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Recent Advances in the Management of Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis is the most commonly diagnosed systemic inflammatory arthritis. Women, smokers, and those with a family history of the disease are most often affected. Criteria for diagnosis include having at least one joint with definite swelling that is not explained by another disease. The likelihood of a rheumatoid arthritis diagnosis increases with the number of small joints involved. In a patient with inflammatory arthritis, the presence of a rheumatoid factor or anti-citrullinated protein antibody, or elevated C-reactive protein level or erythrocyte sedimentation rate suggests a diagnosis of rheumatoid arthritis. Initial laboratory evaluation should also include complete blood count with differential and assessment of renal and hepatic function. Patients taking biologic agents should be tested for hepatitis B, hepatitis C, and tuberculosis. Earlier diagnosis of rheumatoid arthritis allows for earlier treatment with disease modifying antirheumatic agents. Combinations of medications are often used to control the disease. Methotrexate is typically the first-line drug for rheumatoid arthritis. Biologic agents, such as tumor necrosis factor inhibitors, are generally considered second-line agents or can be added for dual therapy. The goals of treatment include minimization of joint pain and swelling, prevention of radiographic damage and visible deformity, and continuation of work and personal activities. Joint replacement is indicated for patients with severe joint damage whose symptoms are poorly controlled by medical management.

KEYWORDS

Rheumatoid arthritis, ESR, hepatitis, CRP, tumor necrosis factor, radiographic damage

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and common systemic inflammatory disease that results in joint deformity and functional disability when not properly managed. The early diagnosis and treatment of RA are imperative for optimal disease control, greater chances of remission, and prevention of permanent clinical and radiographic damage. RA remains a clinical diagnosis although the use and discovery of biomarkers to assist with these goals remain a focus of ongoing research. The 2010 RA Classification Criteria developed by the American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) define a scoring system that includes elements of history, physical exam, and biomarkers that identify patients with RA for the purpose of clinical trial standardization. The criteria have a sensitivity of 84% and specificity of 60% for classification as RA [1-2]. In clinical practice, rheumatologists frequently use these criteria to defend the diagnosis of RA. This review focuses on the four biomarkers included in these criteria that are available for routine clinical use: rheumatoid factor, autoantibodies against citrullinated proteins, erythrocyte sedimentation rate, and C-reactive protein; the multi-biomarker disease activity test is also discussed. A short discussion of investigational biomarkers and outstanding clinical questions follows.Rheumatoid arthritis (RA) is an inflammatory rheumatic disease with progressive course affecting articular and extra-articular structures resulting in pain, disability and mortality (1). Persistent inflammation leads to erosive joint damage and functional impairment in the vast majority of patients (2, 3). The onset of disease is not similar in all patients but varies in regard to type, number, and the pattern of joint involvement. The course of disease may be also different according to the presence or absence of several variables including genetic background, frequency of swollen joints, autoantibody in the serum and the severity of inflammatory process (4, 5). The initial presenting features of early RA do not substantially differ from other inflammatory arthritis. So, prior to definite diagnosis patients with early RA are usually classified as undifferentiated arthritis which difficultly can be discriminated from other inflammatory arthritis. Up to now, early RA was denoted to patients with disease duration of less than 2 years preferentially less than 12 months but currently most rheumatologists are willing to see the patients with symptom duration of less than 6 weeks. At present, "early" RA is regarded as patients with symptom duration < 3 months as early disease (6). However, this term has not been accepted by all researchers yet, since a number of rheumatologists believe that patients have either established RA or undifferentiated inflammatory arthritis (UA) (7,8).

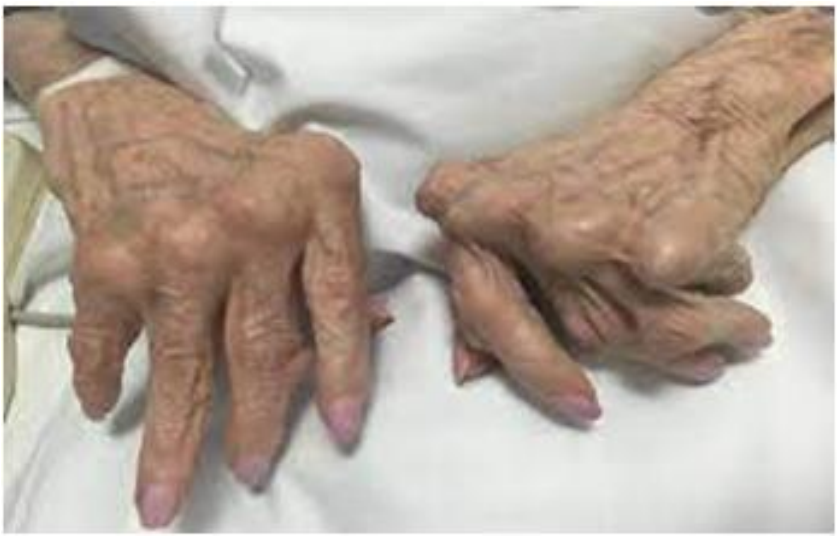
EARLY DIAGNOSIS OF RHEUMATOID ARTHRITIS

Identification of RA at initial presentation and treatment at earlier stage can affect disease course, prevent the development of joint erosions or retard progression of erosive disease (5, 9). Early diagnosis and treatment may affect disease outcomes even to a remission state (10, 11). Recognizing early RA from non-RA at the onset of disease is not straightforward but there is limitation in the use of the American College of Rheumatology revised criteria (ACR criteria) for early diagnosis. Since due to inadequate

clinical or laboratory evidences at onset of arthritis, this criterion is not sensitive enough to identify early RA (4, 12). In a study of Frech cohort, only 50.9% of RA satisfied 1987 ACR revised criteria for diagnosis of RA in 1 year (4). However, in the absence of treatment inflammation will lead to articular damages and bone erosion particularly within the first two years of disease onset (13). Regarding the current concept of "window of opportunity", early diagnosis of RA is essential for initiation of treatment, otherwise, disease will progress to more severe forms requiring more aggressive therapy (10). Application of recently developed diagnostic criteria provided an opportunity to identify and treat those patients with early inflammatory arthritis who progress to future RA. Using this criterion can discriminate inflammatory arthritis who fulfil the 1987 ACR criteria in the future from those who do not develop RA. The new 2010 criteria is a diagnostic tool with higher sensitivity and specificity compared to previous ACR-criteria. The new criteria classify greater number of patients at earlier phase with reasonable discriminative ability (14).

PREDICTION OF EARLY DIAGNOSIS OF RHEUMATOID ARTHRITIS

A patient with inflammatory arthritis may pass several stages from the onset of arthritis to a specific form of rheumatic diseases such as RA (8). The first phase is the period leading up to the onset of arthritis. The second is the period during which persistence or remission is determined. The third and the fourth phases are the evolution into specific form of inflammatory arthritis and the outcome/severity of that arthritis. In some patients, these four phases follow in rapid sequences whereas in other patients the time course may prolong and continue for several months or years. Different genetic backgrounds and environmental factors or treatment can affect the various evolutionary phases of arthritis and alter the natural history of initial inflammatory arthritis. It seems that a considerable proportion of UA, progress to RA, on the other hand about 10% of early RA experience natural remission (8). While earlier treatment of inflammatory arthritis is expected to prevent development of RA and even exert a curative effect for a proportion of patients, on the other hand, inappropriate treatment of patients who do not develop RA is harmful and should be avoided. In this condition, the most important challenge is to predict RA development in those patients who have persistent arthritis. The proportion of UA patients who progress to RA varies considerably across various studies. This may be explained by the differences in inclusion criteria, or in definitions used for diagnosis of UA or RA, characteristics of UA patients, and duration of follow-up period. In a number of published studies, after one year of inclusion proportion UA patients developed RA ranged from 6% to 55%. Studies in which, presence of arthritis at disease onset was mandatory for inclusion, proportion of patients who fulfilled ACR criteria ranged 17-32% (15). Several variables have been regarded as predictors of future RA in patients with early arthritis (table 1). Variables such as duration of morning stiffness in minutes, percentage change in HAQ score after 3 months disease duration and anti-CCP positivity are predictors of persistent arthritis (2, 16). Presence of these findings at baseline can also be used in differentiating persistent arthritis from self-limited arthritis.



CLINICAL MANIFESTATIONS

The onset of RA as polyarticular disease develops insidiously in about three-quarters of patients. Early symptoms of RA may appear as vague pain with gradual appearance without classic symptoms of joint swelling or tenderness. These unusual symptoms are usually non-specific, and may persist for prolong period. Early articular manifestations of RA may be indistinguishable from other rheumatic diseases. Prolong duration of morning stiffness with arthralgia, or arthritis in a limited number of joints may be a clue for considering RA diagnosis (1). Involvement of small joints of the hands or feet with swelling and tenderness particularly symmetric pattern of involvement along with positive compression test is highly suggestive of RA (27, 28). In a study of Quinn et al, painful joints of the hands at baseline were significant predictors of RA (29). Presence of some clinical features such as polyarthritis, symmetric arthritis, hand arthritis, pain upon squeezing the metacarpophalangeal or metatarsophalangeal joints, and morning stiffness greater than 30 minutes can be helpful not only in estimating the future course of arthritis but also in limiting the spectrum of differential diagnosis. Identification of all involved joints by precise clinical examination is essential. Counting the tender and swollen joints, and calculation of disease activity score are logical methods for the determination of disease severity and response to treatment (30).

LAB. TESTS

Abnormal values of the laboratory tests are the most typical features of RA. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) provide the best information about the acute phase response. The level of CRP was shown to be significantly correlated with the severity of disease as well as radiographic changes (31). Auto antibodies such as RF and anti-CCP are very helpful for the diagnosis of RA. Anti-CCP antibody demonstrated a comparable sensitivity but a greater specificity than RF for the diagnosis of RA (18, 17). Combination of anti-CCP and RF increases diagnostic specificity for RA (17). The level of serum anti-CCP can be also helpful in predicting subsequent progression of UA to RA with high accuracy (18). Anti-CCP exerts additional diagnostic ability in recognizing seronegative RA (25). Arthrocynthesis

and synovial fluid analysis can be also helpful for diagnosing inflammatory arthritis as well as in discriminating inflammatory from non-inflammatory arthritis. Assessment of synovial fluid anti-CCP may be very diagnostic in recognizing RA from non-RA arthritis.

IMAGING

Radiographic signs of RA such as joint space narrowing, erosions and subluxation develop at later stage of RA process. Plain radiography is the standard method in investigating the extent of anatomic changes in RA patients. However, there are few data regarding the value of conventional radiographic examination in recent-onset arthritis. Synovitis is the early findings of RA and is strong predictor of bone erosion. Soft tissue swelling and mild juxtaarticular osteoporosis may be the initial radiographic features of hand joints in early - RA (31). In contrast sonography and MRI are more sensitive and seem promising but can be used in a limited center, Sonography is a reliable technique that detect more erosion than radiography especially in early RA (37). The sensitivity of conventional radiography in detection of bone erosion in one study was 13%, whereas, the sensitivity of MRI and US in detection of bone erosion were 98% and 63% respectively (38). For these reasons, there is a trend toward early detection of RA bone erosions by MRI especially in patients with early signs of arthritis. Presence of joint erosions in UA patients may be indicative of progression to RA. In a study by Tami et al. patients with at least 2 MRI-proven symmetric synovitis or bone edema and/or bone erosion progressed to RA at 1 year with a 79.7 % positive predictive value and 75.9% specificity, 68% sensitivity (39). Sonography is also a reliable technique that detects more erosions than radiography especially in early RA. In early RA, sonography can detect greater number of erosions and in a greater number of patients than can radiography (13). The introduction of MRI imaging provides more diagnostic facility in earlier diagnosis of RA and differentiating RA from non-RA diseases. MRI findings may detect additional patients with true RA compared with ACR-diagnostic criteria (40). In addition, MRI is more sensitive than clinical examination to detect synovitis of hands and wrists in RA (41).

DIAGNOSIS

There is no specific test for diagnosis of RA. Up to now, the 1987 ACR revised criteria was applied for diagnosis of RA. Recently, a new criterion has been developed for differentiating patients who may progress to RA (according to 1987 ACR criteria) from those who do not (42). The aim of new criteria is the earlier identification of high risk early inflammatory arthritis for treatment, and preventing development of an arthritic disease that satisfies 1987 criteria. These criteria provide data for earlier treatment and permit more rapid institution of DMADRs therapy. The 2010 new criteria rates on a scale from 0-10 points were assigned in four separate domains of signs and symptoms namely: 1) joint involvement 2) serology 3) duration of symptom 4) acute phase reactants. Patients are definitely diagnosed with RA if they score 6 or more points according to the following criteria (table 2). These criteria can be applied to any patient with at least one involved joint defined as clinical synovitis which cannot be attributed to other entities and there is no explanation for synovitis (42). The new classification criteria present a new approach with a specific emphasis on identifying patients with a

relatively short duration of symptoms who may benefit from early institution of DMARD therapy.

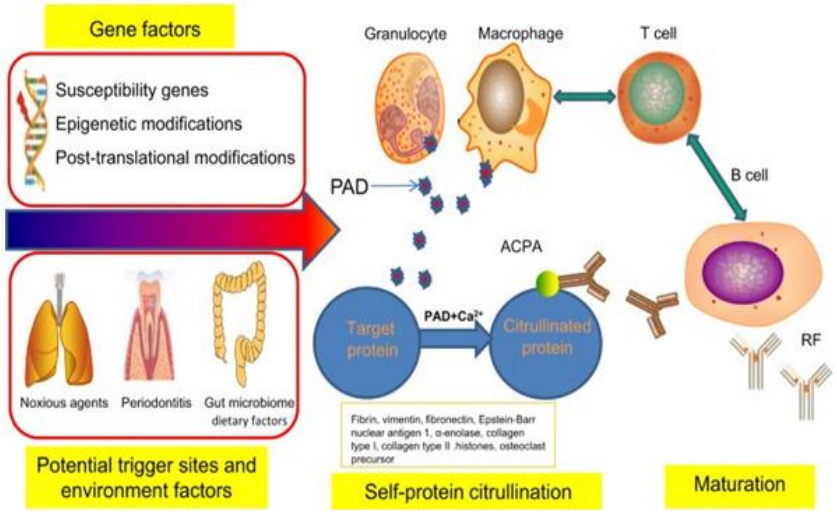
TREATMENT

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

TREATMENT

Biological DMARDS

The marketed biologics available for the treatment of RA include five TNF-targeting drugs, two IL-6 receptor-targeting drugs, one B cell antigen CD20-targeting antibody and one selective T cell costimulatory modulator (Fig. 1). They have all been demonstrated to be highly effective and acceptably safe when used in combination with MTX for the treatment of RA refractory to MTX and/or bDMARDs [1–3]. Some TNF-targeting drugs in combination with MTX have also been demonstrated to exert high therapeutic effects in MTX-naïve RA patients. Ten-year follow up studies on the treatment of RA patients with these bDMARDs have revealed no major safety concerns with long-term use, and almost complete inhibition of progression to structural joint damage and physical dysfunction [4, 5]. Monotherapy with sarilumab, the latest IL-6 receptor-targeting drug among the nine bDMARDs, has been demonstrated to be as effective for MTX-refractory RA as monotherapy with adalimumab, a TNF-targeting drug. The efficacy of sarilumab in a monotherapy setting has been demonstrated to be comparable to that of tocilizumab, which is also an IL-6 receptor-targeting drug [6]. At present, clinical trials are in progress on tocilizumab and sarilumab for the treatment of cytokine release syndrome associated with the new coronavirus disease 2019 (COVID-19). In the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia) study, treatment with tocilizumab or sarilumab improved outcomes, including survival, in critically ill patients with COVID-19 receiving organ support in intensive care units. In the RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial, tocilizumab improved survival and other clinical outcomes in hospitalized patients with COVID-19 and with hypoxia and systemic inflammation. However, in the COVACTA study, the use of tocilizumab did not result in significantly better clinical status or lower mortality than placebo at 28 days in hospitalized patients with severe COVID-19 pneumonia [7–9].

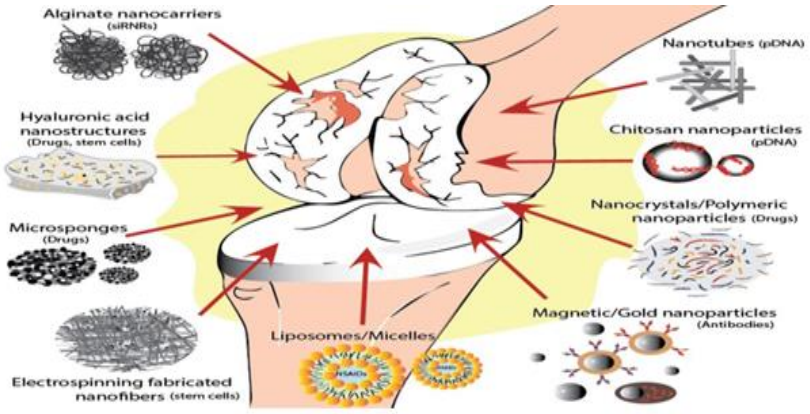


TARGETED SYNTHETIC DMRDAS

To facitinib was developed as a low-molecular-weight compound that competitively binds to the adenosine triphosphate-binding site of JAK3 and specifically inhibits phosphorylation of JAK3. However, tofacitinib also displays potency against JAK1 and to a lesser extent JAK2, and less still TYK2, and is currently designated a JAK inhibitor. It was approved as the first JAK inhibitor for the treatment of RA in the USA in 2012. At present, the JAK1/2 inhibitor baricitinib and JAK inhibitors peficitinib and upadacitinib, and a JAK1 inhibitor filgotinib, have been approved for the treatment of RA (Table 1). However, all the five JAK inhibitors are currently designated as a JAK inhibitor. While *in vitro* intracellular signalling analyses suggest that the therapies are somewhat distinct, in clinical trials they look reasonably similar and long-term observation in the clinic will tell us whether they differ in practice. Phase III international clinical trials have demonstrated that the clinical and structural effects of these JAK inhibitors were significantly more robust and rapid than the effects of placebo in MTX-naïve patients, as well as in RA patients with inadequate responses to csDMARDs such as MTX or bDMARDs such as TNF-targeting drugs [26–31]. Baricitinib and filgotinib are significantly more effective than adalimumab [28, 31], whereas upadacitinib is significantly more effective than adalimumab and the selective T cell costimulatory modulator abatacept [30, 32]. Upadacitinib monotherapy showed statistically significant improvements in clinical and functional outcomes *vs* continuing MTX in an MTX inadequate-responder population [33]. Different from other JAK inhibitors, filgotinib forms active metabolites just after the oral intake and shows characteristic pharmacokinetic patterns of cytokine signalling inhibition [34, 35]. While there are no direct comparative studies between JAK inhibitors, we have reported that baricitinib is significantly more effective than tofacitinib in patients adjusted for patient characteristics using a propensity score-based method known as inverse probability of treatment weighting [36]. In addition, we have also shown that peficitinib is comparable to baricitinib and tofacitinib in terms of efficacy on the basis of a network meta-analysis [37].

TREATMENT OF DIFFICULT-TO -TREAT RA

Despite the advent of various molecular target drugs, multiple drug resistance still remains an important challenging issue that needs appropriate redressal for the treatment of RA. The European Alliance of Associations for Rheumatology (EULAR) defines difficult-to-treat RA based on the following three conditions: (i) resistance to treatment with two or more bDMARDs or tsDMARDs targeting different sites in patients with csDMARD-refractory RA; (ii) the presence of any of the following conditions: moderate disease activity or greater, clinical signs and symptoms indicative of disease activity, inability to taper glucocorticoids, imaging findings of progression, or RA symptoms impairing the quality of life; and (iii) the presence of RA symptoms that are determined to be problems by rheumatologists [50].



DEVELOPMENT OF PRECISION MEDICINE

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

POSSIBILITY OF DRUG HOLIDAY

In the treatment of RA, safe and effective long-term treatment is essential after the induction of remission with MTX and bDMARDs/tsDMARDs. However, the burden of medical expenses and problems of medical economics due to long-term continuous use of drugs

are pressing issues [57, 58]. It is also unknown whether long-term inhibition of TNF and other targets is safe. In remission induction by the RRR (Remicade in RA) study, the HONOR (Humira Discontinuation Without Functional and Radiologic Damage Progression Following Sustained Remission) study and the C-OPERA (Certolizumab-Optimal Prevention of Joint Damage for Early RA) study, we have reported that bDMARD therapy with TNF-targeted drugs can be withdrawn after sustained remission in patients with RA [59–62]. The international consensus indicates that drug withdrawal after remission should be implemented in the order of CS, anti-inflammatory drugs, bDMARDs and csDMARDs. The four conditions required for withdrawal of bDMARDs and csDMARDs were satisfied with the standard criteria for remission including remission sustained for 6 months or longer, remission sustained with the same drug at the same dose for 6 months or longer, and no use of glucocorticoids [63]. Compared with the withdrawal, it is easier to taper drugs with less frequency of disease flares, but formation of anti-drug antibody and the reduced efficacy is more often observed in patients receiving lower doses of bDMARDs such as TNF inhibitors [64].

CONCLUSIONS

There are four classes of bDMARDs and one class of tsDMARDs, including five JAK inhibitors, available for molecular-targeted therapy. In the treatment of RA, clinical, structural and functional remission is a realistic target. The latest JAK inhibitors are effective for overcoming even difficult-to-treat RA. However, the development of new drugs has been difficult because head-to-head comparison with TNF-targeted drugs has been a common approach used in recent phase III clinical trials. Thus, instead of adding new drugs, a top priority may involve advances in therapeutic strategies, including strategies to maintain safety and efficacy in balance, as well as thorough implementation of screening at treatment initiation, and monitoring during treatment. In addition, the differential use of therapeutic drugs and de-escalation of treatment after remission induction are also important issues. Achievement of sustained remission with a drug holiday/withdrawal regime suggests the possibility of achieving a drug-free remission and even cure in the later stages of treatment. However, the factors or drivers that inhibit the transition from remission to cure may exist not only in the immune system, but also in mesenchymal, intestinal, nerve and the metabolic system [65]. Thus, the elucidation of such drivers and approaches to regulate them may serve as an important strategy in addressing the challenges and unmet needs in the management of RA.

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