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B Bresnihan

J Rheumatol 2001;62;4-9

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The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.

Treating Early Rheumatoid Arthritis in the Younger Patient

BARRY BRESNIHAN

ABSTRACT. Early diagnosis and intervention may provide the greatest hope for reducing the disability associated with rheumatoid arthritis (RA). In patients with early RA, accurate diagnosis can be delayed by limited access to a specialist service, slow evolution of the clinical features, and lack of definitive diagnostic criteria. However, acute phase reactants, serologic features including presence of rheumatoid factor, and immunohistologic analysis of synovial tissue can provide the basis for differentiating RA from other forms of arthritis. Factors associated with poorer prognosis in patients with early RA are female sex, larger number of joints involved, elevated levels of acute phase reactants, presence of rheumatoid factor, and radiologic evidence of joint damage. Special treatment considerations in younger persons with RA include issues related to conception, pregnancy, and lactation. Methotrexate, hydroxychloroquine, sulfasalazine, and low dose corticosteroids are usually the mainstays of treatment for younger patients with RA. Recommendations for taking these drugs while considering conception vary with their effect on fertility and on the developing embryo. Sulfasalazine, for example, can be taken during pregnancy but caution is advised for breastfeeding mothers. Leflunomide must be discontinued for 2 years before attempting conception; this time can be shortened if the patient opts for drug washout. (J Rheumatol 2001;28 Suppl 62:4-9)

Key Indexing Terms:

RHEUMATOID ARTHRITIS DRUG TREATMENT FOR RHEUMATOID ARTHRITIS
EARLY DIAGNOSIS OF RHEUMATOID ARTHRITIS
FERTILITY AND FAMILY PLANNING

The potential importance of recognizing and treating rheumatoid arthritis (RA) in its earliest stages has been highlighted^{1,2}. Accordingly, many academic rheumatology centers have developed clinical and research programs that evaluate the pathophysiologic pathways, disease course, and therapeutic interventions in various categories of early arthritis. In general, published studies of early arthritis have included patients presenting one, sometimes 2, years after the onset of the first symptoms. The prevalence of RA is 3 to 4 times greater in women than men. In younger women longterm therapeutic decisions must include consideration of fertility and pregnancy, and complications of prolonged drug usage, including osteoporosis. This review of early RA will focus on some of the issues that are especially relevant to patients aged less than 45 years.

AIMS OF TREATMENT

The primary aim of treatment in early RA is to reduce the symptoms of synovial inflammation. In the initial phases, patients commonly complain of articular pain, stiffness and swelling involving the small joints of the hands and feet, gradually progressing to the larger joints of the upper and lower limbs, the cervical spine and temporomandibular

joints. These focal symptoms are often accompanied by constitutional symptoms such as fatigue, lethargy and some weight loss. Elevation of the acute phase reactants usually denotes the intensity of synovial inflammation.

It is assumed by many that effective early suppression of synovial inflammation will prevent the progression of cartilage and bone degradation and associated functional impairment. However, this assumption remains to be confirmed. For example, it has been asserted that suppression of elevated C-reactive protein (CRP) levels in patients with active RA is associated with improvement in functional scores, whereas persistent elevation of CRP is associated with functional deterioration³. This assertion was initially based on a cohort of 34 study patients with relatively mild disease and the best functional outcome. In response to treatment, CRP levels quickly returned to normal from an initial median value of only 23.5 mg/l. Despite disease duration of only 6 months, these patients with mild RA and normalized CRP values demonstrated continued functional impairment after a further 6 months' followup, and this did not improve during the study period. Secondly, the functional measurements of 44 additional patients with more elevated and totally unresponsive CRP values (median 40 mg/l) failed to improve with treatment over a 2 year followup period, but did not deteriorate. Thus, patients presenting with bad disease do badly and patients with mild disease do well, and alterations in the CRP values may or may not be directly related to the functional response.

From the Department of Rheumatology, St. Vincents University Hospital, Dublin, Ireland.

B. Bresnihan, MD, FRCP, Professor of Rheumatology.

Address reprint requests to Professor B. Bresnihan, St. Vincents University Hospital, Dublin 4, Ireland.

It has also been asserted that effective suppression of elevated CRP values in patients with recent onset RA will reduce the rate of progressive joint damage. For example, in one prospective study this assertion was examined in 228 consecutive patients with symptoms for less than one year⁴. Patients were assigned to high low risk groups according to a formula based on factors that were predictive for progressive joint damage, and were then randomly assigned to either an aggressive experimental or a control treatment strategy. The experimental strategy in the high risk group was designed to provide maximal effect on cumulative inflammatory disease activity, represented by the CRP area under the curve (AUC) values. After 2 years the CRP-AUC in the experimental group was approximately 2000 mg·week/l, compared to approximately 3000 mg·week/l in the control group. Progressive joint damage was observed in both groups with median increases in Sharp scores of 26 and 35, respectively. Thus, the assertion that effective suppression of elevated CRP values will reduce the rate of progressive joint damage in early RA was based on a study in which the treatment effects on both the CRP and joint damage were modest and any direct association must be questioned.

EARLY DIAGNOSIS

For a number of reasons, the diagnosis of RA may be delayed in some individuals who develop the characteristic symptoms of joint inflammation². Firstly, some patients may not seek a medical opinion in the early phases. Secondly, health service pressures, especially in nonacute circumstances, may not permit sufficiently early access to specialist evaluation. Thirdly, there are no definitive diagnostic criteria for RA. Thus, in some patients with clinical synovitis, the precise diagnostic category may remain elusive while the disease manifestations continue to evolve. *Acute phase reactants.* The acute phase response may have some value in predicting a diagnosis of RA in patients presenting with an undifferentiated arthritis (UA). In a prospective study of 3 acute phase measurements, 60 patients presenting to an early arthritis clinic with UA were included. It was observed that the levels of acute phase serum amyloid A (A-SAA) were significantly higher in a group of 14 patients who were subsequently diagnosed as RA than in 28 patients whose arthritis remained undifferentiated and 11 whose arthritis resolved spontaneously during 18 months' followup⁵. The median CRP levels and erythrocyte sedimentation rates (ESR) did not distinguish between patients who subsequently developed features that permitted a diagnosis of RA and those who remained in the UA category. It was concluded that in the early phases of arthritis, elevated A-SAA levels might be of value in differentiating RA from other categories of arthritis.

Serologic features. IgM rheumatoid factor (RF) is a recognized serologic feature of RA. The diagnostic characteristics of IgM RF were studied in 486 patients presenting to an

early arthritis clinic⁶. RA was diagnosed in 149 (31%), and 131 (27%) had UA. IgM RF demonstrated a specificity of 91% and a sensitivity of 54% for the diagnosis of RA with positive and negative predictive values of 74 and 81%, respectively. In the same study, a sensitive ELISA for the detection of antibodies to a citrullinated substrate, cyclic citrullinated peptide (CCP), was employed. Anti-CCP antibodies demonstrated a specificity of 96% and a sensitivity of 48% for RA with positive and negative predictive values of 84 and 81%, respectively. The presence of both IgM RF and anti-CCP antibodies had a specificity of 98% for RA and a positive predictive value of 91%. This study both confirmed the diagnostic characteristics of IgM RF in patients with early RA and suggested that anti-CCP antibodies may have additional value in predicting the diagnosis.

Immunohistologic features. The common immunohistologic features, which have been described in different categories of arthritis where the diagnosis is established, are very variable. However, some features such as lining layer cellularity, the prominence of new blood vessel formation, and adhesion molecule expression may distinguish RA from seronegative arthropathies⁷⁻¹⁰. The value of immunohistologic analysis in the differential diagnosis of early arthritis was evaluated in 95 patients who had been symptomatic for less than one year and followed for at least 2 further years in order to verify the diagnosis¹¹. Using logistic regression analysis, it was observed that higher scores for the numbers of CD38+ plasma cells and CD22+ B cells in the sublining layer were the best markers for discriminating between RA and other non-RA diagnostic categories. In addition to plasma cells and B cells, the number of sublining layer CD68+ macrophages was also identified as a weaker discriminating marker. These results suggested that immunohistologic analysis of synovial tissue from patients with early arthritis might be developed to differentiate between RA and other arthritides.

PREDICTING OUTCOME

While the differential diagnosis of RA may present some difficulties in the early phases, predicting the outcome when the diagnosis is established can be even more uncertain. Nevertheless, some prognostic factors have been proposed from clinical, serologic, immunohistologic, imaging and genetic studies.

Clinical features. Several clinical features, including female sex, younger age, the number of swollen joints at presentation and an elevated acute phase response, have been associated with a worse disease outcome¹²⁻¹⁴.

Serologic features. It has been suggested that seropositivity for RF is independently predictive for joint damage in early RA¹⁵. For example, of 144 patients with symptoms of RA for less than 1 year and followed for a further 2 years, 110

(76%) developed joint erosions⁶. The sensitivity and specificity of IgM RF in discriminating between erosive and nonerosive disease at 2 years were 66 and 79%, respectively, with positive and negative predictive values of 91 and 42%. In the same study, the sensitivity and specificity of anti-CCP antibodies in discriminating between erosive and nonerosive disease at 2 years were 63 and 79%, respectively, with positive and negative predictive values of 91 and 40%. Thus, with respect to joint damage, the prognostic characteristics of both serum IgM RF and anti-CCP antibodies were impressive and very similar.

Immunohistologic features. The first immunohistologic study to seek predictors of outcome in RA demonstrated that synovial lining layer thickness, largely representing macrophage accumulation, best correlated with the clinical course over one year¹⁶. This study did not include radiologic evaluation. In a subsequent study of 12 patients with untreated RA (mean disease duration 22 months), synovial tissue was analyzed before the introduction of a disease modifying antirheumatic drug (DMARD)¹⁷. The degree of radiologic joint damage over one year was also quantified. The results demonstrated that the degree of joint damage correlated significantly with previously identified prognostic factors, including a high index of disease activity and serum IgA RF levels. In addition, joint damage correlated significantly with the number of synovial tissue macrophages, but not with the numbers of other prominent infiltrating cell populations, such as T and B lymphocytes. Synovial tissue macrophages produce the proinflammatory cytokines interleukin 1 (IL-1) and tumor necrosis factor- α (TNF- α), both of which play a critical role in the pathogenesis of RA¹⁸. IL-1 and TNF- α stimulate the production of tissue degrading enzymes, including matrix metalloproteinase-1 (MMP-1), by fibroblast-like synoviocytes and tissue macrophages. Protease production was quantified in synovial tissue samples from 20 untreated patients presenting to an early arthritis clinic and the results correlated with the degree of joint damage over the following year¹⁹. Twelve patients had RA, 1 UA, and 7 had other forms of chronic arthritis. MMP-1, but not cathepsin B or cathepsin L, expression in the synovial lining layer was associated with both greater numbers of CD68+ tissue macrophages and new joint erosions. In conclusion, these immunohistologic studies suggest that in early RA both (1) the number of synovial tissue macrophages producing proinflammatory cytokines and (2) synoviocyte MMP-1 expression may identify patients likely to develop early joint damage.

Imaging. Progressive degradation of cartilage and bone is a characteristic feature of RA. Joint degradation commences very early in the disease course and the rate of progression may be greatest in the earliest phases^{20,21}. One hundred and forty-seven consecutive patients with RA for less than 1 year were studied prospectively for 2 years, of whom 90

were studied for 3 years²². All had biannual radiographs of hands and feet, and 70% had radiographic damage after 3 years. The mean composite score for joint damage increased by 3.2% of the maximum possible score during the first year, compared to 2.1% for each of the subsequent 2 years. Similarly, the mean number of joints that were damaged during the first year was 9.4% of the maximum possible number of damaged joints, compared to 4.5 and 3.3% in the second and third years, respectively. In a similar cohort of 128 patients with RA for less than 1 year, it was observed that the progression of radiologic damage during the first year was independently associated with the degree of joint damage present at baseline¹⁵. Therefore, in early RA, patients demonstrating more extensive joint damage at presentation are most likely to develop further joint damage during followup.

Magnetic resonance imaging (MRI) may also be of some value in predicting the rate of joint degradation in early RA²³. Twenty-six patients with a median disease duration of 1.5 years (range 0.5 to 22 years) had baseline MRI examination of the dominant wrist and the radiologic course was followed for one year. A positive relationship between the MRI-determined synovial membrane volume and the rate of erosive progression in the hand and wrist was observed. However, it remains to be determined whether the MRI characteristics of a single joint such as the wrist will serve as a prognostic marker of more widespread joint destruction.

Genetic features. Susceptibility to RA has been associated with the third hypervariable region of DR β chains, from amino acid 67 through 74²⁴. The HLA-DRB1* alleles that have the strongest association with RA in many, but not all, ethnic and racial groups include DRB*0401, *0404, *0405, *0101 and *1402, each containing the shared epitope (SE), QKRAA. It has been suggested that possession of the SE might be a prognostic factor for progressive joint damage in early RA²⁵. One hundred and twenty (67%) of 179 unselected, consecutive patients attending an early arthritis clinic fulfilled the American College of Rheumatology (ACR) criteria for RA. Of these, 65% were seropositive, 64% were SE+ and 31% had erosions at presentation. Possession of the SE had a relative risk of 4.3 for the presence of erosions after 1 year. The relative risk for erosions associated with RF was 5.9, and 13.5 if either SE or RF was present. Therefore, in this study of early RA, the relative risk of developing joint erosions over 1 year associated with possession of the SE was noteworthy but lower than that associated with RF, and considerably lower than the presence of either SE or RF. The association was further studied in a cohort of 532 patients with inflammatory arthritis and a median disease duration of 28 weeks at initial assessment²⁶. After 2 years, 376 (71%) satisfied the ACR criteria for RA. In this study, possession of at least one SE allele had a relative risk of only 1.9 for developing erosions after 2 years. The relative risk in patients who were homozygous for SE-

bearing alleles was 2.5. However, this effect was restricted to patients whose sera were negative for RF. Moreover, among patients with erosions, possession of the SE had no influence on the severity of joint damage. It was concluded that screening for SE alleles in patients with early arthritis to identify those at risk of subsequent severe disease was not justified. The observed association between SE alleles and joint damage in patients with recent onset seronegative rather than seropositive RA was subsequently confirmed²⁷. This apparent paradox may be explained by further examination of an alternative hypothesis that the HLA and RA association is the result of DR and DQ allele combinations²⁸. In this model, DQ alleles are associated with susceptibility and some DRB1* alleles are protective.

CONVENTIONAL THERAPY

In recent years, rheumatologists have reached a general consensus that the greatest potential for limiting the disability resulting from RA lies in identifying and treating the disease in its earliest phases, before damage has occurred². However, the number of randomized, placebo controlled, clinical trials in patients with RA specifically recruited with a disease duration of less than 2 years is limited^{29,30}. Some large placebo controlled studies of newer therapies, including leflunomide³¹ and etanercept³², in established RA of longer duration have included post hoc analyses of subsets with early RA. Several other randomized, non-placebo controlled clinical trials in early RA have compared the effects of various therapeutic combinations with conventional monotherapeutic strategies. These combined therapeutic regimens have generally included MTX, sulfasalazine, and hydroxychloroquine³³⁻³⁵. The study results indicate that both monotherapeutic and combined DMARD strategies in early RA are safe and efficacious and may delay, but not arrest, progressive joint damage. The combination regimens do not appear to cause more side effects than monotherapy. Moreover, the benefits reported in early RA appear to be similar to those observed in more established disease.

THERAPEUTIC CONSIDERATIONS IN YOUNGER PATIENTS

When considering DMARD therapy in patients under the age of 45 years who have recently developed RA it is necessary to address fertility, pregnancy, and lactation^{36,37}. At present, the drugs most likely to be selected for the younger patient with early RA will include MTX, hydroxychloroquine (HCQ), and sulfasalazine. In the future, leflunomide and cytokine targeted therapies are likely to be administered with increasing frequency to selected younger patients. In many centers, low dose corticosteroid therapy may be recommended in some categories of younger patients with early RA, and may be the mainstay of therapy during pregnancy.

MTX. MTX in doses of up to 30 mg/week does not appear to adversely affect female fertility, but may cause reversible male sterility³⁷. It is embryotoxic, so that women of child-bearing age should use adequate contraception if MTX is recommended for RA. Women who wish to conceive should discontinue MTX at least 3 months, and some advise 6 months, before attempting conception. Women who discontinue MTX in order to conceive should be advised to continue folate supplementation because of the association between folate deficiency, which is induced by MTX, and neural tube defects in the fetus. Similarly, males should discontinue MTX at least 3 months before conception. MTX is contraindicated during pregnancy and lactation.

HCQ. HCQ does not appear to adversely affect female or male fertility. Moreover, there are no reports of harmful effects on either fetal or maternal well being during pregnancy. Nevertheless, it would be prudent to discontinue HCQ in women with RA who are planning conception. HCQ is excreted in maternal milk and is eliminated slowly by newborn infants. Therefore, there is potential for the accumulation of toxic levels in the infants of breastfeeding mothers receiving conventional doses of HCQ and it should be used with caution.

Sulfasalazine. Sulfasalazine does not adversely affect female fertility. In males, sulfasalazine induces reversible infertility due to oligospermia, impaired sperm motility, and increased spermatozoal abnormalities. Sulfasalazine and its metabolite, sulfapyridine, readily cross the placenta to the fetal circulation. Fetal blood concentrations are approximately similar to maternal concentrations³⁸. However, during pregnancy, sulfasalazine does not appear to adversely affect either fetal or maternal well being so that treatment may be continued. It should be administered with caution to breastfeeding mothers as adverse events have been reported in some infants³⁹.

Leflunomide. Leflunomide is contraindicated during pregnancy and lactation. Women of childbearing age must use adequate contraception. A negative pregnancy test before commencing therapy is advisable. Women who receive leflunomide and wish to become pregnant must be informed that a 2 year interval between discontinuing treatment and attempting conception is recommended. Alternatively, if this is impractical, patients may undergo a washout procedure that involves the administration of either cholestyramine 8 g three times daily for 11 days or 50 g of activated charcoal administered 4 times daily for 11 days. In addition, following either washout procedure, verification by 2 separate tests at an interval of at least 14 days and a waiting period of 6 weeks between the first occurrence of a plasma concentration less than 0.02 mg/l and conception is required. Women receiving leflunomide who suspect they may be pregnant should inform their physician immediately. Men receiving leflunomide should also use adequate contraception. Available information does not suggest leflunomide

would be associated with an increased risk of male mediated fetal toxicity. However, to minimize any possible risk men wishing to father a child should consider discontinuing the use of leflunomide and taking cholestyramine 8 g, 3 times daily for 11 days⁴⁰. Following the elimination procedure, plasma levels of less than 0.02 mg/l should be verified on 2 separate occasions at least 14 days apart as recommended for women.

TNF-targeted therapies. Infliximab and etanercept, the only cytokine targeted therapies currently licenced in some countries, are contraindicated during pregnancy and lactation. It would be prudent, though it is not mandatory, to obtain a negative pregnancy test before commencing therapy in women of child bearing age.

Corticosteroids. Low dose prednisolone (7.5 mg/day or less), which is frequently the mainstay of therapy during pregnancy, does not adversely affect either female or male fertility. The usual corticosteroid related side effects, including osteopenia, avascular necrosis of bone, immunosuppression, hyperglycemia and hypertension, may occasionally emerge during pregnancy. In addition, premature rupture of the membranes is occasionally associated with corticosteroid therapy. Neonates born to mothers receiving corticosteroids should be monitored for adrenal suppression, though this is a rare complication.

CONCLUSIONS

A number of features may be of value in establishing an early diagnosis and in predicting the clinical outcome. At present, many patients with early RA attending rheumatology centers will receive sulfasalazine, HCQ or MTX, either in monotherapeutic or in combination regimens. Low dose corticosteroid treatment is advocated by some as a means of reducing progressive joint damage. Newer therapies, such as leflunomide and cytokine targeted treatments, are likely to be used with increasing frequency in selected patients with early RA. In younger patients, particular consideration must be given to issues relating to fertility, pregnancy, and lactation when prescribing these compounds.

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