A Paradigm Shift in Rheumatoid Arthritis over the Past Decade

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Abstract

Recent advances have improved our understanding of the pathogenesis of rheumatoid arthritis (RA), and the development of new therapeutics, including biological agents, have thus made it possible to strive for remission as a primary goal. Biological agents targeting a specific molecule have powerful functional capabilities, and the introduction of biological therapies has brought about revolutionary progress in RA management, culminating in a paradigm shift. There is clear evidence that a delay in treatment initiation and poor control of disease activity are associated with joint damage progression, so treatment should be started immediately after the diagnosis of RA and adapted according to disease activity as assessed by validated composite measures. In this review, we will summarize the changes in the classification and remission criteria and describe the clinical efficacies of biological agents in RA. We also discuss new promising therapies and propose future perspectives in the rheumatology field.

Key words: rheumatoid arthritis, biological agent, paradigm shift, treat-to-target

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that results in joint destruction and is associated with progressive disability and various systemic complications (1). The disease affects from 0.5-1% of adults worldwide and is more prevalent in women than in men. Recent advances in understanding the RA pathogenesis and the development of new therapeutics, including biological agents, have made it possible to aim for remission as a primary goal. Biological therapies that target a specific molecule have played one of the most important roles in this progress and brought about a paradigm shift in the RA treatment strategy. Initiating treatment as soon as possible within the so-called therapeutic “window of opportunity” has been suggested to be important (2), and disease activity should be strictly controlled to ensure successful suppression of inflammation as assessed by validated compound disease activity measures (3). In addition, new global classification criteria, remission criteria, and a treat-to-target strategy have been proposed for RA. This review describes some of the

new insights, strategies, and therapeutics in the RA field.

RA Pathogenesis

RA is mainly characterized by synovial inflammation. Synovitis occurs when leukocytes infiltrate synovial compartments and involves a complex interplay between genotype and environmental triggers. The chronic phase of RA is driven by the accumulation of immune cells, such as T cells, B cells, dendritic cells, and macrophages, with positive feedback loops mediated by interactions among those cells, as well as synovial fibroblasts, chondrocytes, and osteoclasts, via cytokines and cell surface molecules (4-6). Cytokine production that arises from numerous synovial cell populations is central to RA pathogenesis. Among these cytokines, tumor necrosis factor (TNF)- α plays a fundamental role in inducing cytokine and chemokine expression, activating synovial fibroblasts, promoting angiogenesis, and suppressing regulatory T cells. Similarly, interleukin (IL)-6 drives local leukocyte activation and autoantibody production, promoting acute systemic effects (7, 8). Although those two cytokines have been the main targets of new drugs, a myriad

Table 1. 2010 ACR/EULAR Classification Criteria for RA

A Joint involvement*	Score
1 large joint	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
10 joints (at least 1 small joint)	5
B Serology**	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or low-positive ACPA	3
C Acute-phase reactants	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D Duration of symptoms	
<6 weeks	0
≥6 weeks	1

1. Target population: Patients who

- 1) have at least one joint with definite clinical synovitis (swelling)
- 2) with the synovitis not better explained by another disease

2. A score of ≥6/10 is needed for classification of a patient as having definite RA

ACPA: anti-cyclic citrullinated peptide antibodies, CCRP: C-reactive protein, ESR: erythrocyte sedimentation rate, RF: rheumatoid factor

*Large joints: shoulders, elbows, hips, knees, ankles; Small joints: metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, wrists

**Negative, less than or equal to the upper limit of normal (ULN) for the laboratory assay; low-positive, higher than the ULN but ≤three times the ULN; high-positive >three times the ULN

of cytokines and cell-surface molecules are being targeted by drugs under development for RA.

Window of Opportunity and New Classification Criteria for RA

Window of opportunity

Delaying the initiation of treatment after the diagnosis of RA has been associated with a progression of joint damage. In clinical settings where effective drugs can be used to achieve clinical remission and prevent joint destruction, treatment should be initiated even earlier, in the so-called therapeutic “window of opportunity” (9, 10). This conceptual window occurs when early arthritis is less entrenched, has a smaller load of “disease cells,” and is more responsive to treatment. According to this hypothesis, aggressive treatment is more likely to succeed during this phase than later in the disease course, even if the same treatment is applied (11). This window is said to represent a very early phase of the disease, ranging from several months to two years. Although the details of the time frame (when the window opens and closes) have not been clearly determined (2), six months from diagnosis is considered to be an important time point. Early RA was determined as a disease duration of less than six months in recommendations in the treatment of RA proposed by the American College of Rheumatology (ACR) in 2012 (12). In the 2013 European League Against Rheumatism (EULAR) recommendations, it is stated that RA therapy should be adjusted within six months after treatment initiation if the treatment target has not been

reached (13).

New classification criteria

The diagnosis of RA used to be based on the revised ACR classification criteria proposed in 1987 (14). These criteria, which were initially meant for the enrollment of patients in clinical trials but are often used for diagnosis, have had unsatisfactory performance due to low sensitivity, especially in early RA (15). Due to the evidence of better outcomes with new therapeutics and recognition of the window of opportunity, the inadequate performance of the 1987 criteria led to the development of new criteria. In 2010, the ACR and EULAR jointly developed new classification criteria that designed to allow earlier patient classification and treatment (16). The new criteria were developed from inflammatory arthritis data gathered from inception cohorts (17), which subsequently integrated expert opinion (18), and they were finally validated in external early arthritis cohorts. The 2010 criteria include tender and swollen joint counts, acute phase reactants, anti-cyclic citrullinated peptide antibodies (ACPAs) or rheumatoid factor (RF), and symptom duration (Table 1). These clinical and laboratory data are combined into a score ranging from 0 to 10, and a cut-off of six was determined for classifying definite RA. Many researchers have reported the new classification criteria to have good sensitivity but slightly lower specificity than the 1987 ACR criteria (19–24) and overall moderate diagnostic accuracy (25).

Composite Measures for Assessing Disease Activity and New Remission Criteria for RA

Composite measures applied in assessing disease activity

With the new classification criteria and the advent of new therapies, remission has become a realistic goal in RA management. Remission is also regarded as a major therapeutic target in clinical practice, but low disease activity may be regarded as an alternative target (26, 27). However, unlike diabetes mellitus (DM), hyperlipidemia, or hypertension, the musculoskeletal system cannot be assessed with a simple surrogate measure or direct measures (28). The complexity of the signs and symptoms of RA requires the application of composite scores. Since the 1950s, when the first composite tool for measuring disease activity in RA was developed (29), many attempts have been made to improve RA disease-activity monitoring. Among these, the Disease Activity Score with 28-joint counts (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and Routine Assessment of Patient Index Data with three measures (RAPID-3) have been applied frequently because they are accurate reflections of disease activity; sensitive to change; discriminate well among low, moderate, and high disease-activity states; and are feasible for use in clinical

Table 2. Definitions of Disease Activity Measures

Definition	Formula	Remission	LDA	MDA	HDA
DAS28	$0.56 * \sqrt{TJC28 + 0.28 * \sqrt{SJC28 + 0.7 * \ln(ESR) + 0.014 * GH}}$	>2.6	≤3.2	≤5.1	>5.1
SDAI	SJC28+TJC28+PhGA+PtGA+CRP	≤3.3	≤11	≤26	>26
CDAI	SJC28+TJC28+PhGA+PtGA	≤2.8	≤10	≤22	>22
RAPID3	(MDHAQ+Pain VAS+PtGH)/3	≤1.0	≤2.0	≤4.0	>4.0

CDAI: Clinical Disease Activity Index, DAS28: Disease Activity Score with 28-joint counts, ESR: erythrocyte sedimentation rate, GH: general health, HAD: high disease activity, LDA: low disease activity, MDA: moderate disease activity, MDHAQ: Multi-Dimensional Health Assessment Questionnaire, PhGA: Physician global assessment, PtGA: Patient global assessment, RAPID-3: Routine Assessment of Patient Index Data with three measures, SDAI: Simplified Disease Activity Index, SJC: swollen joint count, TJC: tender joint count, VAS: visual analog scale

Table 3. Definitions of New Remission Criteria

In clinical trials	In daily practice
<i>Boolean-based definition</i>	
At any time point, patient must satisfy all of the following: Tender joint count ≤ 1 Swollen joint count ≤ 1 C reactive protein ≤ 1 mg/dL Patient global assessment ≤ 1 (on a 0–10 scale)	At any time point, patient must satisfy all of the following: Tender joint count ≤ 1 Swollen joint count ≤ 1 Patient global assessment ≤ 1 (on a 0–10 scale)
<i>Index-based definition</i>	
At any time point, patient must have a Simplified Disease Activity Index score ≤ 3.3	At any time point, patient must have a Clinical Disease Activity Index score ≤ 2.8

cal settings (30). The definitions of these indices are provided in Table 2.

New remission criteria

Although remission is an achievable goal, the definitions of RA remission differ among studies, and the attainment of this goal is strongly influenced by which set of remission criteria is applied. The widely used definition of remission based on a DAS28 score <2.6 better represents minimal disease activity than remission, as multiple joints can remain swollen or tender at that score (31–33). Therefore, the ACR and EULAR convened a joint committee to redefine RA remission; they proposed two new definitions of remission in 2011 (Table 3), both of which can be uniformly applied and are widely used in RA clinical trials (34). Although good performance has been reported for the new remission criteria, indicating that patients fulfilling the criteria tend to be free from active RA (35–37), several articles have reported that the major reason for not achieving remission based on the new definition is due to the patient global assessment (PGA), which could be influenced by non-inflammatory factors, including low back pain, fatigue, and fibromyalgia (38, 39). The validity of the criteria is still being discussed.

Treat-to-target for RA

Importance of tight control

“Tight control,” in which patients are treated to specified targets with aggressive therapy if necessary, results in beneficial outcomes outside the field of rheumatology. For example, a low glycated hemoglobin (HbA1c) level is widely recognized to a goal in counseling visits because achieving a threshold is understood to drive long-term outcomes in DM (40, 41). Similar procedures are used to avoid future organ damage in the treatment of hypertension, hyperlipidemia, and other conditions. In patients with RA, several clinical trials have demonstrated the advantages of tight control (42–48), thus showing that strategy-driven arms have significantly better results with regard to disease activity, as well as in functional outcomes and radiographic endpoints, when disease activity was taken into account when adjusting treatment.

Treat-to-target for RA

In the context of new developments and accumulating evidence for RA treatments, a task force of rheumatologists and patients with RA developed a set of recommendations on the basis of evidence derived from a systematic literature

Table 4. Recommendations Proposed in Treat-to-Target Task Force

Overarching principles
(A) The treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist.
(B) The primary goal of treating the patient with rheumatoid arthritis is to maximise long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and social participation.
(C) Abrogation of inflammation is the most important way to achieve these goals.
(D) Treatment to target by measuring disease activity and adjusting therapy accordingly optimises outcomes in rheumatoid arthritis.
10 recommendations on treating rheumatoid arthritis to target based on both evidence and expert opinion
(1) The primary target for treatment of rheumatoid arthritis should be a state of clinical remission.
(2) Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity.
(3) While remission should be a clear target, based on available evidence low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease
(4) Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 months.
(5) Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission.
(6) The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions.
(7) Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing composite measures of disease activity.
(8) The desired treatment target should be maintained throughout the remaining course of the disease.
(9) The choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of co-morbidities, patient factors and drug-related risks.
(10) The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist.

Figure 1. Generic algorithm for T2T in RA. The main targets of remission and low disease activity are shown separately, but the approaches to attain the targets and sustain them are essentially identical.

review and expert opinion. The treat-to-target (T2T) activity resulted in four overarching principles and 10 recommendations (Table 4), which were published in 2011 (49). The 10 recommendations are supposed to inform patients, rheumatologists, and other stakeholders about strategies for reaching optimal outcomes in RA. The T2T recommendations suggest adapting therapy if no improvement occurs within

three months or if the treatment target, which is defined as remission in early RA and at least low disease activity in established RA, is not attained within six months (Fig. 1). The T2T recommendations do not deal with any particular type of drug or groups of agents and are importantly generic so that an optimal outcome can be sought irrespective of the availability of specific drugs. An anonymous survey of more

Table 5. Characteristics of Seven Biological Agents Available for Rheumatoid Arthritis in Japan

Biological agents	Infliximab	Etanercept	Adalimumab	Tocilizumab	Abatacept	Golimumab	Certolizumab
Approved year	2003	2005	2008	2008	2010	2012	2013
Target	TNF α	TNF α , LT α	TNF α	IL-6	CD80/86	TNF α	TNF α
Structure	chimeric antibody	TNF receptor/Ig G-Fc fusion	fully human antibody	humanized antibody	CTLA4/IgG-Fc fusion	fully human antibody	polyethylene glycol-modified Fab' fragment
Administration route	IV	SC	SC	IV, SC	IV, SC	SC	SC
Half time period (day)	8-10	3-5	9-16	4-7 (IV) 1-2 (SC)	9 (IV) 13 (SC)	10-14	11-13
Anti-drug antibody* (with MTX) (%)	4.1-27.3	NA	19.3	NA	0-3.0 (IV) 1.1 (SC)	0	1.2-8.2
(without MTX) (%)	NA	NA	44.0	0-3.0 (IV) 3.5-18.0 (SC)	NA	3.3-4.0	10.8-29.9
Dose (mg)	3-10/kg	10-50	40-80	8/kg (IV) 162 (SC)	500-750 (IV) 125 (SC)	50-100	400
Administration interval (week)	4-8	0.5-1	2	4(IV) 2(SC)	4(IV) 1(SC)	4	4

IL: interleukin, IV: intravenous, LT: lymphotoxin, NA: not available MTX: methotrexate, SC: subcutaneous, TNF: tumor necrosis factor

* Anti-drug antibodies reported in clinical trials in Japanese patients with RA according to published articles and information provided in the drug package insert.

than 1,500 rheumatologists on their agreement with the T2T recommendations revealed a very high level of agreement with every item, achieving more than a mean 8.4 points on a 0 to 10 point scale (50). However, such agreement does not necessarily mean that these physicians have implemented the recommendations in their practice. As with every set of recommendations, there are barriers regarding application in practice, mainly because of time or resource constraints (51). Overall, the T2T concept has become widely applicable and is commonly used in clinical practice. Hopefully, it will ultimately provide significant benefits to patients with RA.

New Therapeutics Based on RA Pathogenesis

Biological agents targeting cytokines

Beyond the development of new classification criteria and strategies for RA, there has been great progress in the development of therapeutics based on growing insights into the pathogenesis of RA. Currently, seven biological agents targeting cytokines or cell-surface molecules are available for RA in Japan. Considerable efforts have been made to develop effective and safe drugs, and these biological agents have several distinct characteristics, including the target (TNF, IL-6, or CD80/86), structural type (monoclonal antibodies, receptors/ligands fused to the Fc portion of IgG, or polyethylene glycol-modified humanized Fab' fragment), and the extent of humanization (chimeric, humanized, or fully human) (Table 5). Several multi-center, randomized, double-blind clinical trials of biologics have been conducted in Japan (52-56), and these compounds achieved excellent ACR20 responses in patients who had an inadequate response to methotrexate or disease-modifying antirheumatic drugs (DMARDs) (Fig. 2). Clinical remission occurred in approximately 20-45% of Japanese RA patients in the clinical trials and studies, implying that clinical remission is a

realistic treatment goal (57-60). These studies also demonstrated that functional impairment, as assessed by Health Assessment Questionnaire (HAQ), was significantly improved with biologic treatment. Moreover, in a Japanese trial of tocilizumab (61), increases in the total Sharp score (TSS) and its components and the erosion and joint narrowing scores were significantly lower with tocilizumab monotherapy than in DMARD therapy, providing the first evidence that biologics are superior to DMARDs for inhibiting structural damage. Subsequent clinical trials and studies of other biologic agents with methotrexate revealed a striking inhibition of structural damage, indicating that joint damage in RA can be attenuated (61-67) (Fig. 3). A number of reports have described the long-time effectiveness of biologic treatment from two to as long as eight years. Although treatment regimens vary, it has been shown that early and maintained targeted treatment using biologic agents has functional and radiological benefits (68-70).

Biologic agent safety

While the effectiveness of biologic agents has been well established, their safety continues to be scrutinized. In Japan, post marketing surveillance (PMS) on all available biologic agents has been conducted. PMS data have been collected on all patients with RA who received biologic agents in Japan since 2003, and those reports have revealed the exact frequencies of drug-related adverse events (especially opportunistic infections, such as tuberculosis and pneumocystis jirovecii) and factors that affect drug safety and effectiveness in clinical practice. PMS for infliximab, etanercept, adalimumab, and tocilizumab were recently completed and published (71-74). The primary risk factors associated with serious infection were older age (≥ 60 or 65), concomitant glucocorticoid use, physical functional impairment, and existing lung disease. These data have made it possible to manage RA patients on a biologic agent more safely.

Figure 2. Efficacy of biological agents on the clinical response in Japanese RA patients. MTX: methotrexate

Figure 3. Efficacy of biological agents on the inhibition of radiological progression in Japanese RA patients. The radiological progression rates (Δ mTSS/baseline mTSS) for each biological agent were compared to the placebo used in the clinical trials.

Further developments in therapeutics

Elucidation of the complex intracellular signaling molecules that regulate cytokines and their receptor-mediated functions is facilitating the development of specific small-molecule inhibitors. The Janus kinase (JAK) 1 and 3 inhibitor tofacitinib was recently approved for use in Japan, Russia, and the U.S. Efforts to develop novel biological agents to target other cytokines and intracellular signaling pathways, such as IL-17, B-lymphocyte stimulator (BLyS), a proliferation-inducing ligand (APRIL), granulocyte-macrophage colony-stimulating factor (GM-CSF), JAK 1 and 2, and spleen tyrosine kinase (Syk), are ongoing. The range of available therapeutics is expected to continue to expand.

Conclusion

Significant advances have greatly improved the lives of patients with RA, and it can be said that a paradigm shift has occurred over the last decade. However, important problems remain to be solved, such as persistent synovitis despite intensive treatment and the adverse effects of biological agents. Attention should therefore be paid to differences among patients, and RA treatment should ultimately be individualized to each patient's needs to maximize drug efficacy and minimize any associated risks.

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