Review

Treatment of rheumatoid arthritis with biological agents — as a typical and common immune-mediated inflammatory disease

By Tsutomu TAKEUCHI^{*1,†}

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Abstract: Molecules involved in the disease process facilitated our understanding of pathogenesis of the disease with unknown etiology such as immune-mediated and inflammatory diseases. Moreover, the targeted therapies against the proposed molecular targets by biological agents provide enormous benefits to the patients and societies. Here, I will review recent progress of the biological treatment in the immune-inflammatory diseases by focusing on the rheumatoid arthritis, the disease characterized by persistent polyarthritis leading to joint destruction and disability with autoimmune features, as a role model.

Keywords: immune-mediated inflammatory diseases, rheumatoid arthritis, biologics, cytokines, therapy

Introduction

Molecular and cellular understanding of human diseases is critical for dissecting the mechanisms of pathogenesis and may provide a clue for developing innovative treatment. Among human diseases such as cancers, infections, and metabolic disease, there is a group of inflammatory diseases mediated by immunological mechanisms without apparent etiologies, called immune-mediated inflammatory diseases (IMIDs) including rheumatoid arthritis, inflammatory bowel diseases, and psoriasis.^{1),2)} While the human immune system involves highly complex and coordinated processes, it has been demonstrated that cytokines are overexpressed and T- and B-cells are accumulated in affected tissues in IMIDs.^{1),2)} These key players have been postulated as the potential targets for intervention. Indeed, novel therapeutic antibodies targeted against single molecules that are intimately associated with disease pathogenesis, have led to significantly better outcomes of diseases in clinical practice.³⁾⁻⁵⁾ The therapeutic antibodies are classified into the category of drugs, designated as

“biological agents” or “biologics”, those are bioengineered to target specific proteins or nucleic acids. For instance, a common target of the inflammatory process is tumor necrosis factor (TNF), which is an inflammatory cytokine implicated in the pathogenesis of rheumatoid arthritis. Monoclonal antibodies against single cytokine, TNF alpha (TNF α), have made revolutionary changes in treatment for a range of conditions such as rheumatoid arthritis (RA), inflammatory bowel disease, ankylosing spondylitis, and psoriasis (Table 1). The miracle achieved in the treatment of the IMIDs is reviewed here with a focus on RA, which is a typical and common IMID.^{6),7)}

Pathogenesis of rheumatoid arthritis as a typical and common immune-mediated inflammatory disease

The immune system is beneficial to humans by protecting them from infections caused by bacteria or viruses. There are two major pathways of immunity: innate immunity as the first line of defense and acquired immunity that protects against specific pathogens.⁸⁾ There are unique diseases where inflammation is induced by the immune system, as seen in autoimmunity, and not by infection or malignancy.⁹⁾ The immune-mediated inflammatory diseases include gout, where urate crystals formed in the body elicit inflammation through the innate immune system, and RA, where autoimmunity plays a central role in

^{*1} Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan.

[†] Correspondence should be addressed: T. Takeuchi, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku, Tokyo 160-8582, Japan (e-mail: tsutake@25.keio.jp).

Table 1. Target molecules in immune-mediated inflammatory diseases

target	biologics	RA	JIA	CD	UC	AS	SpA	PS	PsA	CAPS FMF	SLE	pSS	BD	SSc	GCA	TA	AAV	AOSD
TNF α	adalimumab	joint	joint	intestine	intestine	spine	spine	skin	skin&joint	fever	systemic	eye&mouth	mucosa	skin	large vessel	large vessel	small vessel	fever&joint
	certolizumab pegol	joint	joint	intestine	trial	joint	joint	joint	joint				joint					
	golimumab	joint	joint	intestine	joint	joint	joint	joint	joint				joint					
	infliximab	joint	joint	intestine	joint	joint	joint	joint	joint				joint					
IL-6	etanercept	joint	joint	intestine	joint	joint	joint	joint	joint									
	sirolimus	joint	joint	intestine	joint	joint	joint	joint	joint									
	clazakizumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	olokizumab	joint	joint	intestine	joint	joint	joint	joint	joint									
GM-CSF	vobarilzumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	tocilizumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	sarilumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	nanilumab	joint	joint	intestine	joint	joint	joint	joint	joint									
IL-1 β	mavrilumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	canakinumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	rilonacept	joint	joint	intestine	joint	joint	joint	joint	joint									
	anakinra	joint	joint	intestine	joint	joint	joint	joint	joint									
IL-12/23 (p40)	ustekinumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	guselkumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	risankizumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	tildrakizumab	joint	joint	intestine	joint	joint	joint	joint	joint									
IL-17	brazikumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	ixekizumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	secukinumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	brodalumab	joint	joint	intestine	joint	joint	joint	joint	joint									
BAFF	belimumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	bisibimod	joint	joint	intestine	joint	joint	joint	joint	joint									
	sifalimumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	anifrolumab	joint	joint	intestine	joint	joint	joint	joint	joint									
CD80/86	abatacept	joint	joint	intestine	joint	joint	joint	joint	joint									
	rituximab	joint	joint	intestine	joint	joint	joint	joint	joint									
	natalizumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	vedolizumab	joint	joint	intestine	joint	joint	joint	joint	joint									
Integrin $\alpha 4/\beta 1$	etrolizumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	etrolizumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	etrolizumab	joint	joint	intestine	joint	joint	joint	joint	joint									
	etrolizumab	joint	joint	intestine	joint	joint	joint	joint	joint									

© approved, primarily in Japan, except for anakinra and rituximab for RA and abatacept for PsA (September 11, 2017). ○ positive results in Phase 2 or 3 trial, △ proof of concept obtained, × no positive results in Phase 2 or 3,

RA: rheumatoid arthritis, JIA: juvenile idiopathic arthritis, CD: crohn's disease, UC: ulcerative colitis, AS: ankylosing spondylitis, SpA: spondyloarthritis, PS: psoriasis, PsA: psoriatic arthritis, CAPS: cryopyrin associated periodic syndrome, FMF: familial mediterranean fever, SLE: systemic lupus erythematosus, pSS: primary sjogren's syndrome, SSc: systemic sclerosis, GCA: giant cell arthritis, TA: Takayasu arteritis, AAV: ANCA associated vasculitis, AOSD: adult-onset Still's disease

a) Joint appearance (hands)

Early stage

Established stage

Late stage

b) Pathological findings (synovial tissues)

New vessel formation

Lymphocyte infiltration

Synovial hypertrophy

Fig. 1. Clinical and pathological characteristics of rheumatoid arthritis.

perpetuating joint inflammation by breaking tolerance, which surveys and prevents the immune response against self (autoimmunity). RA affects 0.5% to 1.0% of the global population and is recognized as one of the common diseases in humans. RA is characterized by perpetual inflammation in the joint synovium leading to joint destruction and disability (Figure 1).^{4),5)} With respect to the pathogenesis of RA, auto-reactive lymphocytes including CD4+ T cells infiltrate into the joint through adhesion to the vessel wall by $\alpha 4 \beta 1$ integrin-VCAM-1 and $\alpha L \beta 2$ integrin-ICAM-1 as an initial step of inflammation of the joint. After infiltration into the joints, lymphocytes are further activated by antigen-presenting cells mounted with auto-antigens or by abundant extracellular matrix through receptors (Figure 2). An important requirement of T cell activation is co-stimulation through CD28, the absence of which leads to T cell anergy or death. Traditionally, T helper 1 cells are thought to be the T helper subset mediating the disease, but T helper 17 cells that produce IL-17A have been implicated in the pathogenesis.^{4),5)} Activated T cells and B cells work together to interact with synovial cells to produce a

large number of inflammatory mediators, including pro-inflammatory cytokines (TNF α and IL-6), induce matrix metallo-proteinases (MMP), promote synovial proliferation, and induce osteoclast differentiation (Figure 2). Three major cell types of endothelial cells, T and B cells, and synovial cells are present in the synovial tissues in patients with RA.^{4),5)} Through interactions between these cells, pro-inflammatory cytokines such as TNF α and IL-6 are released, thereby facilitating the lowering of the threshold for pain and activating T cells, B cells, and macrophages (Figure 2). Activation of T cells is important in initiation and perpetuation of inflammation in RA. The hypothesis is corroborated by clinical efficacy of abatacept, an inhibitor against the co-stimulating molecule on T cells by substantial numbers of clinical trials. The inflammation is believed to result from or is perpetuated by autoantibodies such as anti-citrullinated peptide antibody and rheumatoid factors.⁵⁾ B cells are thought to be responsible for the production of these autoantibodies. The pathogenic role of CD20+ B cells has been validated by the efficacy of rituximab, a monoclonal antibody against CD20, in clinical trials.

Fig. 2. Pathogenesis of rheumatoid arthritis.

RA treatment in the past

In the past, glucocorticoids and non-steroidal anti-inflammatory drugs were prescribed but they are largely symptomatic treatments and do not sufficiently inhibit joint destruction. Approximately three decades ago, half of RA patients with high disease activity were bed-ridden 10 years after such treatment and their life expectancy was shortened by 10 years compared with the general population. Thus, RA has been recognized as a typical example of an intractable immune-mediated inflammatory disease. Options had previously been limited for patients whose disease did not respond to traditional disease-modifying anti-rheumatic drug (DMARDs) such as methotrexate.

In this regards, enormous efforts have been taken to develop new treatment options based on the molecular understanding for the key targets by biological agents (Figure 3).

Challenges toward miracle medicine: struggles with animal models and proof provided by clinical science

Several animal models of RA exist, including collagen-induced arthritis, collagen antibody-induced arthritis and TNF-alpha transgenic mice, which

share characteristics with human RA. Although these models have limitations and do not encompass the complex mechanisms of RA, they are nevertheless invaluable in exploring disease pathogenesis and validating potential therapeutic strategies. The collagen-induced arthritis model, one of the induced arthritis models, suggested that IL-1 plays a central role in inducing arthritis, and antibodies against IL-1 and IL-1 knockout showed the dramatic prevention of the development of arthritis and inhibition of arthritis and joint destruction in the animal model. On the other hand, immunohistochemical staining of the synovial tissues from RA patients showed increased expression of TNF α not only in synovial-lining cells but also in subintimal tissues.^{5),7)} In addition, it was demonstrated that the anti-TNF α monoclonal antibody could ameliorate collagen-induced arthritis.¹⁰⁾ Given this evidence, there was much debate on whether IL-1 β blockade is more potent than anti-TNF α in clinical efficacy and prevention of joint destruction in these animal models. Following these observations, IL-6 was reported to be an attractive target in arthritis.¹¹⁾ Three agents—a chimeric monoclonal antibody against TNF α infliximab; an IL-1 receptor antagonist, anakinra; and a humanized monoclonal antibody against the IL-6 receptor, tocilizumab—have been tested in clinical

Fig. 3. Structure of biologics.

trials.^{11),12)} The efficacy of infliximab¹³⁾ and tocilizumab¹⁴⁾ was surprisingly excellent and they are widely used in clinical practice after completion of clinical trials and post-marketing clinical studies.^{6),7)} Now, these agents against TNF α and the IL-6 receptor are listed in the European League Against Rheumatism (EULAR) management guidelines and American College of Rheumatology (ACR) Guideline for the Treatment of RA, while IL-1 blockade is no longer positioned as a recommended biologic in RA treatment.^{15),16)} This is because of its modest effect compared with other biologics, and the increased frequency of serious adverse events when used in combination with other biologics. Instead, IL-1 blockade is efficacious in auto-inflammatory diseases, including TNF receptor 1-associated periodic syndrome, as well as juvenile idiopathic arthritis, adult-onset Still's disease, and gout (Table 1). These results again highlighted the importance of clinical science. Similar scenarios were observed with respect to IL-17 blockade, which was shown to ameliorate arthritis in mice models. However, the efficacy and safety of agents against IL-17 and IL-17 receptor failed to show results comparable with those of anti-

TNF and anti-IL-6 receptor.¹⁷⁾ It is interesting to note that the blockade of IL-17 exhibits significant efficacy in patients with spondyloarthritis, psoriasis, and psoriatic arthritis, indicating that IL-17 plays an indispensable role not RA, but in other major immune-mediate inflammatory diseases.¹⁷⁾ The difference between the results of basic research and the clinical trial can be derived from the difference in cell lines and mice strains used in basic research, and the study design with various genetic backgrounds for clinical studies. The comprehensive information from appropriately evaluated basic and early and exploratory clinical studies would lead to the efficient drug development.

Cytokine cascade in RA

Given the efficacy of biologics against different targets, one wonders whether patients who respond to one biologic targeting X will differentially respond to another targeting Y. Also, does group A of RA patients treated with anti-TNF overlap with group B of patients who respond well to anti-IL-6 receptor? One interesting hypothesis may answer part of these questions. Feldmann and Maini found that the level

Fig. 4. Cytokine cascade hypothesis in rheumatoid arthritis.

of circulating IL-6 was significantly decreased several hours after infusing infliximab that target $\text{TNF}\alpha$. This led to the introduction of a cytokine cascade hypothesis that $\text{TNF}\alpha$ is located upstream of IL-6 and regulates the level of IL-6, so that blockade of $\text{TNF}\alpha$ leads to down-regulation of IL-6 in patients with RA.¹⁰⁾ We confirmed this cytokine cascade hypothesis in the majority of RA patients and raised the possibility that a minor cascade from IL-17 to IL-6 and a TNF and GM-CSF circuit exists on top of IL-6 (Figure 4). As shown in the figure, blockade of IL-6 signaling lead to a broad range of changes in biomarkers such as sICAM-1, VEGF, osteonectin, osteopontin, osteocalcin, and bone alkaline phosphatase.¹⁸⁾ Interestingly, regulatory T cells (Treg) are increased after treatment with tocilizumab, indicating that the inhibition of IL-6 signaling may cancel the transcriptional downregulation of Foxp3, a master transcriptional regulator of Treg. Alternatively, inhibition of IL-6 may affect the action of $\text{TGF-}\beta$ on inducing Treg.¹⁹⁾ Importantly, the increased proportion of Treg among CD4^+ T cells is associated with the maintenance of clinical remission of RA in tocilizumab treatment.²⁰⁾

In addition, our other study that analyzed data from the RISING study of infliximab suggested that inhibition of both $\text{TNF}\alpha$ and IL-6 are essential for remission in RA patients.²¹⁾ Even if patients are prescribed infliximab, which blocks $\text{TNF}\alpha$, the inhibition of IL-6 is dispensable for clinical remission.²²⁾ Finally, blocking T cell co-stimulation by abatacept has shown to down-regulate circulating IL-6 levels in RA patients,²³⁾ implying that T cells should play an important role in the cytokine cascade as an upstream position in RA (Figure 4).

Timing of introduction of biologics: ideal positioning of biologics

The timing of the introduction of biologics in RA treatment has been discussed extensively. In the 2015 ACR guideline,¹⁶⁾ initiation of a biologic or combination traditional DMARDs is recommended for patients with symptomatic early or established RA with moderate or high disease activity despite DMARD monotherapy. In the latest EULAR recommendations,¹⁵⁾ addition of a biologic to conventional DMARD is recommended if the treatment goal is not reached by 6 months.

Fig. 5. Timing of introduction of biologics in rheumatoid arthritis. Clinical studies of tocilizumab monotherapy.

The newest clinical trials are currently testing which treatment strategy is the most useful to achieve remission in established RA in Japan (SURPRISE study) and very early RA in the Netherlands (U-Act-Early study).^{24),25)} In the SURPRISE study,²⁴⁾ adding tocilizumab to methotrexate (MTX) for those who respond inadequately to MTX is better than switching to tocilizumab as a significantly higher DAS28 remission rate was achieved at 6 months (69.6% vs. 55.0%, $p < 0.05$). In the U-Act-Early study,²⁵⁾ disease duration of the patients was only 4 weeks after onset of initial symptoms and baseline joint destruction was zero, indicating that the recruited RA patients had very early stage disease. Sustained clinical remission was achieved in 80–90% of patients at 6 months in the tocilizumab monotherapy or tocilizumab + MTX combination groups. When we examined the clinical remission rate of these studies of tocilizumab monotherapy the collected data provided new information with regard to the timing of introduction of biologics in RA—initiation in those with short disease duration results in a greater likelihood of remission (Figure 5). One important clinical question here is whether we can stop biologics or not if we introduce

biologics in earlier duration of the disease. There are several important clinical trials in early RA are reported to date,^{26)–29)} but it is too early to conclude that we can achieve drug free remission by introducing biologics earlier.

Future perspectives

There are several concerns regarding biologics in the treatment of immune-mediated inflammatory diseases. We need to establish useful biomarkers to predict or monitor efficacy and safety.^{6),17),30)} By analyzing the mechanism of action of the biologics, our knowledge is exponentially increased so that innovative tools to guide treatment such as cytokine levels at baseline, monitoring of the concentration of biologics, and DNA chip prediction will be developed that will contribute to personalized or precision medicine in the near future. On-target side effects such as infection should also be managed. The RA patients that are the most difficult to treat are those with co-morbidities such as bacterial or viral infection, interstitial pneumonitis, and other diseases of the major organs. Reactivation of latent infection in RA patients is also problematic. In addition, the

socioeconomic burdens of biologics should be solved by facilitating the development of biosimilars, thereby further cost-cutting the original biologic by efficient bioengineering, and developing targeted synthetic DMARDs that can functionally replace biologics such as cytokine signaling inhibitors (JAK inhibitors, BTK inhibitors, and so on). There are still large unmet needs in RA treatment, and the search for new unique targets, targets located upstream in the cascade, and safer targets are continuing.

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Profile

Tsutomu Takeuchi was born in 1955 in Nagano. He graduated from Keio University School of Medicine in 1980. After completion of post-graduate school of medicine at Keio University, he received Ph.D. degree in 1984. Subsequently, he was a research fellow at Dana-Farber Cancer Institute, Harvard Medical School in Boston from 1985 to 1986 for human immunology. He became Professor of Medicine at Saitama Medical University at 1998 and appointed as vice president of Saitama Medical University at 2004. He became Professor of Medicine at Keio University School of Medicine at 2009 and General Director of Keio University Hospital at 2013, served for 4 years. In August 2017, he is appointed as vice president of Keio University. He has done the pioneering work in the clinical development of biological agents in rheumatology and medicine. He received awards for his research, including the Japan College of Rheumatology, the Uehara memorial, the Naitoh Foundation, and the Waksman Foundation. He served as a chief investigator of the study group by Ministry of Health, Labor, and Welfare, Japan, and a principal investigator of Japanese and global clinical trials against Rheumatoid Arthritis and Systemic Lupus Erythematosus. He serves as a chairman of international committee of the Japanese College of Rheumatology and a member of scientific committee of European League Against Rheumatism. He is the President of Japanese Society for Inflammation and Regeneration and President of Japanese Society for Sjogren's syndrome. He was elected as the president of annual meeting of Asia-Pacific League against Rheumatology at 2020 and the president of 117th annual meeting of the Japan Society of Internal Medicine.