Review Article

Undifferentiated arthritis: predictive factors of persistent arthritis and treatment decisions

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Abstract

A number of patients with inflammatory arthritis due to inadequate clinical or laboratory data do not fulfill diagnostic criteria for a clinical disease categories. These patients with initial diagnosis of undifferentiated arthritis (UA) may remit or progress to a definite well-defined condition such as rheumatoid arthritis (RA) or remain as UA with persistence of inflammatory arthritis. The main objective in the evaluation of these patients is focused on differentiating self-limiting arthritis from those who progress to chronic destructive arthritis such as RA. The study reviews the background data regarding the associated factors of progressive diseases among patients with recent-onset arthritis as well as the evaluation and decision in the management of this population. At present, the major goal should be focused on the early identification of patients, who have progressive course and initiation of appropriate therapy by using Disease Modifying Anti Rheumatic Drugs, (DMARDs) as early as possible to achieve clinical remission.

Key words: *Undifferentiated arthritis, Rheumatoid arthritis, Predictive factor, Treatment.*

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The major goal in the approach of patients with inflammatory arthritis is to prevent joint destruction and further disability. This aim may be achieved by early diagnosis as well as early initiation of treatment to suppress the inflammatory process in patients with any inflammatory joint diseases particulaly Rheumatoid Arthritis (RA). Early treatment with new available therapeutic agents can encourage patients the best possible results with improved outcome (1, 2, 3). RA is the leading cause of morbidity and disability among patients with inflammatory joint diseases, consequently its diagnosis should be considered in the differential diagnosis of any patient with recent-onset arthritis. There is an increasing evidence that the first few months after the symptom onset represents a pathologically distinct phase of disease. This very early phase may translate into a therapeutic window of opportunity during which it may be possible to retard the disease progression and joint destruction as well as induce clinical remission or possibility of permanently switch off the disease process (4-11). At the time of initial presentation of a patient with recent-onset inflammatory arthritis established diagnosis for a definite rheumatic disease such as RA or differentiation of a persistent arthritis from self-limited disease may not be possible because of similarities in articular and laboratory manifestations between the different rheumatic diseases.

Diagnosis of RA is made by the American College of Rheumatology (ACR) Classification Criteria (12) but there is a limitation in the application of this criteria at the onset of RA. Many patients with arthritis who develop RA at later time do not meet the ACR criteria at the time of initial presentation because of inadequate clinical or laboratory evidence to fulfill the criteria, Whereas, in the absence of treatment development of erosions or bone loss all are known to occur due to inflammation particularly within the first two years of RA onset (13).

In approaching patients with arthritis, taking history, clinical examination and proper use of laboratory tests can provide the necessary information for the diagnosis of a well-defined syndrome, However in an important proportion of patients with recent-onset arthritis insufficient data prohibit a definite diagnosis even after a prolonged period of time so the diagnosis remains as undifferentiated arthritis (UA). The term of UA is applied when an inflammatory arthritis is suspected but established classification criteria for any rheumatologic condition are not fulfilled. These patients do not fit into well-known clinical disease categories such as seronegative RA and reactive arthritis. UA is an early stage of a definite rheumatic disease or an overlap syndrome between such diseases, or an unknown, etiologically undefined disease that remains to be differentiated from the other types of arthritis or spondylarthritis (14). A patient who is defined as UA, has the potential for a persistent course without fulfilling the classification criteria for specific rheumatic disease (15).

In any patients with UA, the diagnosis of RA remains a possibility and any efforts should be made to recognize RA from non-RA patients as early as possible. The course of patients with recent-onset arthritis is variable. A number of patients fulfill the criteria for a specific disease such as RA, non-RA rheumatic disease at the time of initial presentation or over the follow-up period. While at the same time, a proportion of these patients remain undiagnosed despite the complete clinical examination and laboratory investigations. During the follow-up period, a number of UA patients achieve a definite diagnosis, while in other patients, achievement of an established diagnosis may last several months or longer. However, many of the patients remain with the diagnosis of UA for an indefinite period. Among those patients with recent-onset arthritis differentiation of patients with persistent course from patients whose disease will be resolved is very important.

The course of patients with recent-onset arthritis

In about half of patients with recent-onset arthritis with disease duration of less than 6 weeks, the symptoms resolve spontaneously. However, about 30 % of them may progress to RA disease (15, 16, 17). In patients with recent onset inflammatory polyarthritis from Norfalk Arthritis Registry, absence rheumatoid factor (RF), absence of ankle swelling and presence of fever in six tender joints, were predictors of remission (18). Many of these patients despite not given a definite diagnosis may have good prognosis. This was observed in the follow-up of 28 patients with UA over 26 month's period. Fifteen patients (54%) went into complete remission, while the diagnosis in 10 (36%) remained unchanged but with partial remission, and 2 patients progressed to RA (19). The outcome of UA patients who has a single joint involvement is better and higher percentage of recovery is expected. In a study of 46 patients with disease duration of more than 3 months, about 50% of patients recovered, whereas, the rest of the patients progressed to either RA or spondylarthritis (20). In the early stage of the disease, up to 50 % of patients had UA (15, 16).

The frequent spontaneous remission of synovitis in patients with symptom duration of < 3 months means that the early treatment with potential toxic drugs should be used for those who are expected to have persistent arthritis (4). Proportion of patients with recent-onset arthritis who are classified as UA can not be predicted but according previous studies range from 15-60%. These variations may be attributed to symptom duration at the time of presentation, duration of follow up period and the status of treatment (19, 21-27). UA has a variable course; 40 to 50 % of UA patients remit spontaneously, while 30% develop RA. Persistence of arthritis may be predicted based on the presence or absence of some clinical or laboratory features which were detected at the time of initial visit or appeared later during the follow-up period. These factors may also be helpful in the selection of diagnostic tests or as a guide for therapeutic decisions (21, 23, 28).

Several clinical or laboratory markers were recognized to predict the course of arthritis or the discrimination of chronic persistent arthritis from self-limited arthritis. The predictive ability for a number of these factors such as disease duration, RF and anti-cyclic citrullinated peptide antibodies (anti-CCP) positivity, presence of bone erosions, duration of morning stiffness, presence of shared epitope and high levels of ESR or CRP were shown in previous studies (2, 18, 24, 29-33).

In a study of patients with mild early inflammatory arthritis by Green et al. disease duration greater than 12 weeks was the strongest associated factor for persistent arthritis. After 6 months follow-up, 94% of patients with disease duration of >12 weeks versus 53% of those < or =12 weeks had persistent disease. The other significant factors for persistent arthritis in this study were presence of shared epitope, RF positivity and fulfillment of ACR criteria at presentation (29). A few other clinical features such as presence of three or more swollen joints, pain upon squeezing the metcarpophalangeal and /or

metatarsophalangeal joints, and morning stiffness greater than 30 minutes were also predictors of persistent arthritis. However, identification of these findings requires an evaluation by a rheumatologist (30). In another study by Mjaavatten et al. anti-CCP positivity and small joint arthritis were consistent predictors of chronic arthritis in patients with very early arthritis (31).

A model comprised of 7 variables were developed for prediction of arthritis outcome at first visit of patients with early arthritis by Visser et al. This model consisted of duration of symptom at first visit, morning stiffness > or=1 hour, arthritis in 3 or more joints, bilateral compression pain in the metatarsophalangeal joints ,RF positivity, anti-CCP positivity ,and the presence of erosion (hand/feet). The application of this model to an individual patient resulted in 3 clinically relevant predictive values for discrimination of self-limiting arthritis, persistent nonerosive arthritis and persistent erosive arthritis (32).

In a study of 518 patients with UA by Thabet et al. presence of 2 or more erosions at baseline was associated with the risk of persistent disease in 68% of patients (15). In patients of recent onset inflammatory polyarthritis from Norfalk Arthritis Registry, RF titer, high baseline CRP value, and high baseline HAQ score were all predictors of poor outcome. There was also a strong association between possession of the shared epitope and the development of erosions (33). The association between the high titer of anti-CCP and RF and persistent arthritis was observed in other studies as well (34, 35). In a study of 376 patients with recent-onset arthritis with median duration of 32 days, 174 patients had persistent arthritis after one year. The likelihood for persistent disease increased with increasing levels of both anti-CCP and RF (36). In a follow-up study of patients with UA by author and colleagues, the serum anti-CCP level in UA patients who progressed to RA was significantly higher than those who progressed to non-RA diseases (34).

In another study by Raza et al. in patients with synovitis of <3 months' duration a combination of anti-CCP antibodies and RF demonstrated a high specificity and positive predictive value for the development of persistent inflammatory arthritis fulfilling the criteria for RA (36). In a study of 173 patients with early inflammatory arthritis who were followed up for 24 months period by El Miedany et al. persistent arthritis was observed in 80 patients. Duration of morning stiffness, percentage change in HAQ after 3 months, and anti-CCP positivity were the predictors of persistent arthritis (37). The extent of joint involvement and pattern of arthritis may also be used as prediction of persistent arthritis.However, the sensitivity of clinical examination in the detection of synovitis is low when compared to contrast-enhanced MRI or ultrasound examination (38).

Progression to rheumatoid arthritis and predictive factors

A significant proportion of patients with persistent arthritis progress to RA. Earlier identification of RA and discrimination of RA from non-RA diseases is essential, because early aggressive treatment might offer an effective means to retard disease progression in RA and avoiding inappropriate treatment of patients who will not develop RA. The challenge is to predict RA development in patients with persistent arthritis who are following with initial diagnosis of UA. Predicting factors of persistent arthritis are largely similar with predictive factors of RA. This was shown in a study of 570 UA patients and 676 RA patients were included in the Leiden Early Arthritis Clinic cohort by de Rooy et al. In this study, older age, male gender, longer symptom duration at first visit, involvement of lower extremities, BMI, high acute phase reactants, presence of IgM-RF, anti-CCP2 antibodies anti-modified citrullinated vimentin antibodies, and HLA-DRB1 shared epitope alleles were predictive factors the for fulfilment of the 1987 ACR-RA criteria and for persistent arthritis (39).

The proportion UA patients who progress to RA vary considerably according to different studies. This may be explained by the differences in inclusion criteria, definition used for UA or RA, characteristics of UA patients, and duration of follow-up period. The reported proportions one year after inclusion range from 6% to 55%. However, in the cohorts that presence of arthritis was essential for inclusion and the diagnosis of RA was confirmed by the ACR criteria the reported rates of progression to RA were lower at 17-32% (40). Presence of some components of the ACR criteria such as polyarthritis, symmetric arthritis, RF and radiographic erosions in these patients may be considered as predictors of future RA (24, 41).

A prediction rule consisted of 9 clinical variables was developed by Van der Helm et al. to predict the risk of RA development among patients with recent-onset arthritis to guide individual treatment decision. In this study, the prediction score of several factors such as sex, age, localization of symptoms, morning stiffness, the tender joint count, the swollen joint count, the C-reactive protein level, RF positivity, and anti-CCP positivity were determined and

the accuracy of the prediction was estimated by calculation of area under the curve values (42) In a study of 318 patients with recent-onset arthritis by van Gaalen et al. the likelihood of RA development in patients with initial diagnosis of UA who were serum anti-CCP positive, increased by OR= 37.8 (95% CI, 13.8-111.9).Progression to RA was observed in 40% of these patients occurred after 3 years of follow-up (24). The diagnostic ability of anti-CCP and RF was shown in meta-analysis by Nishimura et al. In this study anti-CCP antibodies were more specific than RF for diagnosing RA and may better predict erosive disease (43). In a study of 60 patients with UA who were followed up for a median duration of 14 months by the author and colleagues, 16 patients (26.6%) progressed to RA within the follow-up period, whereas, 26 patients progressed to other non-RA diseases and 18 patients remained as UA. In this study, anti-CCP predicted subsequent development of RA at sensitivity of 75% and specificity of 68.1% and accuracy of 73.3% (34). In a study of patients with UA polyarthritis with recent-onset arthritis by Jansen et al. after 3 years follow-up anti-CCP testing combined with IgM – RF testing predicted the diagnosis of RA with high specificity and acceptable sensitivity (44).

In a study by Quinn et al. 100 consecutive patients with UA of the hands were followed for 12 months. RA developed in 14% and remission observed in 13% of patients. In this study, RF positivity and painful joint at baseline were significant predictors of RA (45).

In another study of 92 consecutive patients with recent-onset arthritis by Glennas et al. after a 5 year of longitudinal observation, 48% of patients fulfilled the RA criteria, while 41, 4% remained with the diagnosis of UA, and 10.8% had oligoarthritis with polymyalgic symptoms. Symmetrical involvement of small and medium size joints, severity of symptoms at onset, number of swollen joints, duration of morning stiffness, higher disease activity, and higher HAQ for functional disability were predictors of RA (26).

In a study of 77 patients with UA by Jonsenn et al. with median symptoms duration of 3.5 months, after one year follow up, 32 (42%) patients had a progressive disease. A progressive outcome was associated with older age, higher disease activity and arthritis of the hands at baseline (46).

In patients with recent-onset arthritis, criteria diagnoses for RA are not sufficient for persistent disease. This was shown in a study of 45 patients by Mau et al. who fulfilled the ACR criteria for definite RA at the onset of the study but after a follow-up period of 9±3 months, 15 patients went in to remission, 5 patients could not be classified as RA due to inadequate criteria. Only 21 patients remained on initial diagnosis of RA (21).

In a study of 43 patients with peripheral inflammatory arthritis who did not meet to any specific diseases and were evaluated at baseline and 14 to 60 months later by Morel et al. remission occurred in (12) 28%, RA developed in (18) 42% of patients, whereas the diagnosis of 7 cases remained as UA at latest follow up. In the rest of patients diagnosis was psoriatic arthritis in 2, siogren syndrome in 2, lupus in one and paraneoplastic syndrome in one (27).

In general, various rate of progression from UA to RA among previously published studies can be attributed to non uniformity of study population or duration of follow up periods. The rates vary from 6.2% to 65% over a follow – up periods of 1-9 years (25, 27, 46, 48).

Investigation of UA patients

Clinical evaluation

In approaching patients with recent arthritis who were classified as UA, taking history and a complete clinical and laboratory examination is essential. Identification of clinical features suggestive of RA such as polyarthritis, symmetric arthritis, hand arthritis, bilateral compression pain on metcarpophalangeal and /or metatasophalangeal joints, and morning stiffness greater than 30 minutes can be helpful in estimating the future course of arthritis. This information can also narrow the spectrum of differential diagnosis (16, 32, 42).

The number of swollen and tender joints particularly small joints of hand should be determined in cases with hand or feet joint involvements, These variables in conjunction with acute phase proteins such as ESR and CRP can be used for calculation of disease activity score (DAS).The efficacy of treatment can be estimated by comparison of changes in DAS28 value before and after treatment in patients with RA (49).

Laboratory tests

In patients with UA, there is a great need to accurately predict the development of a well-defined diagnosis such as RA or other rheumatic diseases for the purpose of both diagnosis and treatment. Autoantibodies such as RF and anti-CCP are required to be assessed. Anti-CCP test demonstrated high specificity in diagnosis of RA and allow accurate prediction of RA in patients with UA. (16, 23, 24, 34, 36, 50-52).A combination of anti-CCP and RF increases the specificity for diagnosis of RA (44, 51, 52).The level of serum anti-CCP has an additional predictive ability for

subsequent progression of UA to RA with high accuracy (35). Arthrocynthesis and synovial fluid analysis can be also helpful for diagnosing inflammatory arthritis as well as in differentiation of inflammatory and 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 in the discrimination of RA from non-RA patients was shown in a cross-sectional study by the author and colleagues. In this study, synovial fluid anti-CCP in patients with RA was significantly higher than non-RA diseases (53).

Assessment of serum CRP level and ESR are of particular importance. Increased levels of these inflammatory markers indicate higher disease activity. Serum CRP levels increase along with activity of RA. We have shown a relationship between serum CRP levels and disease activity in RA (54). Furthermore, the efficacy of treatment can be shown by the changes in serum CRP and ESR level. Serum CRP and ESR decrease in correlation with DAS28 decrement during treatment of RA with DMARDs (49).

Imaging and radiolographic investigations

There are a few data regarding the value of conventional radiographic examination in recent-onset arthritis. Radiographs of hand and feet are far easier to obtain than MRI imaging or ultrasonography which seem promising but can be used in limited centers. However the sensitivity of radiography in detection of bone erosion in the early stage of disease is low because they occur later (55, 56). The sensitivity of conventional radiography in detection of bone erosion in one study was 13%, whereas the sensitivity of MRI and US were 98% and 63% respectively. For these reasons, there is a trend toward early detection of RA bone erosions by MRI especially in patients with early signs of arthritis. The 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 % PPV and 75.9% specificity, 68% sensitivity (57).

Treatment and outcome

The early diagnosis and treatment of recent RA has become a prime objective for rheumatologists and clinicians who care for patients with arthritis. Patients with RA are at increased risk of progressive joint cartilage damage, disability, and increased morbidity and mortality due to inflammation. The outcome of patients with UA who evolve into RA regarding radiographic progression, functional disability, and disease activity is similar to patients who initially present with RA itself. This was illustrated in a study of 330 patients with UA, 91 of them progressed to RA over a year later. These patients were compared with 62 patients who had presented with RA (58).

The inflammatory process at the early stage of RA is at its peak, therefore, the rate of appearance of erosions and the rate of bone loss are all maximal at the early stage of disease. The patients who are often left untreated during this period of maximal inflammation are therefore likely to deteriorate, while suppressive treatment may be greatly beneficial at this time (10).

It has been shown that patients with active disease over three years on average lose 20% their bone mass from the hip. Consequently, significant proportion patients with RA have low bone mass. This was shown in a study of our RA patients. In this study, femoral neck osteoporosis was observed in 45% of RA patients versus 30.4% of age-marched controls (59).

Early diagnosis coupled with aggressive therapy can alter the natural course of RA, however this issue requires further studies. However, if there is a window of opportunity which can change the outcome substantially should be determined (62). Modern treatment of RA is shifting toward aggressive antirheumatic therapy in an early phase of the disease, all therapies would act better if were used at earlier stage of disease. (1, 51, 60, 61) It is recommended then that the therapy initiated in accordance with disease activity with the aim of achieving clinical remission or the lowest possible level of disease activity (62). A growing body of evidence has emphasized the consistent clinical and radiographic benefits of early aggressive treatment in RA patients. The time elapses between the onset of arthritis and initiation of treatment is also very critical for preservation of joint health, therefore, treatment of patients with UA before definitive diagnosis is expected to improve outcome.

At present, treatment decision can not be restricted to patients who have established RA. After 3 months of symptoms therapy with conventional DMARDs as well as biologic agents reduce disease activity and limit the development of damage though may not cure RA. Pathological mechanisms involved in the initiation of RA appear to be distinct from those deriving the persistence of the established disease. The very early phase of synovitis in patients destined to develop RA (within the first 12 weeks) represents a pathologically distinct stage of the disease and intervention may have qualitatively different effect

compared with later intervention. The first three months of symptoms in RA thus represent a biologically distinct phase of the disease. In this phase, synovial environment may modulate fibroblast function leading to the production of factors facilitating the formation of the lymphoid aggregates that characters the established RA (4).

The decision to start DMARDs in patients with recent – onset UA is complicated by lack of adequate knowledge in predicting the course of arthritis in this population. There is still uncertainty about the optimal time point of DMARDs introduction. Methotrexate (MTX) is the first choice conventional DMARDs and the main therapeutic agent which should be used at the initiation of treatment in RA. Its efficacy and safety was shown in several studies (63-65).

In a study of 20 patients with very early RA with median disease duration of 3 months efficacy of MTX was compared with 20 late early RA with medial disease duration of 12 months. After 36 months, a significant difference of improvement in DAS28 was found in favor of very early patients (1). Administration of MTX in patients with initial diagnosis of UA defers the development of RA and decreases radiographic erosions compared with the placebo. This was shown in a study of 110 patients with UA. In this study, treatment with MTX to decrease DAS, less than 2.4 points was compared with placebo in progression to RA. Treatment continued for 12 months and medication was tapered and discontinued and patients were followed up for 30 months. Progression to RA in MTX group was 40% compared with 53% in the placebo group. Patients in MTX group fulfilled the ACR criteria later than placebo group (P=0.04) and fewer patients showed radiographic progression over 18 months period (P=0.046). This study provides evidence for the efficacy of MTX treatment in postponing the diagnosis of RA (66).

It is possible to substantially enhance the clinical efficacy early in the course of the disease by intensifying treatment with MTX aiming for remission. Early treatment of RA may induce remission in a substantial number of patients. The range of remission varied from 17-33% according to the criteria used for remission (64). Very early intervention with conventional DMARDs is cost-effective, while on the contrary the cost-effectiveness of very early intervention with biologic therapy remains uncertain (7).

In a study of early RA by Durez et al. administration of MTX alone resulted to remission in 40% at week 52, but on the other hand, MTX in combination with intravenous methylprednisolone or in combination with infleximab resulted in remission at 70% in both groups (9). Administration of glucocorticoid in patients with recent onset arthritis may be useful diagnostic / therapeutic approach (29). The importance of time to first DMARDs and response to treatment in patients with inflammatory polyarthritis were shown in 624 subjects who were followed up for 10 years. The patients treated for less than six months from symptom onset experienced a non-significant improvement in function compared with those never treated, and a significant benefit for each additional month of treatment within 6 months of the onset of symptoms. The patients who discontinued their first DMARD within 6 months experienced a significant deterioration in long-term function, while those who continued their first treatment for > 3 years experienced an improvement (8).

In a comparative study of 206 patients with recent-onset arthritis, the radiological progression was compared with regard to time from disease onset to DMARD (sulfasalazine or chloroquine) initiation. In 109 patients, treatment was started after 4 months vs. treatment after 15 days in 97 patients. In the patient subgroup without radiological erosion at baseline ,the radiologic score after two years was 2 with early DMARD therapy and 4 with delayed therapy (P=0.08). Among the patients with radiologic erosion at baseline who were treated early showed no score progression after 2 years, whereas those treated later worsened by 12 points (P=0.002). The combination DMARD therapy in recent-onset polyarthritis was shown to be more effective than monotherapy with regard to disease remission and radiologic progression (11).

In a study of 205 recent-onset polyarthritis randomized to treatment with sulfasalazine 2 gr/day or MTX 7.5-15 mg/ weekly alone or combination of both sulfasalazine and MTX for 1 year, there was no significant difference with respect to proportion of response to treatment, radiological erosion between the three groups (67).

The effects of early corticosteroid therapy in recent-onset arthritis were shown by Boer et al. in COBRA study. In this study, administration of 60 mg daily prednisolone with either sulfasalazine or MTX and tapering corticosteroid to nothing at 28 weeks resulted to significantly lower erosions and higher response rate after 28 weeks in corticosteroid group compared with both sulfasalazine or MTX alone. These findings demonstrated additional benefits of steroids (70). A rational use of glucocorticoid in patients with recent-onset arthritis has a minimal impact on bone mass. Their use was associated with an increase in BMD in

the ultra distal region of the forearm, although it induced a significant loss of BMD in the medial region of the forearm (70). Administration of low dose prednisone co-medication in association with step-up DMARDs therapy over two years in early RA with disease duration of less than one year resulted to higher percentages of remission by OR=1.96 (95%CI 1.21-3.18) with higher probability of sustained remission during second year by OR= 4.48 (95% CI 1.35-14.8) compared with not low-dose prednisone (70)

The benefits of early prednisolone therapy by 10 mg/day compared with placebo for six months and continuation of treatment with sulfasalazine was shown by Van Everdine in a study of 81 patients with recent-onset arthritis. Both radiological erosions and HAQ Scores were significantly lower in steroid group after 1 and 2 years (71). Intraarticular glucocorticoid injections can also provide beneficial effects in controlling inflammation (29).

With Intraarticular steroid therapy as an adjunct to MTX treatment controls of synovitis was better and the rate of erosion development was shown to be slower (4). In a study of patients with undifferentiated chronic monoarticular disease, using intraarticular corticosteroid benefited over 50% of patients (20). In conclusion, the recent-onset arthritis is an important issue which could have a good prognosis if diagnosed and treated early. A large proportion of these patients have a self-limited course which may go into remission without aggressive treatment. However, the progressive course and subsequent development of RA and joint destruction would be expected to be observed in a substantial proportions of these patients. Identification of associated factors of persistent disease or predictive factors of RA development require a complete clinical examination and rational using serological tests. At present, serum anti-CCP alone or a combination with RF are known predictor factors of persistent disease or progression to RA. Furthermore, the presence of these serological markers in combination with a number of clinical findings such as polyarthritis, symmetric arthritis and compression pain in metatarsophalangeal or metacarpophalangeal joints are helpful for treatment decision. In the treatment of patients, with initial diagnostic of UA efforts should shift from confirmed RA to diagnosing recent-onset polyarthritis. As soon as the recent-onset polyarthrits is diagnosed, the factors predicting chronicity should be evaluated and DMARD therapy be initiated. Combination therapy is probably the best in patients with predictive factors of poor outcomes and initial low-dose glucocorticoid therapy which in this population may be promising.

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