Rheumatoid arthritis: what has changed?

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Introduction

Rheumatoid arthritis (RA) is the most common inflammatory arthritis affecting approximately 1% of the population. The diagnosis of RA still evokes a picture of a patient crippled with bilateral, symmetric deformities of hands and feet in the mind of most doctors. Less than 15 years ago, RA was regarded as a chronic destructive disease leading to joint deformities and severe functional decline with work disability reported in 60% of patients after 10 years [1]. As a systemic disorder, it has also been linked to multiple organ system complications and increased mortality, predominantly due to accelerated cardiovascular disease.

Fortunately, over the last two decades, significant advances in the treatment and management of RA have been made and are changing the way we perceive RA. New treatment strategies have shown their ability to slow disease progression. New biologic agents that have been shown to be able to arrest joint damage are now available. Moreover, when these agents are used in early disease, a significant proportion of patients can achieve remission, a state with no apparent disease activity or inflammation. Another major advance has been the recognition of the importance of early treatment, emphasizing the need for early diagnosis. Therefore, rheumatologists ideally see patients within weeks of symptoms onset, and as a result, the clinical course and treatment of RA have undergone major changes.

Clinical presentation: what has changed?

Seeing patients earlier

The classic presentation of RA is the insidious and progressive onset of pain and swelling involving small joints of hands and feet in a symmetrical fashion. The pain can seem to move from one joint to the other but usually ends up spreading to involve more joints and reach the classic symmetric distribution affecting small and medium joints. However, RA may start in atypical fashion. It can have a very sudden onset with marked systemic features such as fatigue, fever, and weight loss or present as polymyalgia rheumatica syndrome (pain and morning stiffness in hip and shoulder girdles), oligo- or even as monoarthritis, or bilateral carpal tunnel syndrome. A palindromic pattern can also be seen. This usually consists of episodes of pain and swelling in one joint at a time that comes on very quickly and leaves as quickly. Episodes usually last less than 24–48 h.

Previously, because intervention did not seem to impact on the long-term prognosis of RA, no emphasis was made on the importance of early diagnosis and treatment. Most patients had already developed a full-blown disease and were fulfilling the American College of Rheumatology (ACR) criteria for RA when they first presented to a rheumatologist. Despite being developed as a classification tool, these criteria are often used to make the diagnosis of RA. To fulfil the ACR criteria, a patient must have four out of the following seven criteria: (1) morning stiffness of more than an hour, (2) synovitis of three or more joint areas, (3) hand involvement, (4) symmetric distribution, (5) subcutaneous rheumatoid nodule(s), (6) positive rheumatoid factor, and (7) radiographic changes.

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More recently, the accumulating evidence for the benefits of early treatment has emphasized the need for early diagnosis and is changing the way people with RA first present to rheumatologists. Guidelines now recommend that patients should be referred to and seen by a rheumatologist, ideally within 6 weeks after the onset of symptoms [2]. However, the ACR criteria for RA lack sensitivity and specificity especially in patients whose symptoms are less than 12 weeks. As rheumatologists see patients earlier, a sizable proportion of patients do not fulfil the ACR criteria when they first present. Frequently, patients present with a picture of undifferentiated arthritis (UA)—a form of arthritis that does not fulfil the classification criteria for RA. In early arthritis clinics in Western Europe, up to 50% of new patients being seen in early arthritis clinics are diagnosed with UA, exceeding the number of RA [3].

A sizeable proportion of patients with UA will have spontaneous resolution. The main challenge is then to differentiate the patients who still progress to develop RA from those who will remit spontaneously. At present, most rheumatologists are using a combination of clinical features, laboratory tests, and imaging techniques to try to predict which patients will have persistent inflammatory that may be erosive or not. Which will be the best way to accurately predict the outcome of patients with UA is still an area of research at the moment.

Clinical course: what has changed?

RA is an autoimmune disease in which the immune system attacks the synovium (lining of the joint). This results in synovial cell hyperplasia, inflammatory cell infiltration, and formation of new blood vessels. This inflammation leads to destruction of the cartilage, periarticular osteoporosis, bone erosion, joint misalignment, and deformity with subsequent weakness of surrounding tissues and muscles. Patients experience pain and loss of function. It can affect any synovial joint in the body leading to severe disability. Just a few decades ago, treatments for RA were not effective nor well tolerated, and due to ongoing inflammation in their joints, most of the patients went on to develop classic deformities such as the boutonnière and swan-neck deformities in the hand.

Fortunately, we are now able to act on this inflammatory process to control the disease activity, preventing further bone damage and resulting in less joint deformity. Recently, a study compared measures of disease activity and joint damage in RA patients of different eras in the same clinical setting. Patients in 2000 had significantly better outcomes than the patients in 1985, including clinical measures of disease activity, such as the number of tender and swollen joints, radiographic score, and functional status [4]. As

these results were obtained prior to the widespread use of the newer biological therapies, this difference is mainly explained by a better utilization of the conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX). With the growing use of the biologic agents that have demonstrated better clinical and radiological outcomes over the use of single DMARD therapy, the prognosis of RA will hopefully improve further.

Treatment: what has changed?

New goal: remission

For many years, the treatment goal for RA was to control symptoms and limit functional decline, but there is now accumulating evidence that a significant proportion of patients with RA can achieve remission, a state with no apparent disease activity and absence of joint damage and disability progression. With the availability of new therapies and new treatment strategies, studies have even demonstrated the possibility of drug-free remission in some patients [5]. Therefore, treatment should no longer simply target symptom control but aim at remission.

New strategies

The best way to achieve remission is to (1) start treatment as early as possible and (2) assess disease activity on a frequent basis to achieve tight control [3, 5].

The earlier, the better

Recent evidence has shown that patients with RA should be started on treatment as soon as possible. A meta-analysis has shown that patients who receive early treatment had sustained benefit in radiographic progression over 5 years [6]. Shorter disease duration was the strongest predictor of improvement in disease activity, and delayed treatment led to more radiographic progression. There is also accumulating evidence to support the concept of a ‘window-of-opportunity’ [3], a timeframe early in the course of the disease where there may be a disproportionate long-term improvement. Early treatment may alter the long-term disease process and perhaps even cure it. Thus, it is imperative to identify RA as early as possible to allow early treatment and induce long-term remission.

Tight control

Tight control involves frequent assessment of disease activity with therapy adjustments if disease activity is not

suppressed below a predefined level, ideally remission. Several studies using this strategy have reported higher remission rates than “routine care” [7]. Assessment of disease activity should be undertaken at 1- to 3-month intervals and can use various instruments including tender and swollen joint count, patient and physician visual analogue scales, inflammatory markers, and various composite measures. Annual hand and feet radiographs are also recommended. Questionnaires looking at functional assessment can also be used to complement monitoring of the disease activity. Imaging has already found a role in assessing disease activity in the research environment, and it seems likely that, in the future, this may increasingly be translated into the clinical setting.

Therapeutic options

Management should include patient education, physical/occupational therapy, and lifestyle measures such as smoking cessation and regular exercise [2].

Currently, early institution of a DMARD is the cornerstone of the treatment. A DMARD should be started in every patient once the diagnosis has been confirmed. Methotrexate is the most commonly used DMARD and is generally used first. Sulphasalazine and leflunomide are considered the best alternatives. Hydroxychloroquine is also often used in combination therapy but rarely used alone in RA because of a lower response rate. Other conventional DMARDs include azathioprine, cyclosporine, and gold salts [2].

Combinations of DMARDs with or without prednisone are often used in patients not adequately controlled with one agent alone. Patients with significant disease activity and/or poor prognostic factors can also benefit from a more intensive therapy at baseline. However, there is no clear evidence of the superiority of one combination over another [8], and proof of efficacy of combining conventional DMARDs after MTX failure is limited [7].

Glucocorticoids are often used for symptomatic relief while awaiting the effect of the disease-modifying therapy, which can take several weeks. However, low-dose oral glucocorticoids, especially when used in combination with DMARDs, have actually been proven to be effective in slowing radiographic progression but not in improving function. However, due to concerns about systemic side effects, their place in the treatment algorithm of RA still needs to be defined. Frequent use of intraarticular steroids has also been shown to be of benefit [7] with a better safety profile. The risk of septic arthritis is in the order of 1 per 15,000 procedures. Other potential side effects are fat atrophy and depigmentation at the site of injection, minor hemorrhages, systemic reaction with flushing, and minor psychological changes, as well as a flare of inflammation with the use of crystalline form of steroids [9].

New agents: biologics

Biologics represents the latest family of agents available to treat RA. Thanks to molecular biology, a better understanding of the pathophysiology of RA has led to the development of these new drugs that act on the different inflammatory pathways involved in the disease process. They include tumor necrosis factor (TNF) blocking agents, rituximab, abatacept, and tocilizumab.

Anti-TNF agents

Agents that block TNF-alpha have been shown to be extremely effective; TNF is a cytokine that plays a central role in the inflammatory process in RA. These include etanercept, infliximab, and adalimumab. They can provide rapid control of inflammation and have proven long-term efficacy in terms of clinical outcome and structural damage both in early and established disease. The combination of MTX and biological agents has been shown superior to MTX alone with a more rapid onset of action. Widespread use of these combinations has been restricted by the increased cost and concerns about the long-term safety of biological agents. At present, their use is mainly limited to RA patients who have failed a combination of conventional DMARDs, as they are not reimbursed as initial treatment in most countries.

However, their use in early disease is gaining support from several recent studies. One-year results from the Combination of Methotrexate and Etanercept in Active Early Arthritis (COMET) Trial have reported a 50% remission rate in the patients on the combination therapy compared to 28% of patients on MTX only [10]. The long-term data from the BeSt study, which looked at different treatment strategies in early RA, have shown similar data with a 41% remission rate in the patients initially treated with infliximab and MTX [11]. Moreover, more than half of those patients were able to stop the infliximab and 18% were in drug-free remission at 4 years.

Rituximab

Rituximab acts by depleting B cells and has proven efficacy in patients with RA who have failed to respond to DMARDs and anti-TNF agents. It is licensed for patients having failed anti-TNF agents and is given in association with MTX. The usual regime is two infusions given 2 weeks apart. Patients with a good response can be treated again but not less than 6 months after the first infusion.

Abatacept

Abatacept is a fusion protein that binds CD80/86 and inhibits T cell activation. Used in combination with MTX, it

provides improvement of the disease activity and less radiographic damage both in MTX and anti-TNF inadequate responders. Data even suggest that efficacy benefits may increase over time. It is well tolerated in combination with DMARDs but should not be used with anti-TNF agents.

Tocilizumab

Tocilizumab is a humanized anti-interleukin-6 receptor monoclonal antibody. Given as a monthly intravenous infusion in association with MTX, it has been reported to reduce disease activity and improve quality of life, including fatigue. It is currently being investigated in phase III trials.

Other emerging biologic agents

Various other B cell-targeted agents and completely humanized anti-TNF agents are currently being studied. Agents targeting different pathways of inflammation are also being developed. One example is denosumab, an anti-RANKL human monoclonal antibody. It can inhibit radiographic bone erosions but has shown minimal effect on joint symptoms.

Conclusion

Over the past 20 years, we have witnessed significant changes in the presentation, clinical outcome, and treatment of RA. Recognition of the importance of early diagnosis and treatment has made rheumatologists see patients earlier, and a growing number of patients now present with an undifferentiated arthritis. There has been major improvement in clinical outcomes with fewer patients developing bone damage, joint deformities, and functional disabilities. These advances are largely explained by the combination of early treatment and tight control with DMARD therapy as well as the newer biologic agents. With appropriate management, remission is now a realistic goal, and drug-free remission possible. However, many issues still need to

be addressed such as best choice of initial therapy as well as best timing, predictors of response to therapy, and optimal positioning of the biologic agents. As we answer those questions, the prognosis of RA will hopefully continue to improve.

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