 6 months between two groups of patients. The first group [strategic biologic DMARDs (bDMARDs)] included 26 patients treated with biologics that were selected according to peripheral lymphocyte phenotypes as determined by 8-color flow cytometry. The second group (standard bDMARDs) included 38 patients who started treatment with a TNF-i (i.e., IFX or ADA) that was selected by their attending physician according to the EULAR or GRAPPA treatment recommendations.

HLA-DR and CD38 were used as activation markers, and the cut-off points were set at 1.5% for activated Th1 cells and 1.2% for activated Th17 cells, based on interquartile ranges for healthy individuals. The results revealed that PsA patients could be classified into four groups based on lymphocyte phenotypes: $CD3^+CD4^+CXCR3^-CCR6^+CD38^+HLA\text{-}DR^+$ activated Th17-dominance, $CD3^+CD4^+CXCR3^+CCR6^-CD38^+HLA\text{-}DR^+$ activated Th1-dominance (six patients), activated Th1/Th17-high (four patients), and activated Th1/Th17-low (six patients).

The following treatments were then administered to patients according to their lymphocyte phenotype: UST for patients with activated Th1-dominance (activated Th1 > 1.5%, activated Th17 < 1.2%); SEC for patients with activated Th17-dominance (activated Th1 < 1.5%, activated Th17 > 1.2%); ADA for patients with activated Th1/Th17-high (activated Th1 > 1.5%, activated Th17 > 1.2%) and major joint complaints; SEC for patients with activated Th1/Th17-high (activated Th1 > 1.5%, activated Th17 > 1.2%) and major skin complaints; and ADA for patients with activated Th1/Th17-low (activated Th1 < 1.5%, activated Th17 < 1.2%) .

Regarding the selection of biologics for patients with activated Th1/Th17-high, TNF-i was administered to those presenting major joint complaints defined as moderate or higher disease activity based on the simplified disease activity index (SDAI) or DAS28 (ESR), regardless of PASI. SEC was administered to those presenting major skin complaints defined as PASI > 10 and low or no disease activity based on SDAI or DAS28 (ESR).

Six months after the commencement of biologics, the standard bDMARDs treatment group showed significant improvement, (SDAI, from 18.5 to 9.41; PASI, from 9.9 to 3.9). The strategic bDMARDs treatment group also showed significant improvement (SDAI, from 16.2 to 3.52; PASI, from 8.36 to 2.40). In addition, TJC, swollen joint count, patient global assessment, CRP, ESR, DAS28 (ESR), SDAI, and PASI had significantly decreased in both groups at 6 months. No significant differences in changes in these variables were observed between the two groups. However, it is noteworthy that biologics were more effective for suppressing disease activity in the strategic bDMARDs treatment group and sufficiently controlled PsA in all patients, whereas some patients in the standard bDMARDs treatment group were resistant to treatment. Furthermore, comparison of the efficacy of biologics between these groups showed that the proportion of patients achieving MDA based on SDAI was significantly higher in the strategic bDMARDs treatment group (92.3%) than in the standard bDMARDs treatment group (55.2%). The proportion of patients achieving MDA based on DAS28 (ESR) and ACR20 response rate was also significantly higher in the strategic bDMARDs treatment group than in the standard bDMARDs treatment group.

Assessment of the therapeutic effect of each biologic showed that the most effective biologic was TNF-i (i.e., ADA and IFX) in both the strategic and standard bDMARDs treatment groups, followed by SEC (although assessment was difficult in the standard bDMARDs treatment group) and UST. Comparison of the effects of the drugs between the two groups showed that both TNF-i and UST were more effective in the strategic bDMARDs treatment group than in the standard bDMARDs treatment group (SEC was administered to only one patient in the standard bDMARDs treatment group). Together, these results indicate that the reason for the differences in therapeutic effects between the groups is not that biologics with good therapeutic effects were administered to the strategic bDMARDs treatment group or that less effective biologics were administered to the standard bDMARDs treatment group, rather the strategies per se might have contributed to the better treatment responses. However, the IL-17 inhibitor (SEC) was not directly compared to other biologics because difficulty in administering SEC was observed in one patient in the standard bDMARDs treatment group and the number of patients treated with each biologic was small. Thus, it remains unknown whether SEC is actually as effective as the other biologics. Studies in larger cohorts are needed for more detailed analysis.

SEC is the only IL-17 inhibitor investigated in this study because it was the only one covered by health insurance in Japan at study initiation. Because GSL and BRO are currently available, further analysis including these biologics is important. The SDAI and ACR response rates were used to assess therapeutic effects; as with previous clinical trials, these assessment indicators may be insufficient. Assessment using composite measures such as MDA, which is a recently established treatment target, appears important.

Our results demonstrate the possibility of using precision medicine for PsA treatment, wherein biologics are selected

based on the results of peripheral lymphocyte analysis (Fig. 1). Favorable treatment responses were obtained only by analyzing Th cell subsets. HLA-B27 and many other variants of the major histocompatibility complex class I loci (HLA-B39, HLA-Cw6, HLA-B38, and HLA-B08) are reported to be genetic risk factors [40–42] for PsA. Variants of the HLA-B27 region contribute to disease susceptibility through direct presentation of an arthritogenic peptide to cytotoxic $CD8^+$ T cells. HLA-B27 variants also have been shown to cause homodimerization or misfolding of HLA-B27, allowing for binding with high affinity to killer cell immunoglobulin-like receptor 3DL2 (KIR3DL2) on IL-17^+CD4^+ T cells in

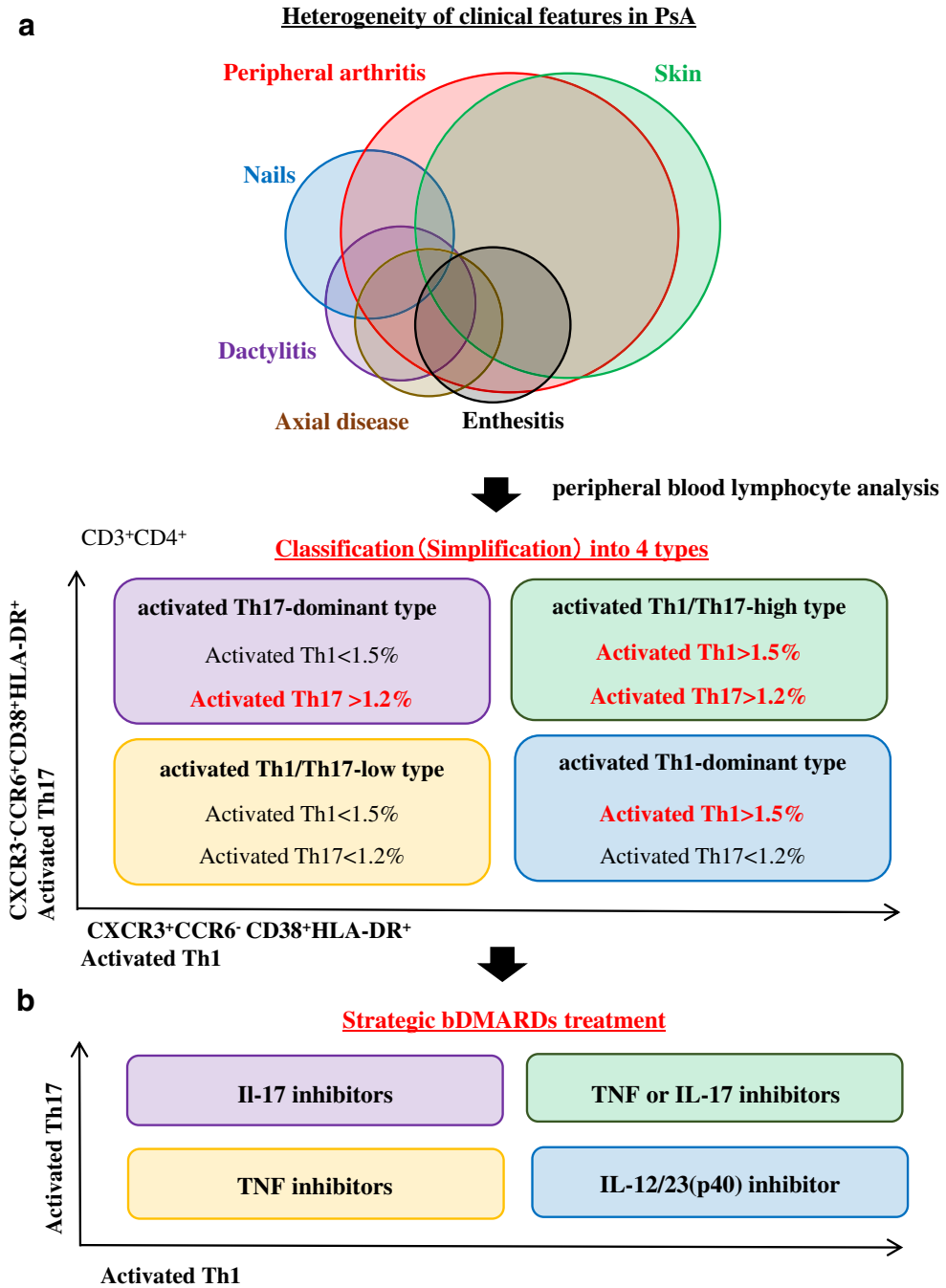

Fig. 1 **a** PsA were classified into the following 4 types: $CD3^+CD4^+CXCR3^-CCR6^+CD38^+HLA\text{-}DR^+$ activated Th17-dominant type, $CD3^+CD4^+CXCR3^+CCR6^{-\ +}CD38^+HLA\text{-}DR^+$ activated Th1-dominant type, activated Th1/Th17-high type, and activated Th1/Th17-low type. **b** Strategic bDMARDs treatment based on lymphocyte phenotypes: IL-12/23(p40) inhibitor for patients with activated Th1-dominance; IL-17 inhibitors for patients with activated Th17-dominance; TNF inhibitors for patients with activated Th1/Th17-high and major joint complaints; IL-17 inhibitors for patients with activated Th1/and major skin complaints; and TNF inhibitors for patients with activated Th1/Th17-low

blood or synovial fluid, resulting in upregulation of Il-23 [43–46]. Thus, the pathology of PsA depends on not only $CD8^+$ T cells but also $CD4^+$ T cells. The results of the present study also support the involvement of Th cell subsets ($CD4^+$ T cells). However, the involvement of many types of immunocompetent cells, such as tissue-resident memory T cells, mucosal-associated invariant T cells, invariant natural killer T cells, and γδ T cells, has recently been reported [47•]. Studies are needed to evaluate changes in these immunocompetent cells and $CD8^+$ T cells in response to treatment and during disease relapse.

Our present investigation is an open-label study including Japanese patients with differences in background factors, such as concomitant MTX use. Our study also has several limitations. The procedures used are complicated, limiting their use to a small number of institutions. We observed no clinical features that aligned with the 4 lymphocyte subtypes. Thus, the four subtypes cannot be distinguished by clinical features. Future studies should aim to establish a simpler classification system using blood cytokine concentrations, biomarkers, and other indicators. We believe that peripheral lymphocytes profiles together with the profiles of cytokines in blood or synovial fluid will contribute to more precise PsA classification. Further clinical trials will be needed to test this hypothesis.

Conclusions

Unlike RA, PsA frequently exhibits only peripheral arthritis as well as various other symptoms, such as skin lesions, spondylarthritis, enthesitis, nail lesions, dactylitis, and uveitis. Treating all of these symptoms with one biologic agent is a goal as well as a challenge. Selection of the optimal biologic for each individual patient is important for achieving this goal and will require further clinical trials to establishment selection guidelines.

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Compliance with Ethical Standards

Conflict of Interest Y. Tanaka received speaking fees and/or honoraria from Daiichi-Sankyo, Astellas, Eli Lilly, Chugai, Sanofi, AbbVie, Pfizer, YL Biologics, Bristol-Myers, Glaxo-SmithKline, UCB, Mitsubishi-Tanabe, Novartis, Eisai, Takeda, Janssen, and Asahi-kasei, and research grants from Mitsubishi-Tanabe, Bristol-Myers, Eisai, Chugai, Takeda, Abbvie, Astellas, Daiichi-Sankyo, Ono, MSD, Taisho-Toyama. S. Nakayamada received speaking fees and/or honoraria from Bristol-Myers, Sanofi, Abbvie, Eisai, Eli Lilly, Chugai, Asahi-kasei and Pfizer (less than $10,000 each), and also research grants from Mitsubishi-Tanabe, Takeda, Novartis and MSD.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Greb JE, Goldminz AM, Elder JT, et al. Psoriasis. Nat Rev Dis Primers. 2016;2:16082.
2. McGonagle D, Lories RJ, Tan AL, et al. The concept of a "synovio-entheseal complex" and its implications for understanding joint inflammation and damage in psoriatic arthritis and beyond. Arthritis Rheum. 2017;56:2482–91.
3. McGonagle D, Gibbon W, Emery P. Classification of inflammatory arthritis by enthesitis. Lancet. 1998;352:1137–40.
4. Rapp SR, Feldman SR, Exum ML, Fleischer AB Jr, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol. 1999;41:401–7.
5. Mease PJ. Psoriatic arthritis: update on pathophysiology, assessment and management. Ann Rheum Dis. 2011;70:i77–84.
6. Roubille C, Richer V, Starnino T, McCourt C, McFartane A, Fleming P, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. Ann Rheum Dis. 2015;74:480–9.
7. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum. 2004;50:2264–72.
8. Mease PJ, Ory P, Sharp JT, Ritchlin CT, Van den Bosch F, Wellborne F, et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Ann Rheum Dis. 2019;68:702–9.
9. Antoni CE, Kavanaugh A, van der Heijde D, Beutler A, Keenan G, Zhou B, et al. Two-year efficacy and safety of infliximab treatment in patients with active psoriatic arthritis: findings of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). J Rheumatol. 2008;35:869–76.
10. Kavanaugh A, Krueger GG, Beutler A, Guzzo C, Zhou B, Dooley LT, et al. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. Ann Rheum Dis. 2007;66:498–505.
11. Kavanaugh A, McInnes IB, Mease P, Krueger GG, Gladman D, van der Heijde D, et al. Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of a randomised, placebo-controlled trial (the GO-REVEAL study). Ann Rheum Dis. 2014;73:1689–94.
12. Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis. 2014;73:48–55.

13. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013;31:780–9.
14. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis. 2014;73:990–9.
15. Kavanaugh A, Puig L, Gottlieb AB, Ritchlin C, You Y, Li S, et al. Efficacy and safety of ustekinumab in psoriatic arthritis patients with peripheral arthritis and physician-reported spondylitis: post-hoc analyses from two phase III, multicentre, double-blind, placebo-controlled studies (PSUMMIT-1/PSUMMIT-2). Ann Rheum Dis. 2016;75:1984–8.
16. Deodhar A, Gottlieb AB, Boehncke WH, Dong B, Wang Y, Zhuang Y, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. Lancet. 2018;2:2213–24.
17. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;386:1137–46.
18. Strand V, Mease P, Gossec L, Elkayam O, van den Bosch F, Zuazo J, et al. Secukinumab improves patient-reported outcomes in subjects with active psoriatic arthritis: results from a randomised phase III trial (FUTURE 1). Ann Rheum Dis. 2017;76:203–7.
19. Kavanaugh A, McInnes IB, Mease PJ, Hall S, Chinoy H, Kivitz AJ, et al. Efficacy of subcutaneous secukinumab in patients with active psoriatic arthritis stratified by prior tumor necrosis factor inhibitor use: results from the Randomized Placebo-controlled FUTURE 2 Study. J Rheumatol. 2016;43:1713–7.
20. Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis. 2017;76:79–87.
21. Nash P, Kirkham B, Okada M, Rahman P, Combe B, Burmester GR, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet. 2017;389:2317–27.
22. van der Heijde D, Gladman DD, Kishimoto M, Okada M, Rathmann SS, Moriarty SR, et al. Efficacy and safety of ixekizumab in patients with active psoriatic arthritis: 52-week results from a Phase III Study (SPIRIT-P1). J Rheumatol. 2018;45:367–77.
23. Coates LC, Kishimoto M, Gottlieb A, Shuler CL, Lin CY, Lee CH, et al. Ixekizumab efficacy and safety with and without concomitant conventional disease-modifying antirheumatic drugs (cDMARDs) in biologic DMARD (bDMARD)-naïve patients with active psoriatic arthritis (PsA): results from SPIRIT-P1. RMD Open. 2017;3:e000567.
24. Mease PJ, Genovese MC, Greenwald MW, Ritchlin CT, Beaulieu AD, Deodhar A, et al. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. N Engl J Med. 2014;370:2295–306.
25. Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, et al. European league against rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis. 2016;75:499–510.
26. Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta-Felquer M, Armstrong AW, et al. Group for research and assessment of psoriasis and psoriatic arthritis 2015 treatment recommendations for psoriatic arthritis. Arthritis Rheumatol. 2016;68:1060–71.
27. Coates LC, Moverley AR, McParland L, Brown S, Navarro-Coy N, O'Dwyer JL, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. Lancet. 2015;386:2489–98.
28. Coates LC, FitzGerald O, Merola JF, Smolen J, van Mens LJJ, Bertheussen H, et al. Group for research and assessment of psoriasis and psoriatic arthritis/outcome measures in rheumatology consensus-based recommendations and research agenda for use of composite measures and treatment targets in psoriatic arthritis. Arthritis Rheumatol. 2018;70:345–55.
29. Gossec L, Coates LC, de Wit M, Kavanaugh A, Ramiro S, Mease PJ, et al. Management of psoriatic arthritis in 2016: a comparison of EULAR and GRAPPA recommendations. Nat Rev Rheumatol. 2016;12:743–50.
30. Singh JA, Guyatt G, Ogdie A, Gladman DD, Deal C, Deodhar A, et al. Special article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthritis Rheumatol. 2019;71:5–32.
31. Nash P, McInnes IB, Mease PJ, Thom H, Hunger M, Karabis A, et al. Secukinumab versus adalimumab for psoriatic arthritis: comparative effectiveness up to 48 weeks using a matching-adjusted indirect comparison. Rheumatol Ther. 2018;5:99–122.
32. Mease PJ, Kavanaugh A, Coates LC, McInnes IB, Hojnik M, Zhang Y, et al. Prediction and benefits of minimal disease activity in patients with psoriatic arthritis and active skin disease in the ADEPT trial. RMD Open. 2017;3:e000415.
33. Stober C, Ye W, Guruparan T, Htut E, Clunie G, Jadon D. Prevalence and predictors of tumour necrosis factor inhibitor persistence in psoriatic arthritis. Rheumatology (Oxford). 2018;57:158–63.
34. Maneiro JR, Souto A, Salgado E, Mera A, Gomez-Reino JJ. Predictors of response to TNF antagonists in patients with ankylosing spondylitis and psoriatic arthritis: systematic review and meta-analysis. RMD Open. 2015;1:e000017.
35. Naik GS, Ming WK, Magodoro IM, Akinwunmi B, Dar S, Poulsen HE, et al. Th17 inhibitors in active psoriatic arthritis: a systematic review and meta-analysis of randomized controlled clinical trials. Dermatology. 2017;233:366–77.
36. Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, et al. Anifrolumab, an anti-interferon-α receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. Arthritis Rheumatol. 2017;69:376–86.
37.•• Miyagawa I, Nakayamada S, Nakano K, Kubo S, Iwata S, Miyazaki Y, et al. Precision medicine using different biological DMARDs based on characteristic phenotypes of peripheral T helper cells in psoriatic arthritis. Rheumatology (Oxford). 2018. https://doi.org/10.1093/rheumatology/key069 **This report demonstrates the possibility of precision medicine based on the peripheral lymphocytic phenotypes in patients with psoriatic arthritis**.
38. Nakayamada S, Kubo S, Yoshikawa M, Miyazaki Y, Yunoue N, Iwata S, et al. Differential effects of biological DMARDs on peripheral immune cell phenotypes in patients with rheumatoid arthritis. Rheumatology (Oxford). 2018;57:164–74.
39. Maecker HT, McCoy JP, Nussenblatt R. Standardizing immunophenotyping for the human immunology project. Nat Rev Immunol. 2012;12:191–200.
40. Haroon M, Winchester R, Giles JT, Heffernan E, FitzGerald O. Certain class I HLA alleles and haplotypes implicated in susceptibility play a role in determining specific features of the psoriatic arthritis phenotype. Ann Rheum Dis. 2016;75:155–62.

41. Jadon DR, Sengupta R, Nightingale A, Lindsay M, Korendowych E, Robinson G, et al. Axial Disease in Psoriatic Arthritis study: defining the clinical and radiographic phenotype of psoriatic spondyloarthritis. Ann Rheum Dis. 2017;76:701–7.
42. Bowes J, Ashcroft J, Dand N, Jalali-Najafabadi F, Bellou E, Ho P, et al. Cross- phenotype association mapping of the MHC identifies genetic variants that differentiate psoriatic arthritis from psoriasis. Ann Rheum Dis. 2017;76:1774–9.
43. Allen RL, O'Callaghan CA, McMichael AJ, Bowness P. Cutting edge: HLA- B27 can form a novel β2-microglobulin- free heavy chain homodimer structure. J Immunol. 1999;162:5045–8.
44. DeLay ML, Turner MJ, Klenk EI, Smith JA, Sowders DP, Colbert RA. HLA- B27 misfolding and the unfolded protein response augment interleukin-23 production and are associated with Th17 activation in transgenic rats. Arthritis Rheum. 2009;60:2633–43.
45. Colbert RA, DeLay ML, Klenk EI, Layh-Schmitt G. From HLA-B27 to spondyloarthritis: a journey through the ER. Immunol Rev. 2010;233:181–202.
46. Bowness P, Ridley A, Shaw J, Chan AT, Wong-Baeza I, Fleming M, et al. Th17 cells expressing KIR3DL2+ and responsive to HLA-B27 homodimers are increased in ankylosing spondylitis. J Immunol. 2011;186:2672–80.
47.• Taams LS, Steel KJA, Srenathan U, Burns LA, Kirkham BW. IL-17 in the immunopathogenesis of spondyloarthritis. Nat Rev Rheumatol. 2018;14:453–66 **This review discuss the immunopathogenesis of spondyloarthrits including psoriatic arthritis**.