

# Recent progress in treatments of rheumatoid arthritis: an overview of developments in biologics and small molecules, and remaining unmet needs

Yoshiya Tanaka  <sup>1</sup>

## Abstract

**Abstract.** Through treatment with biological DMARDs (bDMARDs) or targeted synthetic (tsDMARDs) such as Janus kinase (JAK) inhibitors in addition to MTX, clinical remission has become a realistic therapeutic goal for the majority of patients with RA, and sustained remission facilitates prevention of joint damage and physical dysfunction. Long-term safety and sustained inhibition of structural changes and physical dysfunction by bDMARDs have been reported. The development of next-generation bDMARDs and expansion of their indications to various autoimmune diseases are expected. Five JAK inhibitors show comparable efficacy to bDMARDs, and the latest ones are effective for overcoming difficult-to-treat RA regardless of prior medications. Patients treated with JAK inhibitors should be adequately screened and monitored for infection, cardiovascular disorders, thrombosis, malignancies and so on. Advances in therapeutic strategies, including the differential use of therapeutic drugs and de-escalation of treatment after remission induction, are prioritized.

**Key words:** rheumatoid arthritis, treatment, clinical trial, remission, safety, DMARD, csDMARD, tsDMARD, bDMARD

## Rheumatology key messages

- There are four classes of biological DMARDs and five Janus kinase inhibitors available for molecular-targeted therapy in RA.
- Some Janus kinase inhibitors reveal comparable safety to biological DMARDs and are effective for overcoming difficult-to-treat RA.
- Therapeutic strategies, including precision medicine and drug de-escalation, will be the next targets in RA.

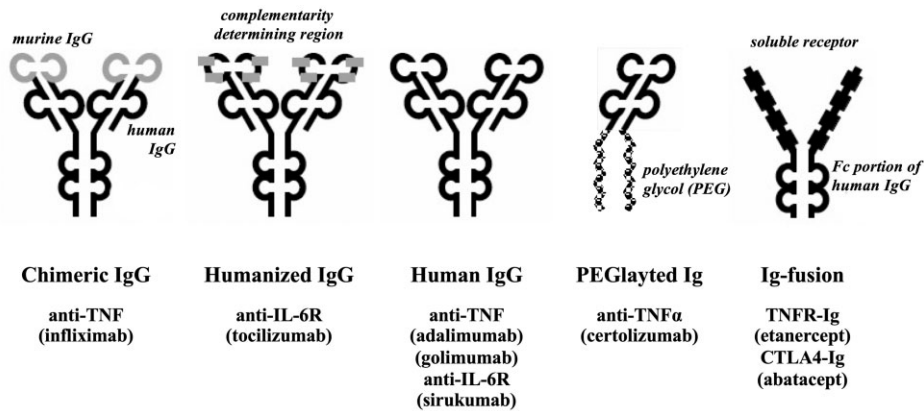
## Introduction

RA is a typical autoimmune disease with polyarthritis revealed as its primary pathological manifestation. Without appropriate treatment, RA inevitably causes irreversible damage to the structural joints and is often accompanied by multiple organ damage. Joint damage progresses in the early stages after onset, and the deformed joints cause irreversible physical dysfunction.

Therefore, a prompt and appropriate diagnosis along with treatment is indispensable for the clinical management of RA. The 21st century has marked a paradigm shift in the treatment of RA. Biological DMARDs (bDMARDs), which are made from living organisms or contain components of living organisms, target TNF, IL-6 receptors and others; and targeted synthetic DMARDs (tsDMARDs), such as Janus kinase (JAK) inhibitors, have been introduced in addition to conventional synthetic DMARDs (csDMARDs), such as MTX. Since the introduction of these drugs, clinical remission has become a realistic therapeutic goal for the majority of RA patients. Sustained remission facilitates prevention of structural joint damage over a long period of time, in addition to preventing progression of physical dysfunction [1–3]. This article aims to provide a comprehensive overview

<sup>1</sup>The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan  
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Correspondence to: Yoshiya Tanaka, The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, 1-1 Iseigaoka, Kitakyushu 807-8555 Japan. E-mail: tanaka@med.uoeh-u.ac.jp

**Fig. 1** Biological DMARDs approved for RA

For the treatment of RA there are five TNF-targeting drugs, two IL-6 receptor-targeting drugs, one B-cell antigen CD20-targeting antibody and one selective T-cell costimulatory modulator, each of which are marketed. \*ABT-122, a bispecific antibody, is not approved yet.

of recent advances and unfulfilled needs in the treatment of RA.

## Biological DMARDs

The marketed biologics available for the treatment of RA include five TNF-targeting drugs, two IL-6 receptor-targeting drugs, one B cell antigen CD20-targeting antibody and one selective T cell costimulatory modulator (Fig. 1). They have all been demonstrated to be highly effective and acceptably safe when used in combination with MTX for the treatment of RA refractory to MTX and/or bDMARDs [1–3]. Some TNF-targeting drugs in combination with MTX have also been demonstrated to exert high therapeutic effects in MTX-naïve RA patients. Ten-year follow up studies on the treatment of RA patients with these bDMARDs have revealed no major safety concerns with long-term use, and almost complete inhibition of progression to structural joint damage and physical dysfunction [4, 5]. Monotherapy with sarilumab, the latest IL-6 receptor-targeting drug among the nine bDMARDs, has been demonstrated to be as effective for MTX-refractory RA as monotherapy with adalimumab, a TNF-targeting drug. The efficacy of sarilumab in a monotherapy setting has been demonstrated to be comparable to that of tocilizumab, which is also an IL-6 receptor-targeting drug [6].

Since these bDMARDs have been approved for the treatment of RA, their indications have been expanded to include the treatment of >10 autoimmune diseases. For example, infliximab and adalimumab are prescribed for the treatment of psoriasis, IBD, Behçet's disease, etc., and tocilizumab is indicated for the treatment of GCA, Takayasu's arteritis, adult Still's disease, etc., while rituximab is indicated for the treatment of microscopic polyangiitis. Particularly, the indications for tocilizumab have been expanded to include the treatment of cytokine release syndrome associated with chimeric antigen receptor T cell therapy.

At present, clinical trials are in progress on tocilizumab and sarilumab for the treatment of cytokine release syndrome associated with the new coronavirus disease 2019 (COVID-19). In the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia) study, treatment with tocilizumab or sarilumab improved outcomes, including organ support in intensive care units. In the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial, tocilizumab improved survival and other clinical outcomes in hospitalized patients with COVID-19 and with hypoxia and systemic inflammation. However, in the COVACTA study, the use of tocilizumab did not result in significantly better clinical status or lower mortality than placebo at 28 days in hospitalized patients with severe COVID-19 pneumonia [7–9].

On the other hand, although biologics targeting IL-17 or IL-12/IL-23 have failed to demonstrate efficacy in RA treatment, their use in a wide range of diseases such as psoriasis and PsA has contributed to the expansion of their indications. However, newly developed biologics that target cytokines such as GM-CSF and IL-20 have failed to show superiority over TNF-targeting drugs. Consequently, the development of new biologics has become more challenging [10, 11].

Meanwhile, the development of next-generation biologics based on structurally modified antibodies is gaining interest [12–16]. Certolizumab pegol is an anti-TNF antibody prepared by conjugating only humanized Fab fragments, an antigen recognition site, with polyethylene glycol. It is already being marketed and widely used as a drug with enhanced biostability and homing to inflamed tissues [17, 18]. Vobarilizumab is an anti-IL-6 receptor antibody preparation one-tenth the size of a human antibody with high affinity to the antigen, and is derived from a *Camelidae* antibody with only a heavy chain but no light chain. This preparation has been examined in a phase II international clinical trial that yielded significant results [19]. In addition, bispecific

antibodies that simultaneously recognize two or more types of antigens are currently being developed using various structures that are artificially formed based on combinations of two Fab fragments and an Fc fragment. However, ABT-122, which is a bispecific antibody against TNF and IL-17, has not been demonstrated to be equivalent or superior to anti-TNF antibodies with respect to efficacy in the treatment of MTX-refractory RA [20]. Although a study has shown that romilkimab, a bispecific antibody against IL-4 and IL-13, inhibits the progression of sclerema in systemic sclerosis, the study was discontinued because it was less effective on lung function [21]. Rozibafusp (AMG 570), a bispecific antibody against inducible T cell costimulator ligand expressed by follicular T cells and soluble B cell activating factor stimulating B cells, is currently being examined in phase II clinical trials on RA and SLE [22]. Attention is drawn to whether the effects of structurally diverse bispecific antibodies exceed the high efficacy of available bDMARDs such as a TNF inhibitor adalimumab.

### Targeted synthetic DMARDs

Orally administered low-molecular-weight compounds that are as effective as biologics have garnered increasing attention recently. Because of their low molecular weight, they enter a cell through the plasma membrane, bind to intracellular signalling molecules in a lock-and-key manner, and inhibit their target molecules. An enzyme that phosphorylates signalling molecules is called a kinase. Of at least 518 kinases described to date, JAK enzymes are typical tyrosine kinases. When cytokines bind to receptors, they phosphorylate the associated JAK. Phosphorylated JAK activates the intracellular components of the receptors and binds to signal transducers and activators of transcription (STATs). When STATs are phosphorylated, they enter the nucleus and induce transcription [23–25].

Tofacitinib was developed as a low-molecular-weight compound that competitively binds to the adenosine triphosphate-binding site of JAK3 and specifically inhibits its phosphorylation of JAK3. However, tofacitinib also displays potency against JAK1 and to a lesser extent JAK2, and less still TYK2, and is currently designated a JAK inhibitor. It was approved as the first JAK inhibitor for the treatment of RA in the USA in 2012. At present, the JAK1/2 inhibitor baricitinib and JAK inhibitors peficitinib and upadacitinib, and a JAK1 inhibitor filgotinib, have been approved for the treatment of RA (Table 1). However, all the five JAK inhibitors are currently designated as a JAK inhibitor. While *in vitro* intracellular signalling analyses suggest that the therapies are somewhat distinct, in clinical trials they look reasonably similar and long-term observation in the clinic will tell us whether they differ in practice. Phase III international clinical trials have demonstrated that the clinical and structural effects of these JAK inhibitors were significantly more robust and rapid than the effects of placebo in MTX-naïve patients, as well as in RA patients with inadequate responses to csDMARDs such as MTX or

bDMARDs such as TNF-targeting drugs [26–31]. Baricitinib and filgotinib are significantly more effective than adalimumab [28, 31], whereas upadacitinib is significantly more effective than adalimumab and the selective T cell costimulatory modulator abatacept [30, 32]. Upadacitinib monotherapy showed statistically significant improvements in clinical and functional outcomes vs continuing MTX in an MTX inadequate-responder population [33]. Different from other JAK inhibitors, filgotinib forms active metabolites just after the oral intake and shows characteristic pharmacokinetic patterns of cytokine signalling inhibition [34, 35]. While there are no direct comparative studies between JAK inhibitors, we have reported that baricitinib is significantly more effective than tofacitinib in patients adjusted for patient characteristics using a propensity score-based method known as inverse probability of treatment weighting [36]. In addition, we have also shown that peficitinib is comparable to baricitinib and tofacitinib in terms of efficacy on the basis of a network meta-analysis [37].

Furthermore, JAK inhibitors bring the robust inhibition of bone erosion in RA. For instance, compared with placebo, baricitinib significantly inhibited joint inflammation and radiographic joint damage progression in RA patients during phase III studies, which were comparable to those observed with adalimumab, and these effects continued over 1 and 2 years in the long-term extension study. These findings were supported by pre-clinical studies, which showed that baricitinib has an osteoprotective effect, increasing mineralization in bone-forming cells [38]. We also reported that osteoclasts derived from dendritic cells by stimulation of IL-4, GM-CSF, M-CSF and receptor activator of NF- $\kappa$ B ligand (RANKL) played pathological roles in chronic inflammatory and destructive synovitis via osteoclastic bone resorption and that such dendritic cell-derived osteoclasts could be potential targets of JAK inhibitors [39, 40].

On the other hand, there is a consensus that the short- and long-term safety of JAK inhibitors are almost comparable to that of bDMARDs [26, 41, 42]. Studies on the safety of tofacitinib for up to 9.5 years have shown that the incidence rates of infections, opportunistic infections, serious infections, malignancies, thrombosis and cardiovascular disorders remain constant over time [43]. However, the incidence rates of opportunistic infections, including herpes zoster, are slightly higher for JAK inhibitors, except for filgotinib [26, 35]. Furthermore, Pfizer announced that the prespecified non-inferiority criteria for the co-primary endpoints of major adverse cardiovascular events and malignancies were not met for the primary comparison of the combined tofacitinib doses (5 or 10 mg twice daily) versus TNF inhibitors, etanercept or adalimumab in their regular use in the ORAL Surveillance trial in January 2021 [44]. Based on the announcement, the European Medicines Agency recommended that tofacitinib should only be used in patients >65 years of age, patients who are current or past smokers, patients with other cardiovascular risk factors,

TABLE 1 JAK inhibitors, targeted synthetic DMARDs, approved for RA in Japan

Drug name	Structure (MW, Da)	Dose	Original targets	AUC <sup>a</sup> (ng·h/ml)	Cmax <sup>a</sup> (ng/ml)	Tmax <sup>a</sup> (h)	T1/2 <sup>a</sup> (h)	Indication	Marketed <sup>c</sup> (year/month)
Tofacitinib	505.49	5 mg, BID	JAK1/3	387	141	0.75	3.14	RA, JIA, PsA, UC	2013/7
Baricitinib	371.42	4 mg, QD (2 mg)	JAK1/2	297	50.7	0.88	6.39	RA, AD, COVID-19	2017/9
Peficitinib	407.3	150 mg, BID (100 mg)	JAK3	2524 <sup>b</sup>	648	1.8	7.5	RA	2019/7
Upadacitinib	389.38	15 mg, QD (7.5 mg <sup>d</sup> )	JAK1	235	26.3	3.0	8.25	RA, PsA, AS	2020/4
Filgotinib	541.58	200 mg, QD (100 mg)	JAK1	6.08 (81.4 <sup>e</sup> )	3.77 (5.09 <sup>e</sup> )	0.5 (1.5 <sup>e</sup> )	10.7 (16.7 <sup>e</sup> )	RA	2020/11

<sup>a</sup>Pharmacokinetics in Japanese healthy volunteers. <sup>b</sup>Pharmacokinetics of single administration of peficitinib 200 mg are shown. <sup>c</sup>Marketed in Japan, and peficitinib is not approved in USA, EU and the UK. <sup>d</sup>Upadacitinib 7.5 mg QD of is also approved only in Japan. <sup>e</sup>Pharmacokinetics of GS-829845, which is an active metabolite of filgotinib, are shown. AUC: area under the curve; AD: atopic dermatitis; BID: twice a day; COVID-19: coronavirus disease 2019; JAK: Janus kinase; MW: molecular weight; QD: once a day; UC: ulcerative colitis. Only baricitinib 2 mg QD is approved for RA in USA

and patients with other malignancy risk factors, if no suitable treatment alternative is available, in June 2021 [45]. The similar risk assessments will be required for other JAK inhibitors. Thus, although JAK inhibitors are orally administered, they should not be prescribed without careful consideration. Patients should be adequately screened and monitored for infection, cardiovascular disorders, thrombosis, malignancies, etc.

Currently, many drugs are being studied to expand their indications to facilitate drug repurposing. Such studies have led to the approval of tofacitinib for the treatment of ulcerative colitis and PsA, baricitinib for the treatment of atopic dermatitis and upadacitinib for the treatment of AS. Meanwhile, it has been shown that baricitinib may mitigate cytokine storms in COVID-19 and simultaneously inhibit viral proliferation in infected cells [46, 47]. Consequently, baricitinib has been approved for use in combination with remdesivir in patients requiring supplemental oxygen by the Pharmaceuticals and Medical Devices Agency, Japan, and the US Food and Drug Administration has issued an Emergency Use Authorization to permit the emergency use.

In addition to JAK inhibitors, drugs targeting spleen tyrosine kinase (Syk) and Bruton's tyrosine kinase (Btk) are currently being examined in multiple clinical trials. Syk binds to B cell and Fc receptors and is involved in the activation of B cells, mast cells, etc., in addition to bone resorption by osteoclasts. Although a clinical trial demonstrated that fostamatinib, an oral Syk-targeting drug, is effective for the treatment of RA, the development of this drug has been discontinued because the results failed the commercial target based on the radiographical changes in assessed joints [48]. Btk induces the differentiation and activation of B cells and is also involved in the activation of mast cells, production of cytokines and differentiation of osteoclasts. Among several clinical trials of Btk-targeting drugs in progress, a Btk inhibitor fenebrutinib demonstrated comparable efficacy to adalimumab in RA patients with an inadequate response to MTX in a phase II trial (ANDES study) [49]. Meanwhile, genome-wide association analysis has identified the multiple genes encoding Toll-like receptor (TLR)-mediated signalling in RA. IL-1 receptor-associated kinase 4 (IRAK4) and receptor interacting protein 1 (RIP1) kinase play pivotal roles in activation of innate immunity and production of multiple cytokines such as type I IFN through TLR-mediated signalling. Phase II trials using IRAK4 inhibitors and RIP1 inhibitors as novel agents to suppress inflammation and joint destruction in RA are currently being undertaken [50, 51].

## Remaining unmet needs

### Treatment of difficult-to-treat RA

Despite the advent of various molecular target drugs, multiple drug resistance still remains an important challenging issue that needs appropriate redressal for the treatment of RA. The European Alliance of Associations

for Rheumatology (EULAR) defines difficult-to-treat RA based on the following three conditions: (i) resistance to treatment with two or more bDMARDs or tsDMARDs targeting different sites in patients with csDMARD-refractory RA; (ii) the presence of any of the following conditions: moderate disease activity or greater, clinical signs and symptoms indicative of disease activity, inability to taper glucocorticoids, imaging findings of progression, or RA symptoms impairing the quality of life; and (iii) the presence of RA symptoms that are determined to be problems by rheumatologists [50]. The available bDMARDs are increasingly less effective according to the number of previously failed bDMARDs, and the treatment refractory rate for bDMARDs further increases in patients with difficult-to-treat RA. However, the JAK inhibitors upadacitinib and filgotinib remain therapeutically effective in patients with difficult-to-treat RA and exert their effects regardless of prior medications [52, 53]. Comparable efficacy was also observed in patients treated with baricitinib and with  $>3$  or  $\leq 3$  prior bDMARDs in a phase III study [54]. Furthermore, by an integrated safety analysis of five different phase III trials of upadacitinib, it had comparable short- and long-term safety with active comparators such as MTX and adalimumab, except for increased risk of herpes zoster and creatine phosphokinase elevations [41, 42]. If these inhibitors are safe and effective in actual clinical practice, their use may provide an effective remedy for the treatment of difficult-to-treat RA.

### Development of precision medicine

As various molecular target drugs are used for many immune and infectious diseases, it is necessary to establish new therapeutic systems and strategies based on their differential application. This is a particularly important issue in the treatment of rheumatic diseases, such as highly diverse RA. On the other hand, although biologics targeting TNF, IL-17 and IL-12/IL-23 (p40) are approved for the treatment of PsA associated with destructive SpA, the differentiation of their use is unknown. We have analysed the peripheral lymphocyte phenotypes using 8-colour flow cytometry in patients with PsA registered in our department's registry [55, 56]. Based on the expression of chemokine receptors, we have classified the phenotypes into four types: Th17 dominant, Th1 dominant, hybrid and normal phenotypes. Subsequently, the patients with Th17 dominant, Th1 dominant, and hybrid or normal phenotypes were administered IL-17 antibody, p40 antibody and TNF-targeting drugs, respectively. Such differential drug administration was associated with a  $>90\%$  reduction in the number of patients with an absence of improvement compared with conventional treatment with biologics. Our results suggest that pathological stratification of diseases associated with characteristic cytokines by analysing lymphocytes and other parameters might enable selection of optimal molecular target drugs based on the pathology and development of precision medicine.

### Possibility of drug holiday

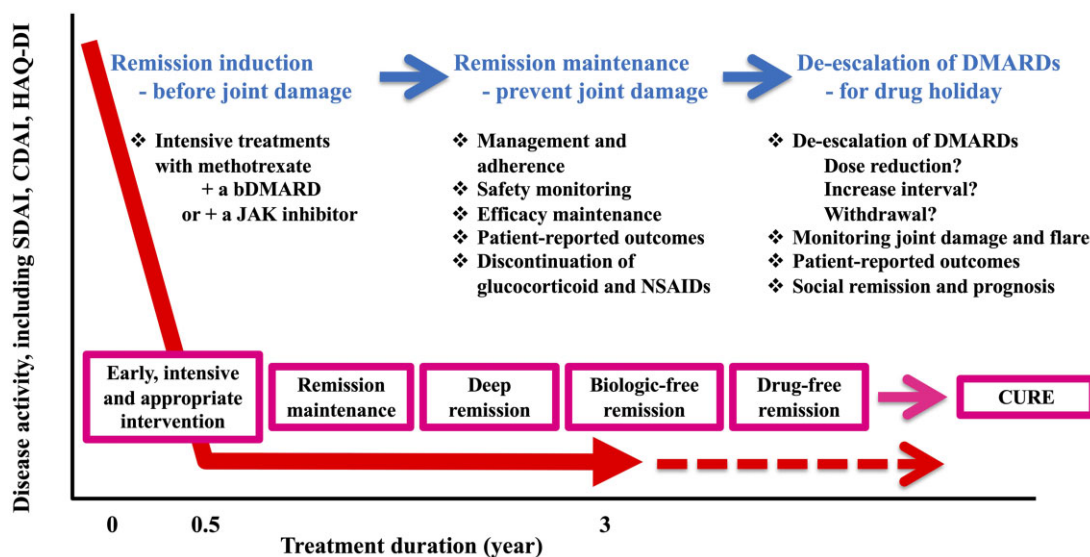
In the treatment of RA, safe and effective long-term treatment is essential after the induction of remission with MTX and bDMARDs/tsDMARDs. However, the burden of medical expenses and problems of medical economics due to long-term continuous use of drugs are pressing issues [57, 58]. It is also unknown whether long-term inhibition of TNF and other targets is safe. In remission induction by the RRR (Remicade in RA) study, the HONOR (Humira Discontinuation Without Functional and Radiologic Damage Progression Following Sustained Remission) study and the C-OPERA (Certolizumab-Optimal Prevention of Joint Damage for Early RA) study, we have reported that bDMARD therapy with TNF-targeted drugs can be withdrawn after sustained remission in patients with RA [59–62]. The international consensus indicates that drug withdrawal after remission should be implemented in the order of CS, anti-inflammatory drugs, bDMARDs and csDMARDs. The four conditions required for withdrawal of bDMARDs and csDMARDs were satisfied with the standard criteria for remission including remission sustained for 6 months or longer, remission sustained with the same drug at the same dose for 6 months or longer, and no use of glucocorticoids [63]. Compared with the withdrawal, it is easier to taper drugs with less frequency of disease flares, but formation of anti-drug antibody and the reduced efficacy is more often observed in patients receiving lower doses of bDMARDs such as

TNF inhibitors [64]. Despite great controversy on whether drug tapering or withdrawal is more appropriate, both drug tapering and withdrawal must contribute to the reduction of medical expenses and adverse events. Strategies to taper and withdraw drugs can be applied to other diseases as well (Fig. 2).

### Conclusions

There are four classes of bDMARDs and one class of tsDMARDs, including five JAK inhibitors, available for molecular-targeted therapy. In the treatment of RA, clinical, structural and functional remission is a realistic target. The latest JAK inhibitors are effective for overcoming even difficult-to-treat RA. However, the development of new drugs has been difficult because head-to-head comparison with TNF-targeted drugs has been a common approach used in recent phase III clinical trials. Thus, instead of adding new drugs, a top priority may involve advances in therapeutic strategies, including strategies to maintain safety and efficacy in balance, as well as thorough implementation of screening at treatment initiation, and monitoring during treatment. In addition, the differential use of therapeutic drugs and de-escalation of treatment after remission induction are also important issues. Achievement of sustained remission with a drug holiday/withdrawal regime suggests the possibility of achieving a drug-free remission and even cure in the later stages of treatment.

Fig. 2 Treatment strategies of RA towards drug holiday and ‘cure’



Intensive treatment is required for inducing remission in RA, but subsequently maintaining remission with high adherence and safety is prerequisite for a good long-term outcome. Achievement of sustained remission with a drug holiday/withdrawal regime suggests the possibility of achieving a drug-free remission and even cure in the later stages of treatment. However, the factors or drivers that inhibit the transition from remission to cure may exist not only in the immune system, but also in the mesenchymal, intestinal, nerve and the metabolic systems. bDMARD: biological DMARD; CDAL: Clinical Disease Activity Index; HAQ-DI: HAQ Disability Index; JAK: Janus kinase; SDAI: Simplified Disease Activity Index.

However, the factors or drivers that inhibit the transition from remission to cure may exist not only in the immune system, but also in mesenchymal, intestinal, nerve and the metabolic system [65]. Thus, the elucidation of such drivers and approaches to regulate them may serve as an important strategy in addressing the challenges and unmet needs in the management of RA.

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### References

- Smolen JS, Aletaha D, Barton A *et al.* Rheumatoid arthritis. *Nat Rev Dis Primers* 2018;4:18001.
- Smolen JS, Landewé RBM, Bijlsma JWW *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;79:685–99.
- Tanaka Y. Rheumatoid arthritis. *Inflamm Regen* 2020;40:20.
- Weinblatt ME, Bathon JM, Kremer JM *et al.* Safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and longstanding rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2011;63:373–82.
- Keystone EC, Breedveld FC, van der Heijde D *et al.* Longterm effect of delaying combination therapy with tumor necrosis factor inhibitor in patients with aggressive early rheumatoid arthritis: 10-year efficacy and safety of adalimumab from the randomized controlled PREMIER trial with open-label extension. *J Rheumatol* 2014;41:5–14.
- Burmester GR, Lin Y, Patel R *et al.* Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. *Ann Rheum Dis* 2017;76:840–7.
- Gordon AC, Mouncey PR, Al-Beidh F *et al.*; REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021;384:1491–502.
- RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021;397:1637–45.
- Rosas IO, Bräu N, Waters M *et al.* Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. *N Engl J Med* 2021;384:1503–16.
- Weinblatt ME, McInnes IB, Kremer JM *et al.* A randomized phase IIb study of mavrilimumab and golimumab in rheumatoid arthritis. *Arthritis Rheumatol* 2018;70:49–59.
- Šenolt L, Leszczynski P, Dokoupilová E *et al.* Efficacy and safety of anti-interleukin-20 monoclonal antibody in patients with rheumatoid arthritis: a randomized phase IIa trial. *Arthritis Rheumatol* 2015;67:1438–48.
- Kerschbaumer A, Sepriano A, Smolen JS *et al.* Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2020;79:744–59.
- van Roy M, Ververken C, Beirnaert E *et al.* The preclinical pharmacology of the high affinity anti-IL-6R Nanobody<sup>®</sup> ALX-0061 supports its clinical development in rheumatoid arthritis. *Arthritis Res Ther* 2015;17:135.
- Genovese MC, Weinblatt ME, Mease PJ, Aelion JA *et al.* Dual inhibition of tumour necrosis factor and interleukin-17A with ABT-122: open-label long-term extension studies in rheumatoid arthritis or psoriatic arthritis. *Rheumatology (Oxford)* 2018;57:1972–81.
- Allanore Y, Wung P, Soubrane C *et al.* A randomised, double-blind, placebo-controlled, 24-week, phase II, proof-of-concept study of romilkimab (SAR156597) in early diffuse cutaneous systemic sclerosis. *Ann Rheum Dis* 2020;79:1600–7.
- Zhang M, Lee F, Knize A *et al.* Development of an ICOSL and BAFF bispecific inhibitor AMG 570 for systemic lupus erythematosus treatment. *Clin Exp Rheumatol* 2019;37:906–14.
- Carron P, Lambert B, Van Praet L *et al.* Scintigraphic detection of TNF-driven inflammation by radiolabelled certolizumab pegol in patients with rheumatoid arthritis and spondyloarthritis. *RMD Open* 2016;2:e000265.
- Miyazaki Y, Nakano K, Nakayamada S *et al.* Serum TNF $\alpha$  levels at 24 h after certolizumab pegol predict effectiveness at week 12 in patients with rheumatoid arthritis from Tsubame study. *Arthritis Res Ther* 2021;23:154.
- Dorner T, Weinblatt M, Van Beneden K *et al.* Results of a phase 2B study of vobarilizumab, an anti-interleukin-6 receptor nanobody, as monotherapy in patients with moderate to severe rheumatoid arthritis [abstract]. *Ann Rheum Dis* 2017;76.
- Genovese MC, Weinblatt ME, Aelion JA *et al.* ABT-122, a bispecific dual variable domain immunoglobulin targeting tumor necrosis factor and interleukin-17a, in patients with rheumatoid arthritis with an inadequate

- response to methotrexate: a randomized, double-blind study. *Arthritis Rheumatol* 2018;70:1710–20.
- 21 Allanore Y, Denton C, Khanna D *et al.* Efficacy and safety of romilkimab in diffuse cutaneous systemic sclerosis (dcSSc): a randomized, double-blind, placebo-controlled, 24-week, proof of concept study [abstract]. *Arthritis Rheumatol* 2019;71(Suppl 10).
  - 22 Abuqayyas L, Cheng L, Park K *et al.* Safety and biological activity of Rozibafusp Alfa in subjects with rheumatoid arthritis: final results of a phase 1b randomized, double-blind, placebo-controlled, multiple ascending dose study [abstract]. *Arthritis Rheumatol* 2020;72(Suppl 10).
  - 23 Tanaka Y, Maeshima Y, Yamaoka K. In vitro and in vivo analysis of a JAK inhibitor in rheumatoid arthritis. *Ann Rheum Dis* 2012;71:i70–4.
  - 24 O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A. Janus kinase inhibitors in autoimmune diseases. *Ann Rheum Dis* 2013;72:ii111–5.
  - 25 Tanaka Y. The JAK inhibitors: do they bring a paradigm shift for the management of rheumatic diseases? *Rheumatology (Oxford)* 2019;58:i1–3.
  - 26 Nash P, Kerschbaumer A, Dörner T *et al.* Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement. *Ann Rheum Dis* 2021;80:71–87.
  - 27 van der Heijde D, Tanaka Y, Fleischmann R *et al.*; ORAL Scan Investigators. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum* 2013;65:559–70.
  - 28 Taylor PC, Keystone EC, van der Heijde D *et al.* Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med* 2017;376:652–62.
  - 29 Tanaka Y, Takeuchi T, Tanaka S *et al.* Efficacy and safety of peficitinib (ASP015K) in patients with rheumatoid arthritis and an inadequate response to conventional DMARDs: a randomised, double-blind, placebo-controlled phase III trial (RAJ3). *Ann Rheum Dis* 2019;78:1320–32.
  - 30 Fleischmann R, Pangan AL, Song IH *et al.* Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. *Arthritis Rheumatol* 2019;71:1788–800.
  - 31 Combe B, Kivitz A, Tanaka Y *et al.* Filgotinib versus placebo or adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate: a phase III randomised clinical trial. *Ann Rheum Dis* 2021;80:848–58.
  - 32 Rubbert-Roth A, Enejosa J, Pangan AL *et al.* Trial of upadacitinib or abatacept in rheumatoid arthritis. *N Engl J Med* 2020;383:1511–21.
  - 33 Smolen JS, Pangan AL, Emery P *et al.* Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. *Lancet* 2019;393:2303–11.
  - 34 Traves PG, Murray B, Campigotto F *et al.* JAK selectivity and the implications for clinical inhibition of pharmacodynamic cytokine signalling by filgotinib, upadacitinib, tofacitinib and baricitinib. *Ann Rheum Dis* 2021;80:865–75.
  - 35 Tanaka Y, Kavanaugh A, Wicklund J, McInnes IB. Filgotinib, a novel JAK1-preferential inhibitor for the treatment of rheumatoid arthritis: an overview from clinical trials. *Mod Rheumatol* 2021;1–11.
  - 36 Miyazaki Y, Nakano K, Nakayamada S *et al.* Efficacy and safety of tofacitinib versus baricitinib in patients with rheumatoid arthritis in real clinical practice: analyses with propensity score-based inverse probability of treatment weighting. *Ann Rheum Dis* 2021;80:1130–6.
  - 37 Tanaka Y, Okumura H, Kim S *et al.* Comparative efficacy and safety of peficitinib versus tofacitinib and baricitinib for treatment of rheumatoid arthritis: a systematic review and network meta-analysis. *Rheumatol Ther* 2021;8:729–50.
  - 38 Emery P, Durez P, Hueber AJ *et al.* Baricitinib inhibits structural joint damage progression in patients with rheumatoid arthritis—a comprehensive review. *Arthritis Res Ther* 2021;23:3.
  - 39 Narisawa M, Kubo S, Okada Y *et al.* Human dendritic cell-derived osteoclasts with high bone resorption capacity and T cell stimulation ability. *Bone* 2021;142:115616.
  - 40 Tanaka Y. Managing osteoporosis and joint damage in patients with rheumatoid arthritis: an overview. *J Clin Med* 2021;10:1241.
  - 41 Conaghan PG, Mysler E, Tanaka Y *et al.* Upadacitinib in rheumatoid arthritis: a benefit-risk assessment across a phase III program. *Drug Saf* 2021;44:515–30.
  - 42 Cohen SB, van Vollenhoven RF, Winthrop KL *et al.* Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. *Ann Rheum Dis* 2020;80:304–11.
  - 43 Cohen SB, Tanaka Y, Mariette X *et al.* Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. *RMD Open* 2020;6:e001395.
  - 44 Pfizer. *Pfizer shares co-primary endpoint results from post-marketing required safety study of Xeljanz® (tofacitinib) in subjects with rheumatoid arthritis (RA)*. <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-shares-co-primary-endpoint-results-post-marketing>.
  - 45 European Medicines Agency. *Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 7–10 June 2021*. <https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-7-10-june-2021>.
  - 46 Nissen CB, Sciascia S, de Andrade D *et al.* The role of antirheumatics in patients with COVID-19. *Lancet Rheumatol* 2021;3:e447–59.
  - 47 Kalil AC, Patterson TF, Mehta AK *et al.*; ACTT-2 Study Group Members. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med* 2021;384:795–807.
  - 48 Tanaka Y, Millson D, Iwata S, Nakayamada S. Safety and efficacy of fostamatinib in rheumatoid arthritis patients with an inadequate response to methotrexate in



- phase II OSKIRA-ASIA-1 and OSKIRA-ASIA-1X study. *Rheumatology (Oxford)* 2021;60:2884–95.
- 49 Cohen S, Tuckwell K, Katsumoto TR *et al.* Fenebrutinib versus placebo or adalimumab in rheumatoid arthritis: a randomized, double-blind, phase II trial (ANDES Study). *Arthritis Rheumatol* 2020;72:1435–46.
- 50 Wiese MD, Manning-Bennett AT, Abuhelwa AY. Investigational IRAK-4 inhibitors for the treatment of rheumatoid arthritis. *Expert Opin Investig Drugs* 2020;29:475–82.
- 51 Harris PA, Berger SB, Jeong JU *et al.* Discovery of a first-in-class receptor interacting protein 1 (RIP1) kinase specific clinical candidate (GSK2982772) for the treatment of inflammatory diseases. *J Med Chem* 2017;60:1247–61.
- 52 Nagy G, Roodenrijs NMT, Welsing PM *et al.* EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2021;80:31–5.
- 53 Genovese MC, Fleischmann R, Combe B *et al.* Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet* 2018;391:2513–24.
- 54 Genovese MC, Kremer J, Zamani O *et al.* Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med* 2016;374:1243–52.
- 55 Genovese MC, Kalunian K, Gottenberg JE *et al.* Effect of filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy: the FINCH 2 randomized clinical trial. *JAMA* 2019;322:315–25.
- 56 Tanaka Y, Kubo S, Miyagawa I, Iwata S, Nakayamada S. Lymphocyte phenotype and its application to precision medicine in systemic autoimmune diseases. *Semin Arthritis Rheum* 2019;48:1146–50.
- 57 Miyagawa I, Nakayamada S, Nakano K *et al.* Precision medicine using different biological DMARDs based on characteristic phenotypes of peripheral T helper cells in psoriatic arthritis. *Rheumatology (Oxford)* 2019;58:336–44.
- 58 Tanaka Y. Stopping tumour necrosis factor-targeted biological DMARDs in rheumatoid arthritis. *Rheumatology (Oxford)* 2016;55:ii15–22.
- 59 Tanaka Y. Rheumatoid arthritis: DMARD de-escalation - let the patient guide you. *Nat Rev Rheumatol* 2017;13:637–8.
- 60 Tanaka Y, Takeuchi T, Mimori T *et al.*; for the RRR study investigators. Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis, RRR (remission induction by remicade in RA) study. *Ann Rheum Dis* 2010;69:1286–91.
- 61 Tanaka Y, Hirata S, Kubo S *et al.* Discontinuation of adalimumab after achieving remission in patients with established rheumatoid arthritis: 1-year outcome of the HONOR study. *Ann Rheum Dis* 2015;74:389–95.
- 62 Atsumi T, Tanaka Y, Yamamoto K *et al.* Clinical benefit of 1-year certolizumab pegol (CZP) add-on therapy to methotrexate treatment in patients with early rheumatoid arthritis was observed following CZP discontinuation: 2-year results of the C-OPERA study, a phase III randomised trial. *Ann Rheum Dis* 2017;76:1348–56.
- 63 Schett G, Emery P, Tanaka Y *et al.* Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: current evidence and future directions. *Ann Rheum Dis* 2016;75:1428–37.
- 64 Strand V, Goncalves J, Isaacs JD. Immunogenicity of biologic agents in rheumatology. *Nat Rev Rheumatol* 2021;17:81–97.
- 65 Schett G, Tanaka Y, Isaacs JD. Why remission is not enough: underlying disease mechanisms in RA that prevent cure. *Nat Rev Rheumatol* 2021;17:135–44.