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Preface

First of all, we are delighted to be able to provide the "Innovative Rheumatology" to everyone involved in the treatment and research of rheumatoid arthritis. In recent years, the treatment of Rheumatoid Arthritis has undergone tremendous changes due to methotrexate and biologics in large part. Until a decade ago, avoiding joint destruction in rheumatoid arthritis was not realistic for rheumatologist. However, prevention of joint deterioration is now possible, and the quality of life of patients with rheumatoid arthritis in long-term has been able to improve by advances in treatment. However, there are still many problems to be overcome before achieving the treatment of rheumatoid arthritis. All of review articles presented on this book are explaining treatment, basic research, and patient care of rheumatoid arthritis with innovative perspective and ideas. I hope that the ideas that have been described in these articles help the reader to resolve the outstanding issues in rheumatoid arthritis. Finally, the editor would like to thank the wonderful authors for their contribution to this book. Furthermore, I would like to thank Mr. Danijela Duric and Ms. Silvia Valsa of InTech's for their unfailing help.

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Treatment of Rheumatoid Arthritis with Biological Agents

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Additional information is available at the end of the chapter

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1. Introduction

Cytokines and Rheumatoid Arthritis

The term "cytokine" is coined from the combination of "cyto", a prefix which means cell, and "kine", which denotes movement.

Cytokines all have the following features:

1. They are low-molecular-weight glycoproteins that are not hormones.

2. They have an effect at very small concentrations.

3. Different cytokines can have the same function (redundancy).

For example, both tumor necrosis factor (TNF) and interleukin-6 (IL-6) have synovial proliferation activity and destroy articular cartilage and bone.

4. One cytokine can act on various organs at the same time (pleiotropy).

For example, TNF causes synovial proliferation, destroys articular cartilage, and promotes fever.

5. Each cytokine has a specific receptor and acts by binding to that receptor.

Inflammatory cytokines play a central role in rheumatoid arthritis. In the treatment of rheumatoid arthritis with biological agents, the effects of cytokines are suppressed by blocking the cytokine from binding to its specific receptor (Figure 1).

With respect to these cytokines, antibodies and antibody fusion proteins that inhibit the action of IL-1, IL-6, and TNF have already been commercialized, and development of an IL-17 inhibitor is underway (Figure 2,Table 1).

Antibodies for the treatment of rheumatoid arthritis can be divided into three groups: chimeric antibodies, humanized antibodies, and human antibodies. Experimental monoclonal antibodies are usually produced by immunizing a mouse with an antigen, and therefore, the antibody is 100% mouse antibody. When such an antibody is used as a therapeutic agent in humans, it causes a strong anaphylactic reaction. In an effort to reduce as far as possible the content of heterologous proteins, various chimeric antibodies, humanized antibodies, and human antibodies have been developed for the treatment of rheumatoid arthritis.
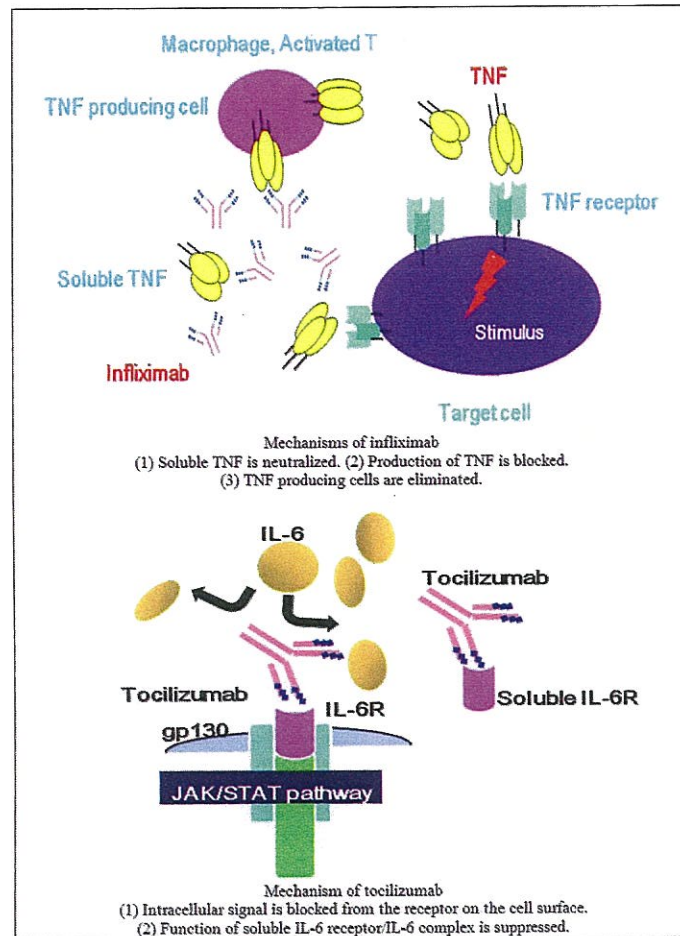

Figure 1. Mechanisms of infliximab and tocilizumab
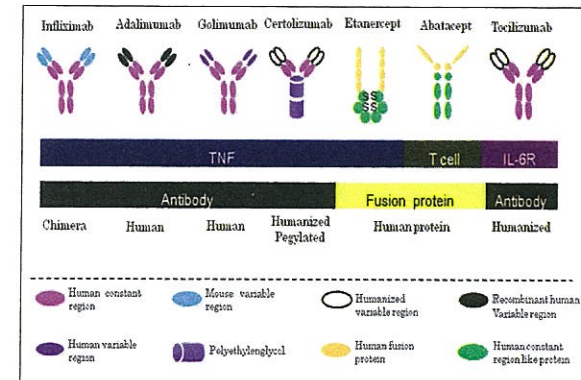

Figure 2. Types of biological agents developed for the treatment of rheumatoid arthritis.

A chimeric antibody is produced first as a mouse monoclonal antibody by immunizing a mouse with an antigen. Then the antigen binding site is preserved as it is, while the Fc site is artificially replaced with one of human origin such as IgG1 or IgG4. In chimeric antibodies, since about 25% mouse protein remains, anaphylactic reactions still occur about 10% of the time when they are administered. There are also reports of treatment with antibody preparations being impaired when antibodies to the chimeric antibody are produced.

A humanized antibody is produced first as a mouse monoclonal antibody, then only the variable parts of the antigen binding site on the heavy chain and light chain of the antibody are left as mouse protein, and the rest is replaced with human protein. Since protein which codes the CDR1, CDR2, and CDR3 regions accounts for about 10% of the total, there is still a small chance of anaphylactic reaction with multiple administrations, though less than that with chimeric antibodies.

Human antibodies are fully human antibodies produced by the phage display method. A typical example is adalimumab. This antibody is produced as follows: An antibody light chain and antibody heavy chain, each with a strong affinity for TNF-α, are selected, and then the two are bound together. Therefore, while it is a fully human protein, it is not an antibody that is physiologically produced in humans. Consequently, it is reported that antibodies against the antibody are detected in 40% of cases or more, reducing the function of the antibody preparation. Combined use of an immunosuppressant to prevent antibody production is recommended.

Another fully humanized antibody on the market is golimumab. This antibody is produced by a method different from that of adalimumab. First, a humanized transgenic mouse is produced, the mouse is immunized with TNF, and the antibodies produced are purified and commercialized. This method has made it possible to produce an antibody which is closer to human than adalimumab.

Target	TNF-				
Product name	Remicade	Enbrel	Humira	Simponi	Cimzia
Non-proprietary name	Infliximab	Etanercept	Adalimumab	Golimumab	Certolizumab pegol
Indications	rheumatoid arthritis, uveitis, Behcet's disease, plaque psoriasis, pustular psoriasis, arthropathic psoriasis, erythrodermic psoriasis, Crohn's disease, ulcerative colitis	rheumatoid arthritis, poly juvenile idiopathic arthritis.	rheumatoid arthritis, poly juvenile idiopathic arthritis, plaque psoriasis, arthropathic psoriasis, ankylosing spondylitis, Crohn's disease	rheumatoid arthritis	rheumatoid arthritis, Crohn's disease
Administration method	Drip infusion	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection
Administration interval	At wk 0, wk 2, wk 6, then every 8 wks	Every 1–2 wks	Every 2 wks	Every 4 wks	Every 4 wks
Structure	Chimeric antibody	TNFR–IgG1 fusion protein	Human antibody	Human antibody	Pegylated humanized antibody
Representative clinical study	ATTRACT[1] ASPIRE[2] ERA[3] TEMPO[4]		PREMIER[5] DE019[6]	GO-FORWARD[7] AFTER[8]	GO-FAST4WARD[9] RAPID2[10]

Target	IL-1Rreceptor	IL-6Receptor	CD80/86	CD20
Product name	Kineret	Actemra (RoActemra)	Orencia	Rituxan (MabThera)
Non-proprietary name	Anakinra	Tocilizumab	Abatacept	Rituximab
Indications	rheumatoid arthritis	rheumatoid arthritis, poly juvenile idiopathic arthritis, systemicrheumatoid juvenile idiopathicarthritis, Castleman's disease	rheumatoid arthritis	rheumatoid arthritis, non-Hodgkin's lymphoma
Administration method	Subcutaneous injection	Drip infusion	Drip infusion	Drip infusion
Administration interval	Every 1 or 2 days	Every 4 wks	Every 4 wks	Day 1 and 15, then every 24 wks
Structure	IL-1 receptor antagonist recombinant protein	Humanized antibody	CTLA-4–IgG1 fusion protein	Chimeric antibody
Representative clinical study	[11, 12]	SAMURAI[13] OPTION[14]	AIM[15] ATTAIN[16]	REFLEX[17] SERENE[18]

Table 1. Characteristics of various biological agents

2. Types of Cytokine Inhibitors (Biological Agents) and their effects on Rheumatoid Arthritis

Cytokine inhibitors used in the treatment of rheumatoid arthritis are inhibitors of IL-1 (anakinra), TNF (infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol), and IL-6 (tocilizumab). In addition, biological agents other than cytokine inhibitors used in the treatment of rheumatoid arthritis include abatacept, which inhibits the action of T-cell co-stimulatory molecules CD80 and CD86, and rituximab, which targets CD20.

These drugs each have a stronger effect than methotrexate(MTX), which is considered to be most effective taken orally, and each has strong action to suppress bone and joint destruction (Figure 3, Figure. 4) [19].

Treatment with any biological agent is more effective than MTX monotherapy, and each suppresses bone and joint destruction.
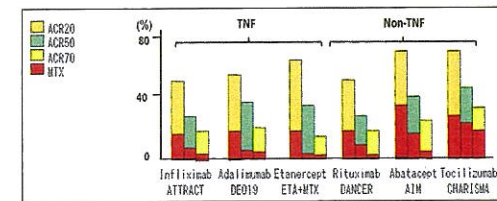

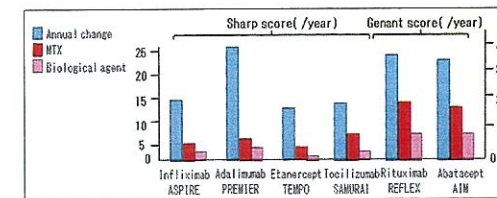Figure 3. Improvement of clinical symptoms with biological agents

Figure 4. Suppression of joint destruction with biological agents

3. Recommendations for the Use of Biological Agents

Opinion is divided on which biological agent should be used to start with when active rheumatoid arthritis is diagnosed. Among typical rankings for the use of biological agents, there is the 2012 recommendation of the American College of Rheumatology (Figure 5) [20].

According to this recommendation, in the United States the first biological agent (1st Bio) recommended for treatment of early rheumatoid arthritis with disease duration of less than 6 months is a TNF inhibitor. For treatment of established RA with disease duration of 6 months or more, a TNF inhibitor and abatacept or rituximab are recommended as the 1st Bio.
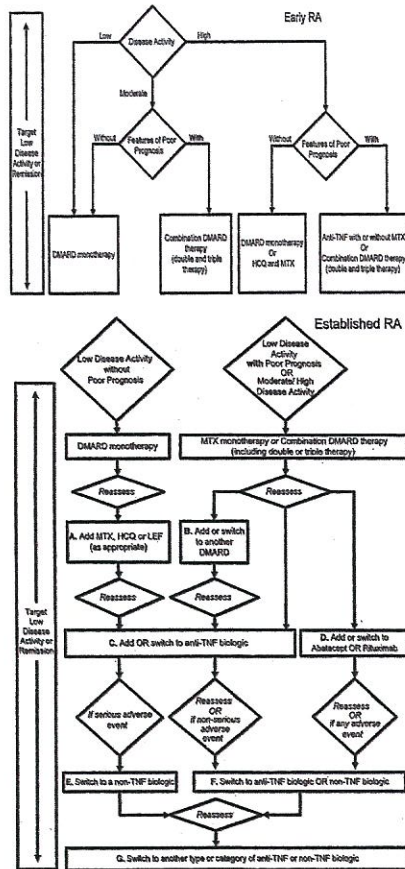

Figure 5. American College of Rheumatology 2012 Recommendation

On the other hand, the British National Institute for Health and Clinical Excellence (NICE) specifies the following guidance on usage (Figure 6) [21–27]:
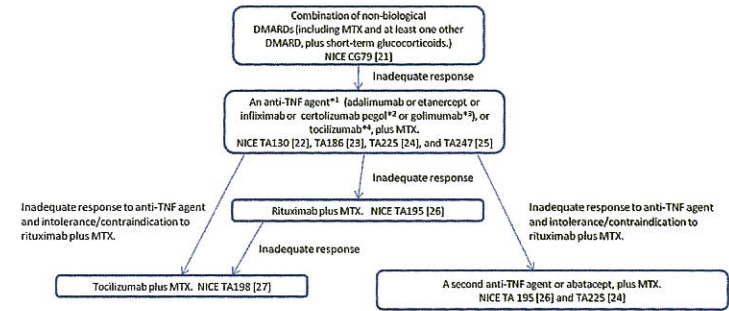
Figure 6. *[1]The annual cost of the biological agent is also specified and does not exceed £9,295 a year.*[2]If certolizumab pegol is the 1st Bio, there should be a system wherein the manufacturer provides the first 12 weeks for free [23]. *[3]If golimumab is used as the 1st Bio, compensation from the manufacturer is necessary so that the drug price of 50 mg and 100 mg is the same [24].*[4]Tocilizumab can be used as the 1st Bio with a discount provided by the manufacturer. Therefore, whichever biological agent is used first, the annual cost of any is £9,295 or less [27].NICE guidance on the treatment of patients with rheumatoid arthritis.

4. Selecting Biological Agents by Efficacy and Safety

Among TNF inhibitors, there are several biological agents to choose from, with no strict standards for which biological agent to use first in either the United States or the United Kingdom. Most physicians choose one based on their own experience. Recently however, data has begun to accumulate suggesting which usage is best.

Regarding efficacy, there is data indicating that etanercept is more effective than infliximab for active rheumatoid arthritis with high levels of anti-cyclic citrullinated peptide antibodies and rheumatoid factor [28]. In addition, among infliximab, adalimumab, and etanercept, it is reported that etanercept shows the highest efficacy in patients with high levels of anti-SS-A antibody [29].

With respect to adverse reactions, the occurrence of tuberculosis among patients treated with anti TNF agents has been shown to be low for the fusion protein preparation etanercept and high for the antibody preparations infliximab and adalimumab. It has been suggested that the reason for this could be that the antibody preparations, unlike the fusion protein preparation etanercept, simultaneously suppress the function of macrophages [30, 31].

Therefore, from the point of view of adverse reactions, etanercept may be the best choice for rheumatoid arthritis patients with a risk of tuberculosis.

The same could possibly be considered for tocilizumab, an IL-6 inhibitor which does not directly suppress macrophage function. A postmarketing survey of tocilizumab as used in a

real-world clinical setting has shown an incidence of tuberculosis of 0.22% [32], which is lower than that of TNF inhibitors.

In comparative studies of related biological agents, almost no difference in efficacy was seen between infliximab and abatacept [33] or between adalimumab and abatacept [34]. However, in a study comparing adalimumab and tocilizumab, tocilizumab was shown to be more effective than adalimumab [35] (Table 2).

	ATTEST Study	AMPLE Study	ADACTA Study
Agents	Abatacept vs. Infliximab	Abatacept + MTX vs. Adalimumab + MTX	Tocilizumab vs. Abatacept
Primary endpoint	DAS28(ESR)	ACR20	DAS28(ESR)
Study period	1 year	1 year	24 weeks
Result	−2.88 vs.−2.25 (n.s)	64.8% vs. 63.4% (n.s)	−3.3 vs. −1.8 (p < 0.0001)

Table 2. Comparative study of related biological agents

Considered this way, the non-TNF cytokine inhibitor (IL-6 inhibitor) tocilizumab could be a biological agent with greater pharmacological effect than TNF inhibitors with fewer adverse reactions due to tuberculosis if used appropriately. Comparison of TNF and IL-6 shows mostly the same pharmacological effects due to cytokine redundancy. Examples of this include the induction of synovial proliferation, induction of inflammatory cytokines, and articular destruction.
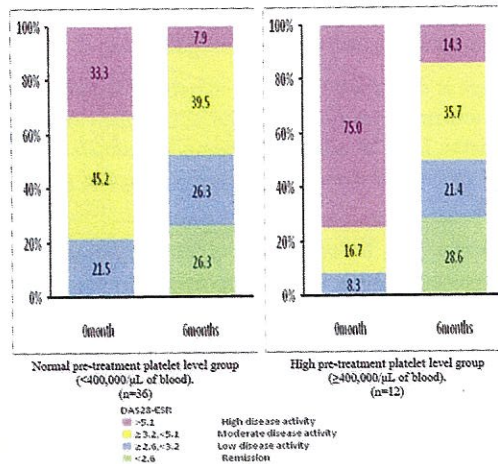
Figure 7. Degree of DAS28 remission with tocilizumab treatment (own data)

However, a characteristic effect of IL-6, which is stronger than that of TNF, is the induction of peripheral platelets in bone marrow megakaryocytes. The effect of IL-6 to induce C-reactive protein in hepatocytes is also thought to be stronger than the effect of TNF.

When the outcomes of cases in which tocilizumab was selected as the 1st Bio were compared in rheumatoid arthritis patients stratified by pre-treatment platelet levels, improvement in rheumatoid activity due to tocilizumab was found to be more marked in patients with high pre-treatment platelet levels (≥400,000 /μL of blood) than in those with normal platelet levels (Figure 7).

From these results, the effects of IL-6 are stronger than the effects of TNF in patients with rheumatoid arthritis of high activity and high platelet levels, which might be a good indication for the use of tocilizumab. In SCID-Hu-RA experimented mouse, which is implanted human RA synovium into back of the severe combined immune deficient (SCID) mouse, human RA synovium is markedly suppressed by tocilizumab treatment in compared with control mouse [36].Tocilizumab not only improves clinical symptoms of rheumatoid arthritis, but is also effective in improving pathological findings in rheumatoid arthritis (Figure 8).

A Control:Saline treatment   B:Indomethacin treatment   C:Tocilizumab treatment
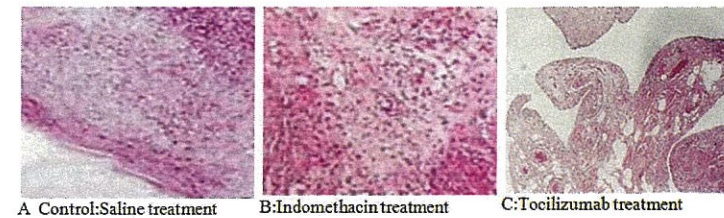
Figure 8. Typical changes in synovial membrane seen with tocilizumab treatment

Inflammatory cells in synovial membrane are suppressed by tocilizumab and replaced by fibrous tissue or adipose tissue.

5. Problems with Biological Agents

Biological agents are a very useful treatment for active rheumatoid arthritis, but there are still many problems which must be solved, including their high cost and the problem of adverse reactions such as infections. As described in the US recommendation and UK guidance, they should probably be used in patients who do not obtain symptomatic relief following treatment with DMARDs.

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Small Molecule DMARD Therapy and Its Position in RA Treatment

Hiroaki Matsuno

Additional information is available at the end of the chapter

1. Introduction

Small molecule disease-modifying antirheumatic drugs (DMARDs) played a central role in drug therapy for rheumatoid arthritis (RA) before biological preparations (biologics) came into extensive use for the treatment of this disease. Unlike non-steroidal anti-inflammatory drugs (NSAIDs) and steroids, which primarily alleviate the symptoms of RA such as pain and inflammation, DMARDs are known to suppress the progression of RA through their action against immunological abnormalities.

To review the history of the clinical positioning of DMARD therapy, until the beginning of the 1990s, DMARDs were used only in patients showing signs of disease progression (e.g., bone erosion) after NSAIDs or steroid treatment within the framework of pyramid therapy [1]. During the 1990s through the 2000s, the strategy and goals of RA therapy have undergone marked changes following the introduction of methotrexate (MTX) as another treatment option, the expansion of MTX as an anchor drug [2,3,4], endorsement of the usefulness of combined drug therapy involving DMARDs [5], the introduction of biologics into RA treatment [6,7,8], and other advances. In 2002, the American College of Rheumatology (ACR) released its Guidelines on RA Management, clearly indicating DMARDs as first-line drugs for the treatment of RA. As a result, NSAIDs and steroids came to be positioned as auxiliary means of treating RA [9].

The small molecule DMARDs that have been used frequently in Western countries are MTX, sulphasalazine (SASP), hydroxychloroquine (HCQ), leflunomide (LFN), and minocycline (MIN). In Japan, where the repertoire of drugs clinically available differs from that in Western countries, HCQ and MIN are not indicated for RA under the national health policy, and bucillamine (BUC) has been a more popular small molecule DMARD than these 2 drugs.

The use of biologics such as TNF inhibitors began to spread around the world within several years of their clinical introduction as drugs that exert rapid action and are expected to improve long-term prognosis and to allow patients with RA to maintain physical function [10]. During the 2000s, revisions of the guidelines on RA treatment and criteria for diagnosis of RA were accelerated in various countries, with the goal of treatment shifting from symptom control (anti-inflammatory analgesia) and delayed disease progression to achievement of disease remission and suppression of disease progression. As an accumulation of clinical trial data became available revealing from a long-term perspective the advantageous effects of biologics not found in small molecule DMARDs, including suppression of progression of bone destruction and physical dysfunction [11,12], biologics began to replace small molecule DMARDs, primarily in patients anticipated to have a poor prognosis and those with rapidly advancing disease. In addition, introduction of biologics into therapy at an early stage of active RA has been recommended in some guidelines because of the benefits expected from this kind of drug for maintaining long-term quality of life in many patients [13].

Nonetheless, there are still several open issues involved in the use of biologics, including:

1. presence of a considerable percentage of patients who fail to respond to treatment with biologics[14],

2. heavy economic burdens for individuals and the community due to high drug prices [15],

3. risk of serious adverse reactions (e.g., infection) in some patients [16,17], and so on.

These issues represent obstacles to the establishment of biologics as a predominant means of treatment for RA. In recent years, several reports have been published in the United States and Europe providing data intended to serve as evidence for the view that treatment with a combination of 3 small molecule DMARDs is expected to improve long-term prognosis of RA to an extent comparable with biologics. Following these reports, in Western countries, the guidelines/guidance on RA treatment have been further reviewed, resulting in restatement of the position that small molecule DMARDs are first-line drugs, and a clear statement that combination therapy with small molecule DMARDs should be tried before the therapy with biologics [18]. This chapter will describe the popular small molecule DMARDs currently used for treatment of RA and present a discussion regarding the current position of small molecule DMARDs in RA treatment guidelines/guidance, as well as its background. In addition, 2 new small molecule DMARDs, tofacitinib and iguratimod, are discussed.

2. Popular small molecule DMARDs

DMARDs is the collective term for a set of drugs known to suppress the progression of RA via action against immunological abnormalities. These drugs do not exhibit the rapid action on symptoms, i.e., inflammation and pain, exerted by NSAIDs and steroids.

DMARDs are additionally capable of delaying the progression of bone destruction, but it is rare that remission of RA can be achieved by DMARD mono-therapy in patients with established RA. DMARDs are generally slow in action, taking 1 to 3 months until manifestation of their effects. The response to these drugs varies greatly among individuals, and a number of patients fail to respond to treatment with DMARDs. Furthermore, patients whose disease activity is initially controlled by DMARDs sometimes cease to respond to the drugs (relapse) during prolonged use. Another characteristic of DMARDs is a high incidence of adverse reactions, with the incidence of adverse events with each DMARD being between 20% and 50%. If adverse reactions are mild, treatment with DAMARDs can be often continued by means of dose reduction or symptomatic treatment, but the risk that patients will develop life-threatening serious adverse reactions, including hematological disorders, renal disorder, and interstitial pneumonia, is common.

Some DMARDs are immune suppressors that are also used for control of host rejection of grafts and treatment of cancer, including MTX, LFN, tacrolimus (TAC), cyclosporine, azathioprine, and cyclophosphamide. The class also includes immune modulating agents, such as SASP, BUC, d-penicillamine, gold compound, and others, as well as HCQ, an anti-malaria agent, and MIN, an antibiotic (Table1).

Here, the popular DMARDs used clinically are described. BUC is approved as a DMARD for treatment of RA only in Japan and Korea, and currently, the use of BUC is almost exclusively confined to Japan, where this drug is still used in quantities as large as SASP, second to MTX among the approved DMARDs.

3. Methotrexate (MTX)

MTX is a folic acid antagonist. The drug has been reported to exert immunosuppressive activity through its action (suppression of proliferation) on immune competent cells by means of DNA synthesis inhibition, and to exert anti-inflammatory activity by inducing pooling of adenosine [19]. Details are unknown about the mechanism of its antirheumatic activity, but the drug has shown excellent efficacy and long duration, and it is the most frequently used small molecule DMARD in the world as an anchor drug for RA treatment [3,4]. The most recent guidelines recommend early initiation of treatment with MTX as a first-line drug in patients with factors associated with poor prognosis such as positive ACPA, bone erosion, extra-articular symptoms, or restricted physical function [18]. Among the antirheumatic drugs, MTX tends to exert its effects relatively early (within 1 to 2 months) and these effects include suppression of joint destruction [20,21].

Drug	Approximate time to benefit	Usual maintenance dose	Toxicities requiring monitoring
Hydroxychloroquine	2–6 months	200 mg twice a day	Macular damage
Sulfasalazine	1–3 months	1,000 mg 2–3 times a day	Myelosuppression
Methotrexate	1–2 months	Oral 7.5–20 mg/week; injectable 7.5–20mg/week	Myelosuppression, hepatic fibrosis, cirrhosis, pulmonary infiltrates or fibrosis
Leflunomide	4–12 weeks (skewed earlier)	20 mg/day in a single dose, if tolerated; otherwise, 10 mg/day	Diarrhea, alopecia, rash, headache, theoretical risk of immunosuppression infection
Bucillamine	1–3 months	100–200 mg a day	Myelosuppression, hepatotoxicity, proteinuria
Tacrolimus	6–12weeks	3 mg a day	Renal insufficiency, anemia, hypertension, Impaired glucose tolerance
Azathioprine	2–3 months	50–150 mg/day	Myelosuppression, hepatotoxicity, lymphoproliferative disorders
D-penicillamine	3–6 months	250–750 mg/day	Myelosuppression, proteinuria
Gold, oral	4–6 months	3 mg twice a day	Myelosuppression, proteinuria
Gold, intramuscular	3–6 months	25–50 mg intramuscularly every 2–4 weeks	Myelosuppression, proteinuria
Minocycline	1–3 months	100 mg twice a day	Hyperpigmentation, dizziness, vaginal yeast infections
Cyclosporine	6–12weeks	2.5–4 mg/kg/day	Renal insufficiency, anemia, hypertension, Impaired glucose tolerance

Table 1 summary of small molecule DMARDs

Adverse reactions to MTX include infection, stomatitis, glossitis, nausea, hepatic dysfunction [22], and others. It is known that these adverse reactions are more likely to appear in patients with compromised renal function and in elderly patients, and that they can be reduced by concomitant use of folic acid or leucovorin [23,24,25]. Interstitial pneumonia and bone marrow suppression are known as serious adverse reactions. Interstitial pneumonia can develop suddenly and is sometimes intractable [26]. Marrow suppression involves impaired hematopoiesis. Both of these reactions are serious and require hospitalization. As a rule, MTX is administered once weekly via an oral or parenteral route at an initial dose level of 7.5 to 15 mg, with the dose being gradually increased up to 25 mg/week if responses are insufficient. In Japan, MTX is only administered orally, at an initial dose level of 6 mg/week. The dose is gradually increased up to 16 mg if responses are insufficient. The weekly dose level may be divided into 1 to 3 doses in 1 or 2 days. It is known that the effects of MTX are strengthened by concomitant use of biologics [27].

4. Sulphasalazine (SASP)

This drug exerts action relatively rapidly (in 1 to 2 months) among the DMARDs. Like MTX, SASP has been reported to exert anti-inflammatory activity by inducing pooling of adeno-

sine [28], and to have immunomodulating effects as well, e.g., suppression of antibody production [29]. The antirheumatic activity of SASP has not been sufficiently clarified, but because it suppresses joint destruction [20], it is considered as an option for treatment of RA with MTX. As compared to other DMARDs, SASP can be characterized by low nephrotoxicity, and the risk for teratogenicity in pregnant women is also considered to be lower with SASP than with other DMARDs. Adverse reactions to SASP include liver disorder, drug eruption, bone marrow disorders, and others. Because the incidence of gastrointestinal disorders as an adverse reaction is high with the bulk form of SASP, it is usually administered in the form of an enteric-coated tablet for the treatment of RA. In Western countries, this drug is usually recommended for treatment at a dose level of 2 to 3 mg/day, while in Japan, the upper limit of the dose level is set at 1 mg/day.

5. Leflunomide (LFN)

LFN is a metabolic antagonist capable of suppressing the proliferation of T lymphocytes through pyrimidine synthesis inhibition [20]. This drug has been reported to suppress joint destruction. It is characterized by the long half-life of its active form. Adverse reactions to LFN include infection, diarrhea, bone marrow disorders, hypertension, liver disorder, nausea, alopecia, and others. Interstitial pneumonia is an adverse reaction that requires utmost caution and is potentially fatal. LFN has been reported to be teratogenic [30,31]. For a couple planning pregnancy, it is necessary for both partners to take cholestyramine to eliminate the active metabolites of LFN completely. Because of the long the half-life of the active metabolite in vivo, the drug is administered at a loading dose level (100 mg) for the first 3 days, followed by administration at a constant dose level (20 mg/day).

6. Hydroxychloroquine (HCQ)

HCQ was used as an anti-malaria agent before it was used as an antirheumatic drug [32]. The anti-malaria activity of HCQ is considered to have no relationship to its antirheumatic activity. HCQ is believed to suppress antigen presentation by elevating the pH of the cytoplasmic compartment of antigen-presenting macrophages [33]. More recently, it was reported that HCQ acts on the toll-like receptor to manifest effects on the immune system [34]. The efficacy of HCQ is less than that of MTX, but HCQ has an excellent safety profile. For this reason, HCQ is used for the treatment of mild RA [35]. Uncombined HCQ treatment does not suppress the progression of bone destruction. Although the tolerability is high, adverse reactions such as nausea and dizziness occasionally appear. Furthermore, the drug has a high affinity for the retina and thus exerts high ocular toxicity. This is the reason that use of the drug is not approved in some countries. Although retinal disorders induced by HCQ are irreversible and if severe can lead to blindness, recovery from retinal disorders is sometimes possible if they are detected early. HCQ is also used occasionally for treatment of articular

and skin symptoms of SLE. For the treatment of RA, the drug is administered at a dose of 400 mg/day.

7. Minocycline (MIN)

The US Food and Drug Administration (FDA) has not approved MIN for treatment of RA. However, a slow efficacy of this drug against RA has been shown in some double-blind trials [36,37,38,39]. Although the usefulness of this drug as a means of treatment for RA is low, it has evidenced effects at early stages of RA. Compounds of the tetracycline family are known to suppress matrix metalloproteinase [40], and this action is believed to suppress narrowing of the joint space in patients with RA. The activity of MIN as an antibiotic is considered to have no relationship to its antirheumatic activity.

8. Bucillamine (BUC)

BUC has been approved as a means of RA treatment in only Japan and Korea. As noted, at present, its use is almost exclusively confined to Japan. BUC is used as frequently as SASP in Japan, and this frequency of use is second to MTX. Its antirheumatic activity is slightly stronger, that is comparable to or higher than, that of SASP [41,42]. For this reason, BUC is used for treatment of mild to moderate RA. The pharmacologic actions that have been reported as likely to be involved in the drug's antirheumatic effects include suppression of cytokine production in the synoviocytes [43], suppression of antibody production from B-lymphocytes [44,45], and suppression of osteoclast differentiation [46]. According to a recent report, the effect of this drug in inhibiting Akt signals is involved in the suppression of antibody production from B-lymphocytes and the suppression of cytokine production by the synoviocytes [47,48]. Numerous adverse reactions including renal disorders and skin disorders are known, with serious adverse reactions including interstitial pneumonia and hematological disorders, and therefore patients must be watched closely. When used for the treatment of RA, BUC is administered at an initial dose of 100 mg/day, with a gradual increase up to 300 mg/day if efficacies are insufficient.

9. Tacrolimus (TAC)

TAC was initially sold as a drug for suppression host rejection of grafts. In 2005, its indication was expanded to encompass treatment of RA. The known effects of TAC include inhibition of the proliferation and differentiation of T lymphocytes involved in persistence of RA-associated inflammation and suppression of inflammatory cytokine production. The effect of this drug on RA is not strong when used as mono-therapy. It shows excellent efficacy when used as an additional drug in combination therapy for patients who have insufficient response to MTX alone [49]. In Western countries, this drug is not used frequently because the results of clinical trials of mono-therapy have been unsatisfactory, and the ACR has not advocated the use of TAC as a means of treating RA because of its insufficient efficacy [18]. Adverse reactions to TAC include headache, renal disorders, hyperglycemia, hyperuricemia, hypertension, and others. Since TAC is less likely to affect the respiratory system, it is occasionally used in patients who have respiratory complications. When used for the treatment of RA, this drug is usually administered at a dose of 3 mg/day, and at 1.5 mg/day in elderly patients.

10. Gold Compound

Two formulations of gold compound (injection and oral-dose preparations) are available. The efficacy and safety profiles partially differ between these 2 forms. Injection is performed intramuscularly once weekly at an initial dose of 50 mg/week, followed by maintenance dosing (once every 2 to 4 weeks). The response rate is relatively high, but effects are usually not evident until after 3 to 6 months. The frequency of discontinuation of treatment due to adverse reactions is high, with skin and mucosal disorders being the most frequent causes for discontinuation. Adequate monitoring for proteinuria and renal dysfunction is necessary, and care is also needed regarding hematological disorders, since leukopenia, thrombocytopenia, and hypoplastic anemia can develop following treatment with this drug. The oral-dose preparation is administered twice daily at a dose of 3 mg/dose. The efficacy of the oral-dose preparation is less than that of the injection and takes up to 9 months to appear. Adverse reactions to the oral-dose preparation are akin to those of the injection, although the incidence of renal and hematological disorders is slightly lower with the oral preparation.

11. Azathioprine

This drug is a purine analog and is shown to exert immunosuppressive effects by antimitotic action induced by inhibiting the synthesis of DNA and proteins. The efficacy of this drug against RA is comparable to that of other slow-acting drugs. Adverse reactions to azathioprine include gastrointestinal disorders, liver disease, leukopenia, and others.

12. Cyclosporine

Cyclosporine is an immune suppressor that is generally used as means of suppressing host rejection of grafts. This drug suppresses the production and physiological actions of interleukin-2 and lymphocyte growth factor, taking 6 to 12 weeks before manifestation of its efficacy against RA. Frequently observed adverse reactions to this drug include renal disorders, hyper-

tension, gingival thickening, increased body hair, and others. Cyclosporine is recommended only for treatment of severe and advanced RA that has failed to respond to other drugs.

13. Cyclophosphamide

Cyclophosphamide is an alkylating agent with nonspecific cytotoxic activity. It suppresses the immune system by disturbing lymphocytes in a nonspecific manner. This dug has been positioned to play an important role in the treatment of SLE and vasculitis. It is rarely used for patients with RA because of strong adverse effects.

14. Changes in the position of small molecule DMARDs in the treatment of RA

According to the pyramid therapy [1] model that had been established by the beginning of the 1990s, RA treatment focused on alleviation of symptoms (pain, inflammation, etc.) with the use of NSAIDs and steroids at sufficiently high doses. Use of antirheumatic drugs was confined to cases with marked progression of bone erosion and other severe manifestations. It was noted that in cases requiring treatment by NSAIDs and steroids inflammation appeared to subside gradually by means of burnout over time. However, the RA itself remained unchanged and bone destruction continued to advance, accompanied by progression of joint dysfunction [50]. The primary drug therapy in those days played only the role of suppressing symptoms (i.e., pain and swelling), and it could not prevent progression of bone destruction, joint dysfunction, and other morbidity.

This situation changed dramatically during the period from the latter half of the 1990s to the 2000s. MTX had become clinically available for use in the treatment of RA in the 1980s to 1990s, and subsequently began to be used extensively as an anchor drug for the treatment of RA [2,3,4]. The term *anchor drug* refers to any drug used as a "protagonist" in the treatment of RA. In the management of RA, MTX was positioned as a drug whose necessity would be determined on the basis of the severity of the disease, and which would become indispensable in cases where the disease severity exceeded a certain level. After the mid-1990s, a series of data were published that provided new evidence of the efficacy of combined DMARD therapy (2 or 3 DMARDs) as compared to DMARD mono-therapy, stimulating active adoption of DMARD combination therapy. During this time, MTX also came to be positioned as a key drug in combination therapy, and to date, the prominence MTX as an anchor drug has not changed [5]. From the late 1990s to the 2000s, biologics, primarily TNF inhibitors, began to be introduced clinically as drugs expected to improve long-term prognosis and to maintain physical function [6,7,8], and by the 2000s, these events had led to an acceleration in some countries to revise existing treatment guidelines and diagnostic criteria for RA, which was accompanied by a shift of the focus of treatment from anti-inflammatory analgesia and delay of disease progression to achievement of disease remission and prevention of progres-

sion. The RA management guidelines that were published by the ACR in 2002 positioned DMARDs as first-line drugs for RA treatment, which were to be started within 3 months after disease onset, while positioning NSAIDs and steroids as auxiliary drugs for symptoms such as pain and inflammation [9]. These guidelines additionally recommended switching patients to different DMARDs if the initially prescribed DMARDs failed to exert sufficient efficacy within 3 months of the initiation of treatment. This guideline clearly positioned MTX as an anchor drug, allowing clinicians to acknowledge that a current framework of RA treatment had been decided at that time. It was also recommended by this guideline that biologics should be used in cases that were failing to respond well to treatment with DMARDs, including MTX. We may infer that in their early days, the clinical use of biologics was confined to intractable cases because this class of drug had not yet been evaluated in a sufficient number of cases (Figure 1).

During the period from the late 1990s to 2000s, as a series of new biologics were introduced and the clinical trial data on these drugs accumulated, it was suggested by some of these data that active use of biologics beginning soon after disease onset might be advantageous in some patients in terms of efficacy of long-term RA management, notably when focusing on the effects of biologics in suppressing progression of bone destruction and physical dysfunction, which were not seen with small molecule DMARDs [11,12]. In some patients, primarily those anticipated to have poor prognoses and those with rapidly progressive RA, biologics began to replace small molecule DMARDs. In 2008, noting this trend, the ACR made public a new recommendation on RA treatment that stated that the use of TNF inhibitors should be recommended as an option for first-line
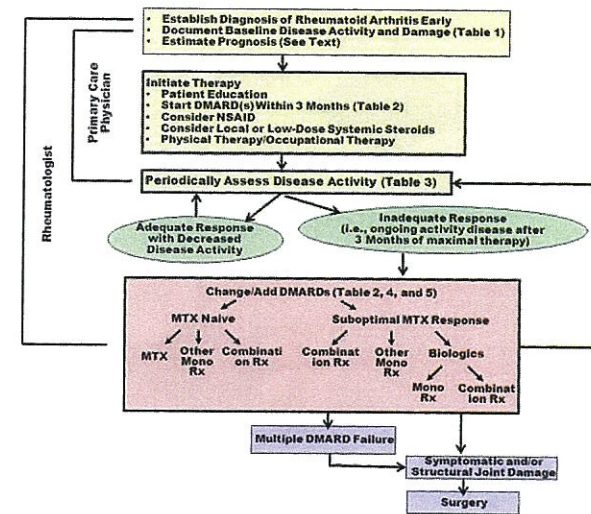

Figure 1. Guidelines for the management of rheumatoid arthritis: 2002 Update

medication for patients with high disease activity at 3 months to less than 6 months after disease onset, and patients with high disease activity and factors associated with poor prognosis at less than 3 months after disease onset [18] (Figure 2). Campaigns promoting a better long-term prognosis by earlier start of treatment with biologics based on these developments and bolstered by financial programs that assisted patients with out-of-pocket payments for biologics created stiff competition over biologics among manufacturers, and has reportedly promoted an increase in the quantity of biologics used for RA treatment. However, there are still many open issues surrounding biologics, including the high percentage of patients who fail to respond to biologics [14], the high price that causes large burdens on individuals and society [15], and the risk of serious adverse reactions such as infection [16,17]. The use of DMARDs, primarily in combination therapy, has also fallen under renewed scrutiny following publication of new studies. These events may stimulate further revision of the current guidelines/guidance on RA treatment.

Restriction of the use of biological preparations due to the necessity of out-of-pocket payment of their cost

Figure 3 illustrates the sales of 3 biological TNF antagonists per 100,000 populations in each country. It shows that biologics are used a lot in European countries such as Norway and Sweden. In these countries, patients are usually required to pay no money or only very small amounts (less than 1,000 yen) as out-of-pocket payment during each visit to a medical facility [10,51]. The consumption tax rate is high (about 20 to 30%) in these countries, and a large portion of the consumption tax collected is spent for social welfare, including medical expense. This is the reason why the out-of-pocket payment is small for patients in these countries.
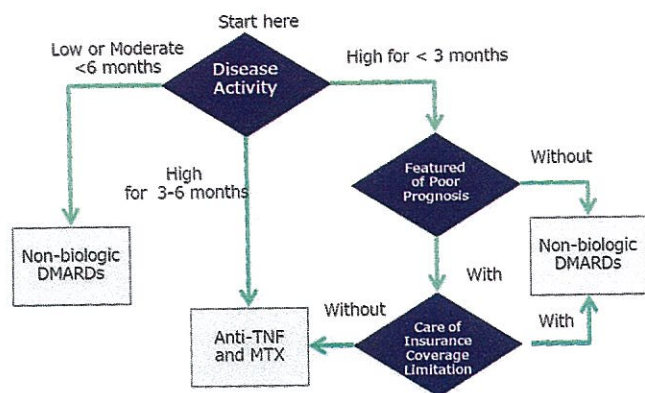

Figure 2. American College of Rheumatology 2008 recommendations on indications for the use of biologic Disease-modifying antirheumatic drugs in patients with RS <6 months

The United States, on the other hand, is the only developed country having no universal public health insurance. Excluding Medicare and Medicaid for elderly people, physically

handicapped citizens and low-income families, healthcare in the United States depends on private sector insurance not mandatory for individual citizens. The premium for private health insurance is high, and a high percentage of uninsured people is often highlighted as a social problem in this country. For individuals covered by health insurance, the out-of-pocket payment is not very large, although it varies depending on the insurance plan selected by individuals. Furthermore, unique campaigns by pharmaceutical companies are available in the United States, promoting the treatment with biologics. Under such campaigns, a majority of individual patient drug cost will be borne by the manufacturer to take over if the patients agree to treatment with specific drugs for a certain period of time and are registered with the treatment programs (RemiStart, Enbrel Support, My Humira, etc).

In Japan, however, annual out-of-pocket payment amounting to about 400,000 to 500,000 yen (about 5000 to 6500 dollars) is needed for many patients receiving treatment with biologics, excluding some patients covered by social welfare programs for reduction of out-of-pocket payment of healthcare expenses (specific physically handicapped individuals, individuals covered by poverty program, and so on). (Japan and Korea are the only countries belonging to the OECD where individuals covered by health insurance are required to make out-of-pocket payment to bear 30 % of health care costs.) This amount of out-of-pocket payment is about 25 times as large as the out-of-pocket payment needed for conventional DMARDs. There are patients who give up receiving treatment with biologics because they cannot afford to pay the expense [51].
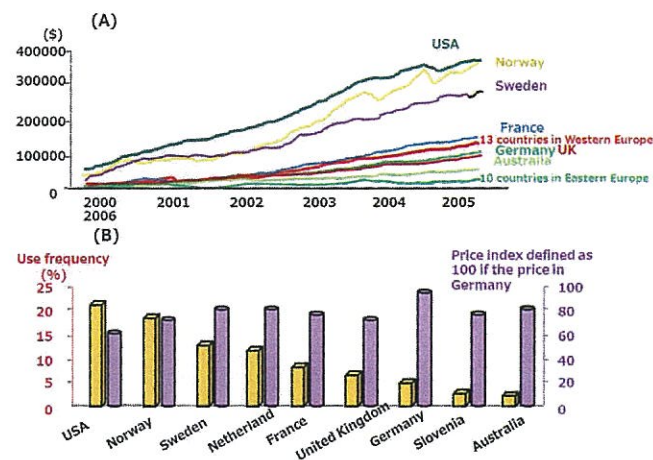

Figure 3. Sales of three biologics TNF antagonists per 100,000 population (A) and Price index and the percentage of patients using biologics TNF antagonist in the world in 2006 (B)

15. Current standard of care for RA

It has been shown that intervention with biologics at early stages of RA is expected to control the disease activity and suppress subsequent joint destruction, thus facilitating remission of RA, biologics free and cure [52]. However, according to the Best study [53], the long-term outcome of treatment differs little among different treatment strategies. It has thus been suggested to be more important to practice tight control through adjusting treatment flexibly depending on the disease activity in individual cases, instead of selecting biologics from the beginning (Figure 4).

In 2012, the ACR published the "2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis," and recommended separate methods of treatment for patients at early stages of RA (less than 6 months after onset) and patients with established RA (6 months or more after onset) [18]. According to the revised guidelines, intervention with biologics is recommended for cases of established RA if the RA cannot be adequately controlled with recommended DMARD therapies (Figure 5). The guidelines also state that use of TNF inhibitors deserves to be considered even in patients with early stage RA if factors associated with poor prognosis are present and the disease activity is high, although it seems to be accepted that biologics have become a mode of treatment that is considered, as a rule, only in cases where the activity of RA cannot be controlled sufficiently by adequate treatment with small molecule DMARDs, including MTX.
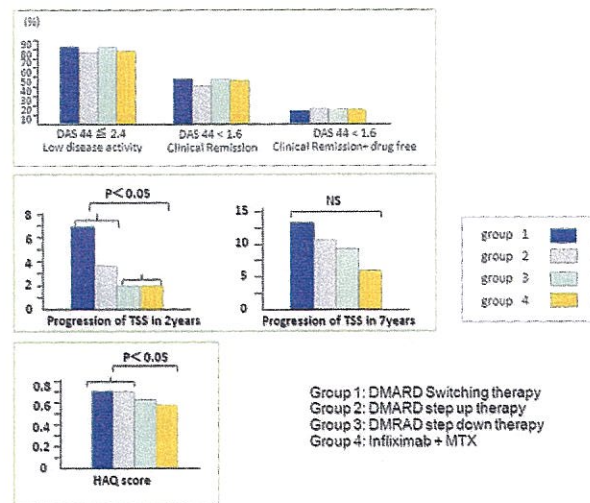
Under the National Health Service (NHS) in the United Kingdom, in which prescription payments for individual patients are borne by the government, RA treatment is guided by the recommendations of the National Institute for Health and Clinical Excellence (NICE) [54]. The procedure for treatment under this system is more concrete than the ACR recommendations, and permits moving to therapy with biologics (anti-TNF preparations) or tocilizumab in cases that are poorly controlled despite attempts of treatment with DMARD combination therapy including MTX, even at the highest possible dose levels (Figure 6). However, permission for the use of these biologics under the British system requires that the manufactures bear any individual drug costs exceeding £9296 per year.

16. Comparison between small molecule DMARDs combination therapy and biologics plus MTX combination therapy

Regarding drug therapy at early stages of RA, the two-year data were recently reported on multicenter comparative clinical studies of three small molecule DMARDs combination therapy (MTX + SASP + HCQ) and biologics plus MTX combination therapy in the United States (TEAR study) [55] and Sweden (Swefot trial) [56]. In the TEAR study, the outcome as to DAS28-ESR did not differ between the oral triple therapy and the etanercept plus MTX combination therapy (first endpoint), and ACR20 and 50 was observed no difference between the two groups. The only significant difference was between two groups for ACR70 (Figure 7). In the

Figure 4. Seven year Results of DAS steered treatment in the BeSt Study: clinical and radiological outcome
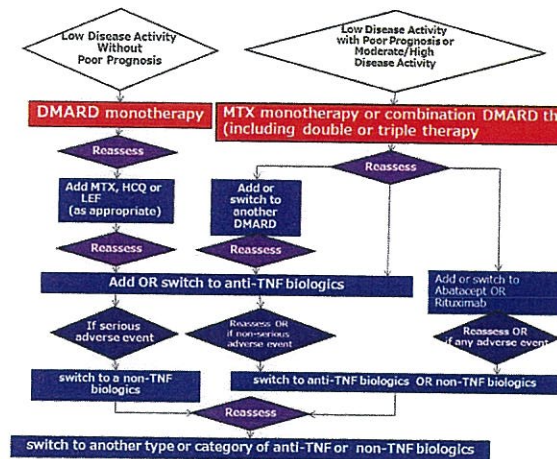

Figure 5. update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis.
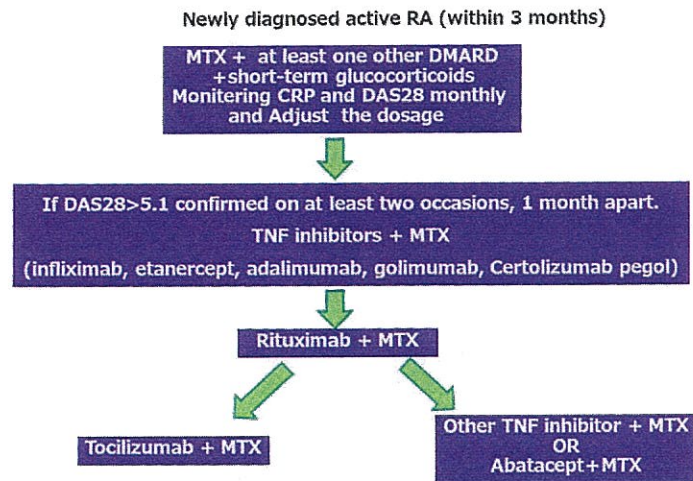
Figure 6. Summary of the management of rheumatoid arthritis in National Institute for Healt and Clinical Exellence guideline for rheumatoid arthritis

Figure 7. Results from the TEAR trial: oral triple Therapy vs. etanercept plus methotrexate in early RA (A): Observed DAS28-ESR,(B): Percentage of participants in TEAR achieving ACR20, 50, and 70 criteria at time of step-up at 6 months and at the 2 year conclusion of the study.

Swefot trial, there was no difference between the three small molecule DMARDs combination therapy group and the infliximab plus MTX combination therapy group in terms of ACR 20, 50 or 70 or EULAR good/moderate response. The TEAR study revealed no difference between the oral triple therapy group and the biologics plus MTX combination therapy group from the 12th month on after the start of treatment, while the Swefot trial disclosed higher efficacy of biologics plus MTX combination therapy during the first 6-12 months of treatment, followed by gradual disappearance of the inter-group difference during the two-year follow-up period. Also according to the long-term data from Best study conducted in the Netherlands [53], there was no significant difference in clinical improvement or the degree of bone/joint destruction on radiographic examination between Group 3 (treatment started with 3 drugs, MTX + SASP + steroid) and Group 4 (treatment started with biological preparations).

Regarding the degree of bone/joint destruction on radiographic examination, both TEAR study and Swefot trial demonstrated significant reduction in the biologics plus MTX combination therapy group, with the inter-group difference being 1-2 in terms of total Sharp Heijde score (full point: 448) of the mean progression of destruction per year relative to the baseline at the start of treatment. It might be thought that it is questionable to use the expensive biologics as the initial means of intervention into RA if only such slight suppression of bone/joint destruction on X-ray can be achieved.
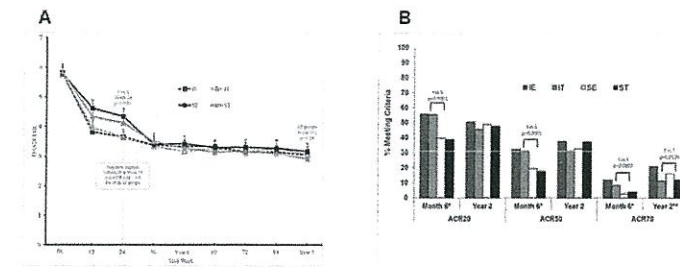
17. Three small molecule DMARD combination therapy in Japan (JaSTAR study)

The ACR recommendation and the NICE (U.K.) guidance state that the three DMARDs combination therapy should be applied before treatment with biologics [18,54]. In Japan, HCQ has not been approved for use in the treatment of RA because of adverse reactions. The three drug combined therapy (MRX + SASP + HCQ) is therefore not practically possible in Japan. We thus started a multicenter comparative clinical study on treatment of early stage RA with three small molecule DMARD combination therapy and biological TNF antagonists plus MTX combination therapy, involving nationwide 32 facilities of rheumatologist in Japan (JaSTAR study: Japan Strategic Treatment of Aggressive RA) [57].

The DMARDs used in the JaSTAR study were MTX, SASP and Bucillamine (Buc). Buc was used instead of HCQ for the following reasons:

1. Buc is a DMARD used frequently in Japan; and

2. this combination of three drugs with Recommendation Level "A" according to the Guidelines of the Ministry of Health, Labour and Welfare seemed to be appropriate for this study [41].

To date, case registration has been completed, achieving the targeting number (160 cases), and each patient enrolled to the study is now under follow-up. Interim analysis of the data during the first 6 months revealed a similar DAS28 remission rate between the three DMARDs combination therapy group and the biological TNF antagonists plus MTX combination therapy group (Figure 8). The treatment continuation rate among the 33 cases where one-year data have been analyzed was superior over the anti-TNF therapy continuation rate previously reported from the DANBIO registry [68] (Figure 9). We are looking forward to the results from final data analysis.
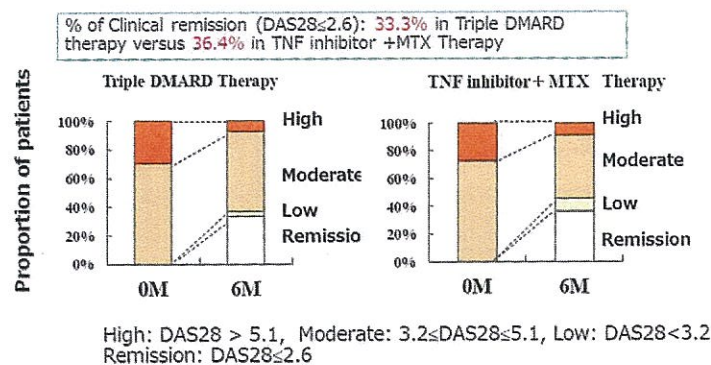
Figure 8. Distribution of disease activity of patients before and after treatment for 6 monts in JaSTAR Study
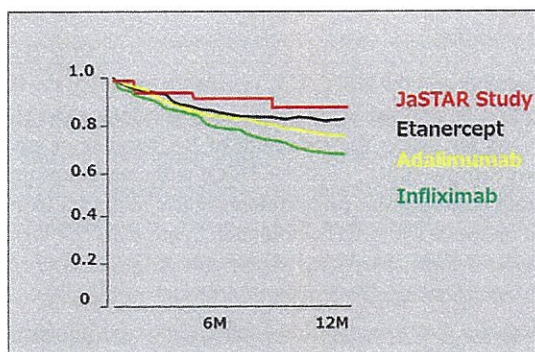

Figure 9. Cumulative continuation rate of triple DMARDs combination therapy in JaSTAR Stady, Cumulative continuation rate of TNF inhibitors in DANBIO study was superimposed.

18. Introduction of new small molecule DMARDs for RA treatment

It is known that among the drugs currently used for treatment of RA, those targeted at cytokines, all of which fall under the category of biologics, have yielded particularly favorable outcomes. However, unless the open issues mentioned above are resolved, it is unlikely that biologics will play a central role in the treatment of RA. In 2012 and 2013, there were 2 new DMARDs scheduled for introduction for RA treatment. One of them, tofacitinib, has been developed with attention focused on the role of cytokines in RA. If tofacitinib is shown in

clinical practice to be a means of RA treatment possessing both the advantages of biologics and the advantages of small molecule DMARDs, it is expected that another paradigm shift will occur in RA management. The 2 new DMARDs are described in further detail below.

19. Tofacitinib

Tofacitinib has been developed as a drug for treatment of RA. It is shown to be an inhibitor of Janus kinase 3 (JAK3), an enzyme reported to be involved in cytokine receptor signal transduction. To date, tofacitinib has been experimentally shown to suppress all JAKs (1 through 3), rather than manifesting selective action against any particular JAK. Tofacitinib suppresses cytokines through inhibition of JAK-stat signals. In May 2012, the US FDA issued an approval recommendation for the use of this drug in adults with moderate or severe RA. According to the results of clinical trials, treatment with tofacitinib for 3 months achieved a semi-favorable (about 50%) ACR20 in patients who were responding poorly to TNF inhibitor treatment, with a placebo group achieving about 25%. Clinical trials have also been conducted for tofacitinib as a first-line drug, and in patients responding poorly to MTX, each yielding favorable outcomes. This drug is therefore reported to be promising not only as an additional option during biologic therapy but also as a first-line drug. Adverse reactions that require caution are elevations in blood cholesterol levels and neutrophilia.

20. Iguratimod

Iguratimod was formulated as a COX2 inhibitor and was later found to have immune modulating activity. It was thus developed as a DMARD. Iguratimod has been shown to be useful in combination with other drugs in patients failing to respond well to MTX. Elevation in liver enzymes is known as an adverse reaction.

21. Conclusion

As detailed herein, small molecule DMARDs have played a central role in treatment of RA since before the introduction of biologics, and it has been shown that modification of DMARD regimens (e.g., consideration of combination therapy beginning soon after disease onset) can improve the long-term prognosis, allowing small molecule DMARDs to serve as valid alternatives for biologics in RA treatment. While it is also known that treatment with biologics is useful in cases of high activity RA, even in these cases, there may be patients for whom combination therapy using existing DMARDs should be considered before introduction of biologics. Further changes in the paradigm of RA treatment are expected pending results of clinical use of new oral-dose small molecule DMARDs that have shown effects similar to both biologics and small molecule DMARDs.

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