Review Article

Rheumatoid Arthritis: Early diagnosis and treatment outcomes

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Abstract

Rheumatoid arthritis (RA) is an inflammatory progressive disease which in the absence of appropriate treatment can lead to joint destruction and disability. Prognosis of RA may be predicted based on the presence of some clinical and laboratory evidences.New criteria for classification of RA provides opportunity for earlier treatment. Initiation of treatment particularly by combination of DMARDs concurrent with short duration of corticosteroid is expected to prevent progressive course and even change the natural course of RA.At present any patients with clinical synovitis in at least one joint may have definite RA, requiring agressive treatment.

Key words: *Rheumatod arthritis,new criteria; early treament,outcome.*

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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).

The importance of early diagnosis of RA

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 criteria 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 criteria 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 RA

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 (7,11).

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. Among patients with iUA, recognizing patients with progressive course particularly those who develop erosive disease is very important. There is a great need to accurately predict the development of a well-defined diagnosis such as RA or other rheumatic diseases for initiation of treatment. Autoantibodies such as rheumatoid factor (RF) and anticylic citrullinated peptide antibodies (anti-CCP) have demonstrated high diagnostic specificity and can allow accurate prediction of RA in patients with UA. (10,17-23). In addition, some clinical or radiological features at baseline may also predict subsequent development of RA. In a study of recent onset arthritis, patients with mean disease duration of 3 months, over a median follow up period of 5 years, the presence of polyarticular disease predicted persistent arthritis and presence of hand arthritis t was the most predictor of a poor outcome (24).

In a French study of early cohort with inflammatory arthritis, presence of swollen joint count, morning stiffness, erosions, RF and anti-CCP at baseline were the most efficient predictors of future development of RA. In this

study, both RF and anti-CCP or either of them alone were predictors of subsequent development of RA (4). In a large cohort of early RA patients with mean symptom duration of 7 months the anti-CCP2 antibody test has differentiated RA from non-RA disease at a specificity of 91% and sensitivity of 81%. In RF-negative patients, the specificity and sensitivity rates 92% and 60% respectively (25).

Table 1. Predictors of future development of rheumatoid arthritis in patients with recent onset arthritis

Clinical variables
Prolonged period of symptom duration
Symmetric arthritis
Hand arthritis
Prolong duration of morning stiffness
Larger number of swollen joints
Larger number of painful joints
Older age
Female sex
Laboratory variables
Presence of HLADRß[1]
IgG –RF positivity
Anti-cyclic citrullinated protein positivity
High level of C-reactive protein (CRP)
High level of erythrocyte sedimentation rate (ESR)
Imaging
Bone erosion in plain radiographs
Bone edema or erosion in MRI

Clinical manifestations

Many rheumatic conditions can be diagnosed or suspected based on taking history and physical examination. Clinical findings are also the mainstay in selecting appropriate diagnostic laboratory tests requested for confirmation of RA or ruling out other rheumatic diseases (26). Sometimes, diagnosis of RA may be possible based on clinical grounds alone, nevertheless there are no disease-specific clinical features or laboratory test to be diagnostic for RA. 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 metcarpophalangeal or metatasophalangeal 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).

Laboratory 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. The diagnostic performance of synovial fluid anti-CCP was shown in a cross-sectional study. In this study, identification of anti-CCP in the synovial fluid of patients with arthritis demonstrated high discriminative ability in recognizing RA from non-RA diseases (32). Acute phase reactants such as ESR and CRP are important tools for both confirmation and severity of inflammation in patients with arthritis. Increased levels of these inflammatory markers suggest higher disease activity (30). These tests may be also helpful in the evaluation of treatment efficacy. The levels of acute phase reactants decrease in correlation with efficiency of treatment as reflected by decrease in DAS value (33).

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).

These findings are representative of synovitis but cannot be shown on conventional radiogaraphs in all patients and are not precise enough and so are unreliable in the regular assessment of synovitis (34). In particular, due to later occurrence of radiographic changes, plain radiography are insensitive for detection of bone erosion which is a characteristic for the diagnosis of RA (27,35). In a study of very recent-onset arthritis with symptom duration <3 months, radiogtaphic bone erosions were observed in 12.8% of initial radiographs compared with 27.6% after one year (36).

In contrast sonography and MRI are more sensitive and seem promising but can be used in a limited centers, 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 criteria 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. This 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 symtome 4) acute phase reactatnts. Patients are definitely diagnosed with RA if they score 6 or more points according to the following criteria (table 2). This criteria can be applied to any patient with at least one involved joint defined as clinical synovitis which can not 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 instittuition of DMARD therapy.

Table 2. The 2010 American College of Rheumatology/ Eroean League Against Rheumatism classification criteria for rheumatoid arthritis.arthritis.

Domains	**description**	**No**	**Score**
Joint Involvement	Median-large joint§	1	0
		2-10	1
	Small joints ±	1-3	2
		4-10	3
		>10 ¥	5
Serology	No positive for either RF or anti-CCP		0
	At least one of these test positive at high titer*		2
	At least one of these test positive at low titer**		3
Duration of synovitis	+/> six weeks		1
Acute phase reactants	Neither CRP or ESR is abnormal		0
	Abnormal CRP or ESR		1

Patients receive highest point level they fulfill within each domain

Joint involvement. Refers to any swollen or tender joint on examination .Distal interphalangeal,1st carpometacapeal and 1st tarsometatarseal joints are excluded from assessment.

§ Shoulder,elbow,knee,ankle

± Small joints refer to metacarpophalangeal,proximal interphalangeal,second through 5th metatarsophalangeal ,thumb interphalangeal and wrist joints.

¥ In this category, at least one of the involved joints must be a small joint;the other joints can include any combination of large additional small jointjoins as well as other such as temporomaibular ,acromioclavicular ,sternoclavicular,etc,et.

* low titer defined as < three times the upper limit of normal> upper limit of normal

** High titer defined as > three times the upper limit of normal

± Large joints r

Treatment

Based on new developed criteria, patients with at least one involved joint may require DMARD therapy in respect to other components of criteria. RA disease may be considered a potentially curable condition during the evolutionary process (from inflammatory arthritis to established condition) and the disease course may be changed by early appropriate aggressive treatment (11). Current knowledge and availability of highly efficient DMARDs or biological therapies encourage the goal of treatment being changed to achieve remission rather than control of inflammation (43). Earlier identificatiin of high risk individuals and a very early use of effective DMARDs is

a key point in patients at risk of developing persistent erosive arthritis (44). This may provide opportunity for prevention of structural damages and long-term disability (3). On the other hand, delay in starting treatment with DMARDs was shown to affect long-term outcome significantly (13). A considerable proportion of UA patients are actually patients with RA in a very early phase and so it is important to identify UA patients who will develop RA and treat them as early as possible (15).

Initiation of treatment

DMARDS are the mainstay of therapy and so should be initiated as early as possible in the course of the disease (1) their very early intervention was shown to be cost-effective (45). All therapies - monotherapy, combination DMARD, biologics - work better in early disease than in long-established RA (43,46). Combination therapy is more effective than monotherapy and has a greater initial effect on clinical remission than on radiographic progression.

In one study, early treatment with 3 DMADRs for two years were compared with one DMARDs for two years The respective remission rates were 40% and 18% after 2 years and 28%, 22% after 5 years. This study demonstated that combination therapy with 3 drugs for the first 2 years limited the peripheral joint damages for at least 5 years (47). Combination therapy can be highly effective especially in patients with early RA.Initial combination therapy exerts greater protection for joint damage and provides earlier clinical improvements (9). Combination therapy using biological agents (infliximab, adalimumab) with methotrexate or biological therapy alone may induce remission in many patients with early RA.Combination therapy should be considered in patients who have risk factors such as high level of anti-CCP, RF, joint erosion in radiographs and those who have shared epitope (46). Results from previous studies suggest that treating high risk patients may slow the progression from early inflammatory arthritis to definite RA and inhibit the progression of joint damage (11). Combination therapy can prevent radiographic progression even in patients with risk factors such as RF or anti-CCP whereas, monotherapy may be ineffective (48).

Steroids

Administration of steroid in combination with DMARDs or with biological therapies in early RA can induce a higher rate of remission, control of radiological progression compared with DMARD monotherapy. This regimen provides better outcome and should be considered in all patients (3,46). Systemic glucocorticoids are also effective in the short-term relief of pain and swelling, and therefore may be considered for these purposes but mainly as a temporary therapy (44). In addition, combination of steroids to DMARD therapy exerts additional effect on bone erosion (see bellow).

Treatment outcomes

Efficacy of treatment on joint damages on radiography. Long-term impact of early treatment on bone radiographic progression in RA was shown in a meta-analysis of 12 studies by Finckh et al. (5). The pooled estimate of effects demonstrated a 33% reduction of radiographic progression in patients treated earlier than 2 years disease duration with DMARDs compared with those treated later. The benefits sustained for up to 5 years (5). Addition of prednisolone to DMARD therapy at the beginning of the initial treatment retards progression of radiographic damages .This was illustrated in a study by Svensson et al. (28) in patients with active RA with disease duration </=1 year. In 2 years, patients who received prednisolone 7.5 mg daily had fewer newly eroded joints per patient versus those without prednisolone. (radiographic progression at 25.9% and 39.3% respectively). The corresponding remission rates in 2 years were 55.5% and 32.8% (28). The effect of treatment with combination of 3 DMARDs on radiographic erosions in early RA was assessed versus single DMARD in a study of Korpela et al. (47). After 5 years, the median Larsen sore in combination therapy was significantly lower than single therapy (11 vs 24, p=0.001)

In another similar study by Harfstrom et al. (49) remisson rate in two years was significantly higher in prednisolone group compared without prednisolone (55% vs 30%) and during longitudinal analysis, prednisolone group had higher probablity of being in remission. Over 4 years,

the changes in bone density did not differ between the two groups (49). In a systematic review, glucocorticoids substantially reduced the rate of progressive erosions in rheumatoid arthritis if given, in addition to standard therapy (50).

Remission

Disease course in RA varies across different studies. In early RA natural remission occurs in about 10% of cases. In a study by Wolfe 14% of 458 RA who were followed-up for over 1000 patient years achieved remission without treatment (51). In another study by Prevo et al. 10% of 227 RA patients who were followed for 4 years achieved remission. In one study which the clinical course in 183 early RA with mean disease duration of 11 months were assessed over 5 years, 20% experienced remission for at least 6 months. More than half of these cases achieved spontaneous remission (52). In another study by Eberhardt et al. remission according to ARA criteria was rare and was achieved only in 7% of patients. A relapsing –remitting disease pattern was observed in 56% whereas, others had persistent course pattern course (53). The long-term outcome of 168 patients with early RA defined as disease duration less than 2 years was propectively assessed over 10 years by Lindqvist et al. After 10 years, 94% of cases managed daily life activities independently (functional class I –II) as measured by HAQ, 20% had almost no disability, 28% were mildly disabled and 10% were severely disabled (54). In a study of 160 patients with early RA who were treated with either combination of 3 DMARDs or a single DMARD for two years, remission achieved in 40% and 18% of groups respectively. After 5 years, the corresponding values for remission were 28% and 22% (48). In patients treated with prednisolone, remission rate was greater than those who did not take prednisolone (49).

The outcome of treatment in 508 patients with recent-onset arthritis according to 4 treatment groups was determined by Allart et al. In this study, functional ability in patients initially treated with three DMADRs (methotreate+ Sulfasalazine+prednisolone) or initiated with methotrexate+ infleximab was compared with those who has been treated with one DMARD alone (methotreaxate or changed to other DMARDs) or step-up to combination therapy (initiated with methtrexate). Improvement appeared earlier and radiographic joint damages progression was significantly lower, remission rate was significantly higher in combination therapy than monotherapy. In addition, more patients could taper antirheumatic drugs and still retained remission and maintained higher life quality measures in formers groups than latter (55).

In conclusion, progressive course of RA may be mitigated or changed by appropriate treatment including combination of DMARDs started at earlier period. Development of new criteria classify RA patients at early phase and permits initiation of treatment for suppression of inflammation and decreasing disease activity. Early combination DMARDs is more effective than monotherapy and short duration of corticosteroid therapy added to treatment program exerts additional benefits in term of disease activity and bone erosions.

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