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INVITED REVIEW

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State-of-the-art treatment of systemic lupus erythematosus

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Abstract

As glucocorticoids and immunosuppressive drugs are non-specific therapeutic agents that cause many adverse reactions, the development of biologicals aiming to control specific molecular targets is anticipated for the treatment of systemic lupus erythematosus (SLE). The antibody targeting B cell-activating factor belonging to the tumor necrosis factor family (BAFF) belimumab was the first biological approved for SLE. At present, many biologicals, such as anifrolumab (anti-type I interferon receptor antibody) and ustekinumab (antibody against interleukin 12/23 [p40]), are in clinical trials. Thus, successful treatments with biologicals targeting "bridging cytokines" produced by dendritic cells, which form a bridge between the innate and acquired immune/autoimmune systems, is of particular interest. Moreover, a phase IIb clinical trial of baricitinib, a low-molecular-weight compound targeting Janus kinase 1/2, in patients with SLE revealed that baricitinib was significantly more effective for relieving arthritis and skin manifestations than placebo, and the trial met the primary endpoint. In the future, it is expected that drugs with better efficacy and safety profiles will be used to apply therapeutic strategies, such as precision medicine, in which different molecular target drugs are used for patients classified by their conditions, and to set a therapeutic goal of the discontinuation of glucocorticoids.

KEYWORDS

biological, innate immunity, JAK inhibitor, systemic lupus erythematosus, treatment

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a typical systemic autoimmune disease, common in women of reproductive age, which causes multiorgan disorder. It affects organs throughout the body, such as the skin, joints, heart, kidneys, serosa, nerves, and blood vessels, and presents with various clinical symptoms. Onset occurs commonly in the third and fourth decades of life, and the male-to-female ratio is between about 1:10. The prognosis of SLE has dramatically improved since the 1960s because of the widespread uptake of glucocorticoid therapy, with survival rates reported to be 90% or higher after 5 years, 70%-90% after 10 years, and 50%-70% after 20 years. Given the age at onset, these survival rates are relatively low. In Japan and overseas, the most common cause of death is infection; thus, the pressing issues are appropriate management of the primary disease and immunosuppressed state by using glucocorticoids, immunosuppressive drugs, and other appropriate drugs, and the development of drugs that cause fewer adverse reactions. The biological belimumab, which is an anti-B cell-activating factor belonging to the tumor necrosis factor family (BAFF) antibody, has been approved for the treatment of SLE, and many molecular targeted drugs are in development. In this article, the progress made in the diagnosis and treatment of SLE has been reviewed.

2 | ESSENTIALS AND ISSUES IN SLE TREATMENT

In 2014, a task force of the European League Against Rheumatism (EULAR), reported the treat-to-target (T2T) strategy for therapeutic goals.[1] The therapeutic target was remission without any systemic symptoms or organ disorders, and the realistic therapeutic goal was the avoidance of relapse or organ disorders. Although no remission criteria were provided, assessment using indices indicating organ disorders and systemic lupus activity, such as the SLE Disease Activity Index (SLEDAI), was recommended.

The need for SLE treatment, the indication for glucocorticoids and immunosuppressive drugs, and initial therapeutic dose are determined by comprehensive assessment of disease activity, major organ disorders, complications such as infection and cardiac diseases. According to the diagnostic and therapeutic algorithm developed by Hahn, which is regarded as a standard therapeutic guideline, the prompt initiation of combination therapy comprising high-dose glucocorticoids and immunosuppressive drugs is recommended for patients with severe organ lesions (eg, lupus nephritis and central nervous system lupus) and high disease activity.[2] The immunosuppressive drugs, intravenous cyclophosphamide pulse therapy (IV-CY) and mycophenolate mofetil (MMF), are recommended, with hydroxychloroquine used concomitantly as a standard mainstay agent.

In contrast, for clinically asymptomatic patients with stable test results, no treatment is recommended. Patients without severe organ lesions may receive palliative therapy or no treatment. The EULAR guidelines recommend hydroxychloroquine or low-dose glucocorticoids for patients without major organ lesions but with symptoms such as arthritis, muscle pain, and fever.[3] For patients who do not respond to treatment and patients whose glucocorticoid doses cannot be reduced to maintenance levels, immunosuppressive drugs, such as azathioprine (AZ) and MMF, should be considered.

When patients respond to initial treatment, glucocorticoid doses are reduced in conjunction with clinical symptoms and laboratory test results as a transition to maintenance therapy. The EULAR recommends a maintenance therapy of minimal-dose glucocorticoids with MMF or AZ. In the T2T strategy, the maintenance therapy should last at least 3 years, with the subsequent aim of glucocorticoid discontinuation.

3 | BIOLOGICAL THERAPY

As glucocorticoids and immunosuppressive drugs are non-specific therapeutic agents that induce many adverse reactions like infection, opportunistic infections, and metabolic abnormalities, development of biologicals to control specific molecular targets is a priority. Belimumab, an anti-BAFF antibody, has already been approved, with many other biologicals in clinical trials (Figure 1). Many biologicals such as CD20 antibodies targeting B cells have appeared promising but did not yield favorable results. However, further strategic development of therapeutic agents, including low-molecular-weight compounds, is expected. The results of a phase IIb clinical trial of baricitinib, a low-molecular-weight compound targeting Janus kinase (JAK) 1/2, in patients with SLE have been published. Further new development is expected.

3.1 | Anti-CD20 and anti-CD22 antibodies

B cells have a central role in the pathogenic mechanisms and pathogenesis of autoimmune diseases, such as SLE.[4] Rituximab, a chimeric antibody targeting the B cell surface molecule, CD20, has been approved for rheumatoid arthritis in many countries except for Japan and investigated for the clinical treatment of SLE. However, the Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) failed to show any significant differences in efficacy between rituximab and placebo.[5] Moreover, 2 patients with SLE treated with rituximab died of progressive multifocal leukoencephalopathy. Consequently, clinical trials were suspended, including a Japanese phase III trial on rituximab for SLE, the phase III Lupus Nephritis Assessment with Rituximab (LUNAR), the Study to Evaluate Two Doses of Ocrelizumab in Patients with Active Systemic Lupus Erythematosus (BEGIN) in the treatment of SLE with a humanized anti-CD20 antibody ocrelizumab, and the Study to Evaluate Ocrelizumab in Patients with Nephritis Due to Systemic Lupus Erythematosus (BELONG) on lupus nephritis. Meanwhile, we reported that 62% of 63 patients participating in a clinical trial positively responded to rituximab, and that it was effective in many of 22 patients with type IV lupus nephritis after 1 year of treatment.[6] Even in six patients with neuropsychiatric SLE (NPSLE), associated with acute impaired consciousness and psychiatric disorder, rituximab relieved clinical symptoms, and some patients showed rapid recovery of consciousness.[7] In addition, because many case reports indicate the efficacy of rituximab, investigator-initiated international clinical trials have been resumed to expand the indication of rituximab to lupus nephritis.

CD22 is an immunoglobulin (Ig) superfamily molecule expressed in the late stage of B cell differentiation. It acts as an inhibitory coreceptor of the B cell receptor and transduces inhibitory signals via the immunoreceptor tyrosine-based inhibition motif (ITIM) in cells. Epratuzumab, a humanized antibody against CD22, binds to CD22 and immediately transduces a negative signal via ITIM. However, the phase III studies of Epratuzumab Versus Placebo in Subjects with Moderate to Severe General Systemic Lupus Erythematosus (EMBODY-1 and EMBODY-2) failed to reveal significant differences, and were subsequently suspended.[8]

3.2 | Anti-BAFF antibody and transmembrane activator and cyclophilin ligand interactor-Ig

BAFF, a typical costimulatory molecule of B cells, is expressed on the surfaces of dendritic cells and macrophages or is produced as

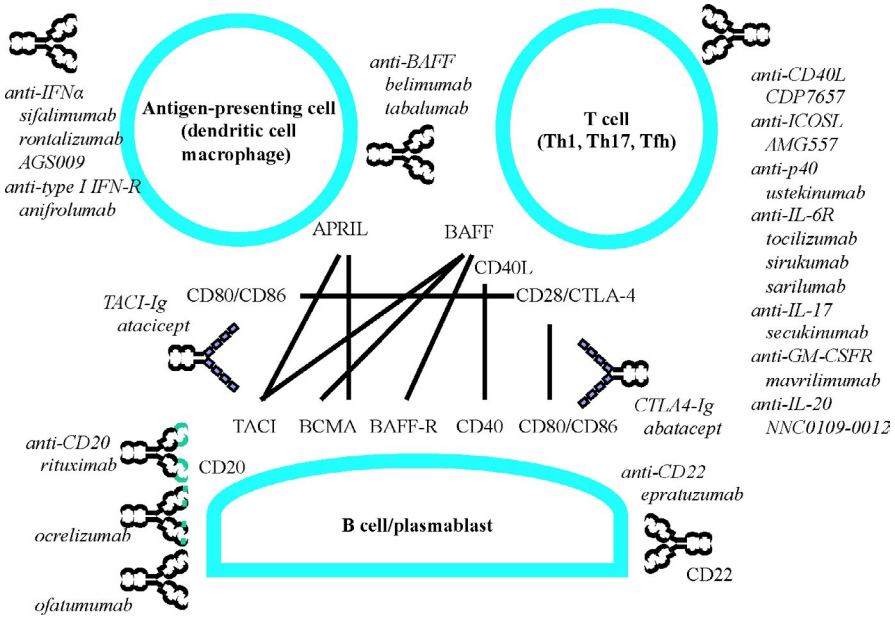

FIGURE 1 The development of biologicals for the treatment of systemic lupus erythematosus. Some of them have already failed in clinical trials

soluble BAFF. It binds to the BAFF receptor, transmembrane activator and cyclophilin ligand interactor (TACI), and B cell maturation antigen on B cells, inducing the inhibition of apoptosis of autoreactive B cells, class switching, and differentiation into antibody-producing cells. In patients with SLE, increased levels of serum-soluble BAFF and serum double-stranded DNA (dsDNA) antibodies are correlated with disease activity and strongly associated with pathogenesis.

In the study of Belimumab in Subjects with Systemic Lupus Erythematosus (BLISS-52), a global phase III trial involving 865 patients with moderate SLE (SLEDAI ≥ 6), belimumab was administered at weeks 0, 2, and 4 and then once every 4 weeks. Belimumab significantly improved the SLE Responder Index (SRI) 4 response rate at week 52 compared with placebo and no significant differences between belimumab and placebo in adverse events, serious adverse reactions, or infections were observed.[9] Thus, belimumab was the first biological approved for the indication of SLE in Europe and the United States. For lupus nephritis, a combination therapy with belimumab and MMF achieved a higher SRI-4 response rate and significantly reduced relapses. In the BLISS-NEA phase III study conducted in northeast Asia (including Japan), belimumab was added for patients with active SLE confirmed by autoantibody positivity who had been receiving the existing standard treatment.[10] After 52 weeks, the SRI-4 response rate was significantly improved in patients compared with the existing treatment. In addition to significant improvements in the musculoskeletal, renal, and immune systems, decreased serum dsDNA antibody levels, increased complement titers, and glucocorticoid-sparing effect, SLEDAI assessment showed that belimumab was safe. Belimumab is expected to be used for both remission induction therapy for refractory SLE and maintenance therapy, with an aim of reducing glucocorticoid doses.

Tabalumab, an IgG4 antibody that recognizes both soluble and membrane-bound BAFFs, was investigated in an international phase III clinical trial on highly active SLE, in which Japan participated.[11] The primary endpoint was not met, and there were no differences in the secondary endpoints, such as glucocorticoid-sparing effect. Atacicept is a fusion protein composed of the extracellular domain of TACI, a receptor for BAFF, a proliferation-inducing ligand (APRIL), and the Fc fragment of human IgG1. It controls B cell activation. In the international phase II APRIL trial of atacicept in patients with SLE, the drug was effective; however, concerns about infection were raised. Currently, atacicept is under evaluation in the international phase III ADDRESS II clinical trial.

3.3 | Anti-interferon-α and anti-type I interferon receptor antibodies

In patients with SLE, blood interferon (IFN)-α concentrations increase with disease activity, and the expression of IFN signature genes is elevated, which is associated with critical organ disorders, such as nephritis and central nervous system lesions, and disease activity.[6,7] In addition, Toll-like receptors are highly expressed in the dendritic cells of patients with SLE, and they bind to stimuli, such as DNA and RNA, released not only by bacteria and viruses but also during apoptosis and NETosis, thereby inducing the production of type I IFN, soluble BAFF, interleukin (IL)-12/IL-23 and other similar proteins. Toll-like receptors are also highly expressed in B cells and bind to stimuli, such as bacteria, DNA, and RNA, to induce class switching of B cells and autoantibody production. Thus, these receptors play an important role in the pathogenesis of SLE through the activation of lymphocytes.

Hence, type I IFN is expected to be a therapeutic target for SLE, and anti-IFN-α antibodies (rontalizumab and sifalimumab), an anti-type I IFN receptor antibody (anifrolumab), and a vaccine preparation inducing anti-IFN-α antibodies (IFN-α kinoid) have been developed. The administration of sifalimumab and anifrolumab suppressed the expression of IFN signature genes. However, a phase II clinical trial using rontalizumab failed to meet the primary endpoint of the British Isles Lupus

Assessment Group (BILAG) Index and was discontinued. A clinical trial of sifalimumab met the primary endpoint of SRI-4, but was discontinued because of regional and ethnic differences in effects. In a phase II clinical trial of IFN-α kinoid, although no significant improvement was observed in the BILAG Index, the rate of Lupus Low Disease Activity State attainment was significantly higher in patients.

In a placebo-controlled study of anifrolumab in patients with moderately to severely active SLE, significantly greater improvement was observed in both the primary endpoints in the anifrolumab group than in the placebo group. It is noteworthy that anifrolumab was more effective in patients with a stronger IFN signature.[12] Global phase III clinical trials (Treatment of Uncontrolled Lupus via the Interferon Pathway [TULIP] 1 and 2) were conducted. In the TULIP 1 trial no significant difference between anifrolumab and placebo groups was observed for the primary endpoint of the SRI-4 response rate at week 52. Similar results were also obtained in patients with a stronger IFN signature. In the TULIP 2 trial the primary endpoint, BICLA (BILAG-based Combined Lupus Assessment) response rate at week 52 was significantly higher in the anifrolumab group, regardless of IFN signature, and significant differences were also observed in the improvement of the Cutaneous Lupus Erythematosus Disease Area and Severity Index, glucocorticoid-sparing effect, and SRI-4 response rate.[13] There was no remarkable difference in the incidence of adverse events between the anifrolumab and placebo groups, except for herpes zoster and bronchitis, which occurred in 7.2% of patients in the anifrolumab group. An application for the approval of the drug is planned to be submitted.

3.4 | IL-12/IL-23 (p40) antibody

Memory T cells are classified into various subsets: T helper 1 (Th1) cells play an important role in the activation of cell-mediated immunity, and T follicular helper (Tfh) cells play an important role in the differentiation and activation of B cells. The cytokine IL-12 induces Th1 and Tfh cells in humans, and serum IL-12 levels are elevated in patients with active SLE.[14] Ustekinumab, an antibody against IL-12/IL-23 (p 40), is approved for the treatment of psoriasis and psoriatic arthritis; its efficacy and safety have been evaluated. In a phase IIb global clinical trial involving patients with highly active SLE, ustekinumab, was compared with placebo. The SRI-4 response rate at week 24, which was the primary endpoint, was significantly higher in the ustekinumab group than in the placebo group. This effect was maintained for up to 1 year, with no major adverse events detected.[15] An international phase III clinical trial is in progress.

4 | FUTURE DEVELOPMENTS

4.1 | Findings based on the results of clinical trials of biologicals

As many disease susceptibility genes for SLE that have been identified by genome-wide association analysis are present in B cells, the activation of B cells, due to autoimmune disorders resulting from abnormal acquired immunity, and the production of autoantibodies, are considered the main pathological features of SLE. After stimulation by Tfh cells and autoreactive T cells, B cells undergo class switching and differentiate into antibody/autoantibody-producing cells. In addition, B cells express major histocompatibility complex molecules, which function as antigen-presenting cells for T cells. Furthermore, B cells produce various cytokines in response to immune system stimulation. Hence, B cells play a central role as responders and stimulators of the immune system and autoimmune pathology. Thus, B cell-targeted therapy has been expected to become a mainstay of the treatment for SLE.[4] However, as mentioned above, treatment with biologicals targeting B cells, such as rituximab and epratuzumab, has been unsuccessful.

Meanwhile, genome-wide association analysis has identified the genes encoding IFN regulatory factor 5, IL-1 receptor-associated kinase 1, and Toll-like receptor 7 as disease susceptibility genes for SLE.[16] These are central molecules of the innate immune system, which is mainly composed of dendritic cells. When Toll-like receptors on dendritic cells of patients with SLE bind to DNA and RNA molecules released during apoptosis and NETosis, dendritic cells produce cytokines and chemokines that induce the differentiation and activation of B and T cells of the acquired immune system. Although excessive suppression of the innate immune system could increase the risk of infection, successful treatments with biologicals targeting cytokines produced by dendritic cells, such as soluble BAFF, type I IFN, and IL-12, which form a bridge between the innate and acquired immune systems, is of particular interest. In the future, development of treatments using biologicals and low-molecular-weight compounds able to target these "bridging cytokines" is expected (Figure 2).

4.2 | Advent of orally administered JAK inhibitors

Biologicals have brought about a paradigm shift in the treatment of autoimmune diseases, including rheumatoid arthritis with their excellent efficacy and safety; they are likely to drive similar changes in the treatment of SLE. However, owing to their large molecular weight, the administration routes of biologicals are limited to injection. The development of low-molecular-weight compounds with comparable efficacy that can be orally administered is warranted. Low-molecular-weight compounds could inhibit intracellular signaling molecules by binding to them in the same way a key fits into a keyhole. In SLE, in which B cells are activated, conferring enhanced antibody-producing functions, the administration of large foreign molecules, such as biologicals, could result in the inevitable regeneration of antidrug antibodies. Therefore, low-molecular-weight compounds are advantageous.

Cytokines and cell surface molecules transduce a variety of intracellular signals by binding to receptors and induce cell functions and the transcription of new cytokines. The enzymes that phosphorylate signaling molecules are called kinases. Of 518 kinases, JAK is a typical tyrosine kinase. JAKs, which form homodimers or heterodimers,

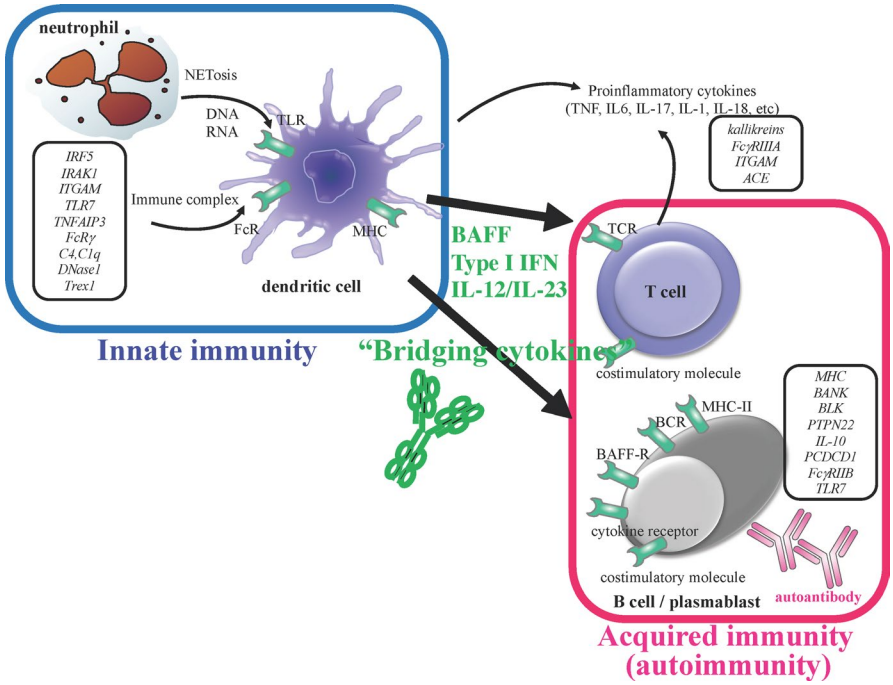

FIGURE 2 "Bridging cytokines" in systemic lupus erythematosus (SLE). Bridging cytokines produced by dendritic cells, which form a bridge between the innate and acquired immune/autoimmune systems would be targets for treatment by biologicals in SLE

are involved in the transduction of various signals. Different combinations of the 4 types of JAKs and 7 types of downstream signal transducers and activators of transcription (STATs) induce transcription of various genes via STATs. Drugs that are currently marketed as kinases include the JAK inhibitor tofacitinib, the JAK 1/2 inhibitor baricitinib, the JAK1 inhibitor upadacitinib, and the JAK inhibitor peficitinib.[17] The concomitant use of these inhibitors and methotrexate has been demonstrated to be clinically similar to, or more effective than, tumor necrosis factor (TNF) inhibitors.[18]

Baricitinib binds competitively to the adenosine triphosphate binding site of JAK 1/2 and controls intracellular signaling induced by gp130 family cytokines (eg, IL-6), IL-12, IL-23, and IFN. Cytokines that bridge the innate and acquired immune systems are the primary target. In an international phase IIb clinical trial of baricitinib involving patients with highly active SLE exhibiting skin and joint symptoms despite the standard treatment, the patients were treated with the standard treatment in combination with placebo or baricitinib. In the 4 mg baricitinib group, significantly more patients achieved resolution of SLEDAI-2000 arthritis or skin manifestations at week 24, met the primary endpoint, and attained an SRI-4 response. Serious infections were observed in a dose-dependent manner.[19] Baricitinib is currently under investigation in a phase III trial. In the future, it is expected that inhibitors of Bruton's tyrosine kinase, spleen tyrosine kinase, and other kinases will be developed alongside JAK inhibitors, such as the JAK1 inhibitor filgotinib and the tyrosine kinase 2 inhibitor BMS-986165.

4.3 | Potential for precision medicine

As SLE is a highly heterogeneous disease, it was difficult to achieve similar therapeutic effects in all patients with the disease by applying B cell-targeted therapy to remove B cells. However, it is noteworthy that a significant difference in therapeutic responsiveness was observed by analysis based on expression level of IFN signature genes, as described above in the global phase IIb trial of anifrolumab.[12] The trial may have marked the first step toward precision medicine for SLE. The objective of precision medicine is the stratification or subgrouping of patients to improve diagnosis and treatment.[20] Since the Human Genome Project was completed in 2003, genetic level information has been available for treatment and monitoring prognosis in the field of cancer treatment. Although our understanding of the pathology of SLE at the genetic level has improved, the heterogeneity of SLE has not been fully elucidated. It is expected that future treatments will be based on the subgroup of the disease at the cellular and molecular levels from information obtained from "omics" analyses, including immunophenotype.[21]

We have attempted to apply precision medicine based on the analysis of peripheral blood lymphocytes using flow cytometry in patients with psoriatic arthritis. Approximately half of patients with psoriasis also have destructive multiple spondyloarthritis. For the treatment of psoriatic arthritis, drugs targeting TNF, IL-17, and IL-12/IL-23 (p40) have been approved, but it is unknown how to use them appropriately. When we performed flow cytometric analysis of peripheral blood lymphocyte phenotypes in patients with psoriatic arthritis, the disease was classified into 4 phenotypes based on the expression of chemokine receptors: Th1-dominant, Th17-dominant, Th1/Th17 hybrid, and normal phenotypes. We then administered anti-IL-17 antibodies to patients with the Th17-dominant phenotype, anti-p40 antibodies to patients with the Th1-dominant phenotype, and TNF-targeted drugs to patients with the normal or Th1/Th17 hybrid phenotype. The proportion of patients without improvement was reduced to less than 10%, compared with that of patients who received conventional biologicals without undergoing lymphocyte

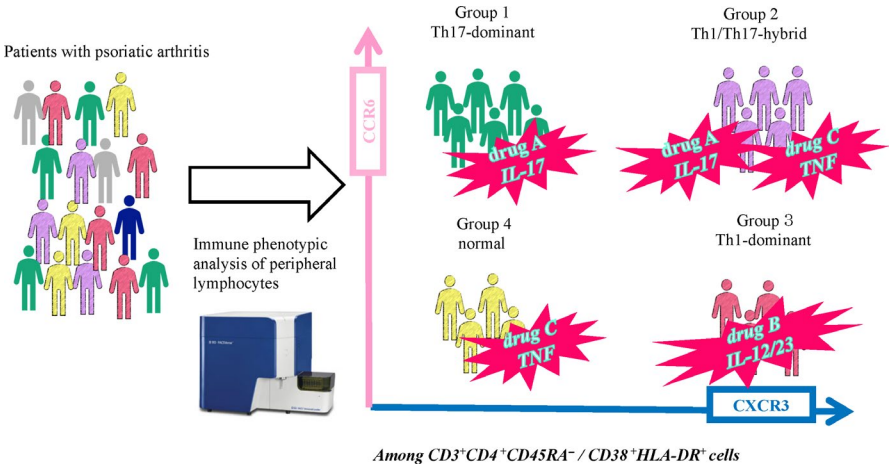

FIGURE 3 Potential for precision medicine in rheumatic diseases and systemic autoimmune diseases. Shown is an example of possible precision medicine for psoriatic arthritis using different biologicals based on immune phenotypic analysis of peripheral lymphocytes

analysis. Our methods were associated with significantly higher therapeutic response rates.[22] Thus, our findings suggested that for the treatment of psoriatic arthritis, therapeutic drugs can be optimized according to pathological conditions through the analysis of peripheral immune phenotypes (Figure 3). We are currently developing new therapeutic systems and strategies to enhance precision medicine for various connective tissue diseases, such as SLE.[23]

5 | CONCLUSION

Biologicals and kinase inhibitors, which target specific molecules, are expected to be highly effective and cause relatively few adverse reactions; however, they sometimes cause opportunistic infections or virus reactivation. The development of drugs with a balanced efficacy and safety profile is an emerging issue. In addition, the introduction of precision medicine by using molecular targeted therapy should enable more efficient treatment of highly diverse immune diseases. The withdrawal of glucocorticoids and other drugs after a certain period of maintenance therapy has been recently discussed. Trials with an outcome of glucocorticoid withdrawal and trials of treatment initiation without the use of glucocorticoids have also been performed. In anticipation of advances that will be made in 10 years, the treatment development designed to cure SLE has commenced.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

YT contributed to the overall review, writing of the manuscript and review of the manuscript.

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