Rheumatoid Arthritis: Why Treating Early?

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Abstract: Joint damage occurs early in rheumatoid arthritis and affects long-term disability. There may be a "window of opportunity" in early rheumatoid arthritis when the rate of disease progression can be slowed down or reset. Early diagnosis and early treatment with disease-modifying drugs or biologics improve long-term outcome in patients with rheumatoid arthritis and give them a different life.

Keywords: Early diagnosis, early treatment, rheumatoid arthritis

Introduction

Treatment of rheumatoid arthritis (RA) before the mid 1980's was a total failure. Most patients were either severely debilitated or died early. This treatment failure was due to several misconceptions: RA was thought to be a benign disease; disease-modifying anti-rheumatic drugs (DMARDs) were thought to be prohibitively toxic; rheumatologists were only consulted when there was significant joint damage and deformities.

RA is not a benign disease. About 75% of patients had radiological evidence of erosions after 2 years. RA results in over 9 million physician visits and over 1/4 of a million admissions a year in the US. Half of the patients became disabled within 5 years and half were severely disabled or dead after 20 years. The average life expectancy was reduced by 10 years and the total disease-related losses in US exceed 26 billions a year.1-3

A study in the early 1990's assessed the toxicity index scores of DMARDs based on symptoms, laboratory abnormalities and hospitalizations due to these drugs.4 As a group, DMARDs were no more toxic than non-steroidal anti-inflammatory drugs (NSAIDs). DMARDs such as methotrexate and azathioprine have similar toxicity index score as indomethacin. DMARDs are safe if they are used with caution.

Joint Damage and Long-term Disability in Rheumatoid Arthritis

Prospective studies has shown that 40% patients with RA developed joint erosions on x-ray within one year and about 80% do so within 2 years after onset of symptoms.5 Even in asymptomatic joints of patients with established RA, synovial biopsy showed characteristic changes of macrophage infiltration with cytokine expression of active inflammation in the synovium.6

Although joint inflammation and disease activity contributes mostly to disability in early RA, joint damage occurs early and progresses at a consistent rate over time. In the first 5 years of disease, disease activity determines disability.7 In established disease of over 8 years' duration, joint damage accounts for about 25% of disability as measured by Health Assessment Questionnaire. Prevention of early joint damage is, therefore, important in preserving long-term function of the patient.

Early DMARD Treatment Improves Long-term Outcome and Patient Quality of Life

In a large prospective follow-up study of 2,888 patients with RA over 20 years, median 9 years, consistent and early use
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of DMARD was associated with a conservative estimate of 30% reduction in disability over the duration of RA.8

In another open randomized placebo controlled study on 119 patients with early RA,9 patients were randomized into 2 treatment groups. The early treatment group received hydroxychloroquine (HCQ) immediately after the diagnosis was made. In the late treatment group, HCQ was started 9 months after diagnosis. Both groups of patients were followed up prospectively for 3 more years. Compared to the early treatment groups, the late treatment group did much worse for both the pain and the physical disability outcomes over the 3 years follow up. A delay of 9 months in starting HCQ, a mild DMARD, has significant impact on long-term patient outcome.

In the past decade, early arthritis clinic has been set up in many European countries. A recent report from one of these clinics compared 2 cohorts of early rheumatoid patients who received different treatment strategies.10

Patients in the first cohort were initially treated with analgesics, and if they had persistent active disease, they were given either chloroquine or sulphasalazine. The median lag time of starting DMARD was 4 months. Patients in the second cohort were treated given similar DMARD within 2 weeks. After one year, there was no increase in joint damage in the early DMARD treatment group. At 2 years, the group that received early DMARD treatment also did better with less erosion on X-ray. A delay of 3-4 months in initiating DMARD makes a difference in long-term outcome in RA patients.

Early treatment of RA is also important in terms of long-term mortality. A recent study examined the long-term mortality outcome of a cohort of 489 patients with RA.11 Early presenters treated early in the course of disease did better than late presenters. In another European prospective study12 of a cohort treated aggressive with DMARD, there was no increase in mortality after 10 years. The use of methotrexate in the treatment of RA was associated with a 60% reduction in mortality and a 70% reduction in cardiovascular mortality.12

**Early Diagnosis of Rheumatoid Arthritis**

Early diagnosis of RA within the first few months is essential for effective treatment and prevention of long-term disability. A study in the early 1990's showed that even in places with excellent access to rheumatology care, the time lag from onset of symptom to diagnosis took about 5-6 months.13 The long lag time includes a delay of the patient to see her family physician, a delay in diagnosis by the family physician, a delay in referral to the rheumatologist and a delay in diagnosis by the rheumatologist in some cases. In general, those with more acute symptoms and less symmetrical arthritis appeared to present to the family physician earlier and were also referred to the specialist sooner than those with insidious symptom and symmetric arthritis.

Since the early 1990's, early arthritis clinic has been set up in several European countries to diagnose and treat RA early. A report by van der Horst-Bruinsma and colleagues14 suggested that early diagnosis of RA was possible. With active public education and active campaign for early referral from family physicians, the lag time between symptom onset and first rheumatological consultation may be shortened by at least 3 months in their experience.

Clinical diagnosis of early RA during the first few months can sometimes be difficult. Symptoms and signs may be less typical; ESR and C-reactive protein may not be raised; Rheumatoid factor may be negative.

The American College of Rheumatology (ACR) published its revised classification criteria for RA in 1987.15 It provides guidelines for organized studies of RA. However, in the past decade, it has also been increasingly used for the diagnosis of RA. Using the ACR criteria to diagnose RA, especially early RA, has its limitations. Firstly the ACR criteria were formulated and validated using patients with long-standing disease. Secondly, making a diagnosis was not the objective of the evaluation from which the criteria were derived. In one recent study,16 applying ACR criteria at first visit showed only 66% sensitivity and 82% specificity for the diagnosis of early RA. In the same study, the sensitivity and specificity of each of the ACR criteria applied at the first visit to patients who were diagnosed to have definite RA 2 years later by a panel of 5 rheumatologists were examined. Several ACR criteria lacked specificity in early RA (Table 1). Highly specific features are often absent in early disease.

To assist in the diagnosis of early RA, other serological markers have been evaluated. Anti-keratin antibodies (AKA), anti-cyclic citrullinated peptide antibodies (anti-CCP), anti-RA33 and anti-Sa have been studied.17-20 These antibodies are highly specific but, except anti-CCP, are even less sensitive than rheumatoid factor (Table 2).
Table 1. Sensitivity and specificity of each of the ACR criteria applied at the first visit for identifying patients who would have a diagnosis of RA 2 years later.26

<table>
<thead>
<tr>
<th>ACR criterion</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>1. Morning stiffness</td>
<td>68</td>
<td>65</td>
</tr>
<tr>
<td>2. Arthritis of &gt;3 areas</td>
<td>80</td>
<td>43</td>
</tr>
<tr>
<td>3. Arthritis of the hand joints</td>
<td>81</td>
<td>46</td>
</tr>
<tr>
<td>4. Symmetric arthritis</td>
<td>77</td>
<td>37</td>
</tr>
<tr>
<td>5. Rheumatoid nodules</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>6. Rheumatoid factors</td>
<td>59</td>
<td>93</td>
</tr>
<tr>
<td>7. Radiographic change</td>
<td>22</td>
<td>98</td>
</tr>
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Table 2. Rheumatoid arthritis-specific antibodies17-22

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td>Anti-keratin antibody</td>
<td>33%</td>
<td>96%</td>
</tr>
<tr>
<td>Anti-CCP ELISA</td>
<td>50-70%</td>
<td>96-98%</td>
</tr>
<tr>
<td>Anti-RA33</td>
<td>29%</td>
<td>100%</td>
</tr>
<tr>
<td>Anti-Sa</td>
<td>19%</td>
<td>98%</td>
</tr>
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Anti-CCP by ELISA assay is developed from the understanding of anti-keratin (AKA) antibody. AKA has been known for a long time to be specific for RA but its use is limited by its low sensitivity and its method of detection. The antigen for AKA is filaggrin. Using synthetic peptides containing citrulline, an amino acid present in filaggrin, a convenient and accurate ELISA assay was recently developed. The anti-CCP ELISA has an excellent specificity as AKA but has a much higher sensitivity. Among the various specific antibodies in RA, anti-CCP ELISA appears to be most promising in early diagnosis. In the study by Kroot and associates, almost 70% of patients with early RA were positive for anti-CCP ELISA.21 In another study, anti-CCP was present in 48% of patients with RA but combining IgM-rheumatoid factor and anti-CCP ELISA gave a predictive value of 91%.22 It appears that anti-CCP ELISA might be very useful in early RA. Whether the anti-CCP will become an additional diagnostic criterion in RA has yet to be determined.

Treatment of Early Rheumatoid Arthritis

Most rheumatologists begin treatment of early RA with single DMARD and quickly replace it with another DMARD or use combined DMARDs in patients who have suboptimal responses to treatment. Hydroxychloroquine (HCQ), sulphasalazine (SSZ) and methotrexate (MTX) are the most often used DMARDs. The choice of treatment depends on many factors, namely, disease activity, functional status, onset of action of drugs, potential drug toxicities, route of administration, underlying medical considerations, plan for pregnancy, social use of alcohol, and cost.

Methotrexate

Many rheumatologists favour MTX as the initial DMARD in patients who have moderate to severe arthritis. Others use MTX even in early disease. MTX has an established track record in the treatment of RA with a favorable safety profile. Compliance is generally good; there are many patients on MTX alone or in combination with other DMARDs for over 10 years. Longitudinal studies and randomized controlled trials show that MTX retards the progression of radiographic erosions.23 It has become the benchmark by which new DMARDs and biological agents are evaluated.

Leflunomide

Several randomized controlled trials have established leflunomide as an alternative to MTX as monotherapy especially in patients who have an inadequate response to MTX or cannot tolerate MTX.24 The reduction in disease activity and in the rate of radiologic progression achieved by leflunomide is comparable to MTX. Sustained response for over 5 years have been reported in some patients. In patients with suboptimal response to full dose of MTX, leflunomide may also be added as combination therapy.25 Common side-effects of leflunomide include elevation of liver transaminases and diarrhoea. Skin rash and weight loss may sometimes occur.

Combination Therapy

Since the mid 1990's, rheumatologists have been prescribing combination DMARDs in patients who failed to respond to conventional monotherapy.26,27 The approach has played a significant role in improving control of RA before leflunomide and anti-cytokines are available. Controversy still remains about whether to initiate combination therapy in sequential "step-up approach", adding one after another, or whether to initiate combination therapy in the early stage, and then apply a "step-down approach" once disease is under good control.

Many different combination therapy have been used. Methotrexate is the backbone in most combination. Triple
therapy, using MTX, SSZ and HCQ, has been shown to be superior to double-DMARD combinations in both early and advanced RA.

**Anti-cytokine Therapy**

Although the etiology of RA is still uncertain, the pathogenesis of RA has become increasing clear. Cytokine imbalance with excess of pro-inflammatory cytokines result in synovitis and joint damage. Activation of T cells and macrophages result in increased cytokine production. Among the different pro-inflammatory cytokines, TNFα plays a pivotal role. Several double-blinded, placebo controlled trials have confirmed that anti-TNFα treatment can reduce disease activity and stop radiological progression in rheumatoid arthritis.28,29

Two biological agents have been used in the past 2-3 years and a third agent has just been submitted for approval by the FDA. Etanercept (Enbrel) is a recombinant soluble TNF-Fc fusion protein. Infliximab (Remicade) is a chimeric (mouse-human) anti-TNFα monoclonal antibody. The fully humanized monoclonal antibody shall be available in the near future.

Both TNFα antagonists are effective in controlling disease activity and in decreasing joint erosions on X-ray. They have a rapid onset of action and are beneficial when combined with MTX.

As TNFα plays an important role in the body defence against infection and in immune surveillance against malignancy, there has been a lot of concern with the use of anti-TNFα agents.30-32 The incidence of serious infections so far reported has been low. Over 70 cases of pulmonary and extrapulmonary tuberculosis have been reported among the 150,000 infliximab users worldwide. Many of these cases are from countries with a low prevalence of tuberculosis. Malignancy rate was comparable to expected rate in the community with no preference in any specific type. Ten cases of aplastic anemia and pancytopenia have been reported with 5 deaths. Demyelinating diseases have been reported with the use of anti-TNFα therapy but all recovered within 6 months after the drug was stopped. Positive ANA and anti-DNA antibodies are common. Anti-TNFα- induced SLE have been reported but all resolved with steriod and drug withdrawal.

Interleukin-1 is another cytokine target of RA treatment. It is important because it is responsible for activation of osteoclasts and metalloproteinases, resulting in joint damage. An interleukin-1 receptor antagonist, Anakinra, has been developed. Adding Anakinra to MTX is shown to be more effective than MTX alone in reducing disease activity and in slowing of radiological progression.33,34

"Window of Opportunity" in Rheumatoid Arthritis Treatment

Rheumatologists have always debated if there exists a period of time during early RA when patients may respond to treatment differently than they would if treatment is delayed. In 1997, the Combinatietherapie Bij Reumatoide Artritis (COBRA) trial reported its initial results.35 155 patients with early RA with median disease duration of 4 months were randomized into 2 groups. The first group received intensive treatment with a combination of SSZ 2 gm/day plus MTX 7.5 mg per week and Prednisolone. Prednisolone was initially given at a high dose, starting with 60 mg per day with rapid reduction to 10 mg over 6 weeks. Prednisolone was completely withdrawn after 28 weeks. Methotrexate was also stopped after 40 weeks. SSZ was continued as maintenance. The second group was given SSZ throughout the treatment period. Result from the 56-week trial showed that COBRA combination therapy was more effective than SSZ monotherapy with respect to suppressing disease activity and slowing radiographic progression. However, the study has been criticized, either because the benefit on disease activity control of the COBRA therapy group disappeared after prednisolone and MTX were stopped, or because of the relatively high dose of steriod used.

However, a follow-up study36 of these patients followed up for 5 years showed that patients who received COBRA combination therapy in the beginning of the trial had less radiological progression compared to those treated with SSZ alone after 5 years. More important was that patients who had a slower rate of radiological progression in the first year after the intensive combination therapy continued to progress at a similar slower rate after wards, with 35% reduction. Composite results from the COBRA trial suggest that there may be indeed a "window of opportunity" when rapid and aggressive suppression of joint inflammation can decrease or reset the rate of radiological progression in future. Similar observation has been reported with the use of etanercept in early rheumatoid arthritis.37 The rate of radiological progression in the etanercept group continues to be slower than in the methotrexate group at 2 years.
Conclusion

Early diagnosis and early treatment with DMARDs or biological agents improves long-term outcome of patients with RA. There is a "window of opportunity" in the early course of disease when the rate of disease progression can be reset. Aggressive treatment with steroid, TNFα antagonists or combined DMARDs are possible options but the best treatment has yet to be determined by appropriate clinical trials.

References

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