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Early Rheumatoid Arthritis

Pitfalls in Diagnosis and Review of Recent Clinical Trials

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Abstract

The treatment of rheumatoid arthritis (RA) has changed dramatically in the past decade as advancements in the understanding of the pathobiology of the disease have led to novel therapeutic agents. The recognition that early diagnosis and treatment leads to improvements in morbidity and mortality has altered the therapeutic strategy such that early therapy is now considered the standard of care.

This review focuses on the challenges in making the diagnosis of early RA, including a broad differential diagnosis for inflammatory polyarthritis, poor performance of the standard classification criteria, difficulty in clinical assessment of synovitis, absence of absolute laboratory tests, inability of conventional radiography to detect bony changes early, and barriers to rheumatology care. Additionally, the pathogenesis of RA is highlighted, with particular emphasis on cytokine biology as it relates to therapeutic regimens. Relevant clinical trials in early RA are reviewed and discussed, including trials of combination disease-modifying antirheumatic drugs and biological therapy. The role of induction therapy as a novel therapeutic approach is highlighted. The search for predictors of response is reviewed and the external validity of the trials is analysed. Finally, the trials in early RA therapy suggest that swift intervention with combinations of medications is required for patients with severe RA. However, further research is

needed to determine which regimen is appropriate for the individual patient with RA.

Rheumatoid arthritis (RA) is a chronic inflammatory multisystem disease that affects approximately 1% of the world's population. RA can lead to crippling disability and premature mortality.[1] Although there is no cure for RA, advances in our understanding of the pathophysiology of the inflammation that is RA have led to novel therapeutic strategies, and a marked improvement in our ability to achieve and maintain remission with disease-modifying antirheumatic drugs (DMARDs) and biological agents that block tumour necrosis factor (TNF)-α. Multiple studies have shown that early diagnosis and intervention with DMARDs is critical for optimal outcomes in both the short- and long-term,[2-5] and it is generally accepted that treatment with combinations of DMARDs yields better results than single DMARD therapy when studied in populations of patients.[6-10] Recent studies have shown that early therapy with biological agents also yields improved long-term outcomes for inflammatory activity, radiographic progression and disability, and this is particularly evident when used in combination with methotrexate.[11,12] Although the early and intensive use of DMARDs and biological agents in the treatment of RA is accepted by most rheumatologists, there are still questions regarding which agent or combination of agents are best suited for an individual patient.

This article discusses the diagnosis of early RA, briefly summarises the pathophysiology of RA to understand the therapeutic targets, reviews currently available therapy, and analyses recent trials in the treatment of early RA.

1. Early Diagnosis

One of the most challenging aspects of treating RA is making the diagnosis early in the course of the disease. The importance of early diagnosis is highlighted by the fact that damaging erosive changes can occur quickly, often in the first year,[13,14] and prompt intervention provides the best outcomes.[2-5,13] Furthermore, patients who present sooner for treatment have a lower mortality than those who present later.[15] Thus, early intervention not only prevents significant morbidity but also influences mortality from RA.

Many disease entities are in the differential diagnosis for inflammatory polyarthritis, such as RA, which complicates an early definitive diagnosis. For example, a patient may have polyarthritis from a self-limited disease such as a viral infection, from another autoimmune disease such as systemic lupus erythematosus (SLE) or may have RA, but is unclassifiable within the first 6–12 months. Therefore, although early diagnosis and treatment of RA is the goal, it is essential that RA is not overdiagnosed and patients are not needlessly subjected to medications with potential toxicities.

Most studies examining RA use the American College of Rheumatology (ACR) criteria, formerly the American Rheumatism Association criteria[16] (table I). These criteria consist of clinical (morning stiffness, symmetric synovitis, rheumatoid nodules), laboratory (rheumatoid factor) and radiographic (erosions) characteristics. For classification purposes, four of seven criteria must be present, with at least 6 weeks of morning stiffness and arthritis. The criteria were developed using the consensus opinion of experts for research purposes in order to standardise (classify) populations under study across centres. In patients with established RA, the criteria are sensitive (91%) and specific (89%) with respect to making an alternative diagnosis of other defined rheumatological conditions, such as osteoarthritis and SLE.[16]

The ACR criteria are also used in studies of patients with early RA to ensure consistency, as well as in clinical practice to help formulate the diagnosis. Unfortunately, certain ACR criteria, such as radiographic erosions and nodules, may not be seen until later in the course of the disease. In fact, in a perfect world, RA patients would all be treated

Table I. Criteria for the diagnosis of rheumatoid arthritis (RA) [reproduced from Arendt et al.,[17] with permission]

Criteria[a]		Definition
1.	Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2.	Arthritis of three or more joint areas	At least three joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle and MTP joints
3.	Arthritis of hand joints	At least one area swollen (as defined in 2) in a wrist, MCP or PIP joint
4.	Symmetrical arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIP, MCP or MTP joints is acceptable without absolute symmetry)
5.	Rheumatoid nodules	Subcutaneous nodules, over bony prominences or extensor surfaces or in juxta-articular regions, observed by a physician
6.	Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of healthy control subjects
7.	Radiographic changes	Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localised in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

a For classification purposes, a patient shall be said to have RA if he/she has satisfied at least four of these seven criteria. Criteria 1–4 must have been present for at least 6 weeks. Patients with two clinical diagnoses are not excluded. Designation as classic, definite or probable RA is not to be made.

MCP = metacarpophalangeal; **MTP** = metatarsophalangeal; **PIP** = proximal interphalangeal.

before developing erosions. The ACR criteria have been applied in patients with early RA with a sensitivity of 40–60% and a specificity of 80–90%.[18] The ability to identify patients who go on to develop persistent, erosive and disabling disease is disappointing, and this is the group arguably the most in need of aggressive initial therapy.[19]

Visser et al.[20] have successfully developed diagnostic criteria for early arthritis using 2-year arthritis outcomes as the gold standard (self-limited vs persistent nonerosive vs persistent erosive). In this model, logistic regression was used to identify seven variables that were able to discriminate at the patient's first visit between the three outcomes. These variables were symptom duration at first visit, morning stiffness (≥1 hour), arthritis in three or more joints, bilateral compression pain in the metatarsalphalangeal joints, positive rheumatoid factor (RF), positive anti-cyclic citrullinated peptide (anti-CCP), and erosive changes in the hands or feet. Validation of this model is needed in other early arthritis populations before its routine incorporation into clinical practice.

Clinicians rely on their clinical skills to diagnose synovitis, an important finding in early RA. Mild synovitis can often be difficult to perceive and obesity can make discernment of synovitis challenging. There are questions concerning the sensitivity of physical examination to detect mild synovitis[21] and the reproducibility of the clinical assessment of synovitis.[22] Imaging techniques such as magnetic resonance imaging (MRI) and musculoskeletal ultrasonography can demonstrate the presence of synovitis not appreciated with physical examination, and detect cortical bony changes much earlier than conventional radiography.[23-27] Detection of synovitis is further enhanced by the addition of power Doppler to conventional grey scale ultrasonography and gadolinium to MRI.[28,29] Although MRI is expensive, time consuming and not tolerated by some patients, advantages include standardised imaging protocols and sequences, and the lack of ionising radiation. Ultrasonography is operator dependent and training is not routinely available in most fellowship programmes; however, it is relatively inexpensive, increasingly available, well tolerated without ionising radiation, allows real time dynamic

imaging and is portable.[30] Overall, once these techniques have been standardised and validated, both modalities may offer significant improvements in the early detection of synovitis and bony erosions, which could lead to more timely and accurate diagnoses of early RA.

Clinicians also use serological tests to aid in the diagnosis of early RA. RF are autoantibodies directed against the Fc portion of IgG. The role that RF plays in the pathogenesis and perpetuation of RA is poorly understood. RF positivity does have prognostic significance in RA, and at high titres it is associated with more severe erosive disease, nodules, vasculitis and other extra-articular manifestations.[31-33] A second serological test employed to help diagnose RA is the anti-CCP. The target antigen of anti-CCP is citrulline, a post-translationally modified arginine residue in filaggrin. RF and anti-CCP may be detectable in serum before the onset of RA.[34]

In a cohort of 238 patients with new onset (<12 months) of synovitis, RF was 66% sensitive and 87% specific, and anti-CCP was only 41% sensitive but 91% specific. Having both RF and anti-CCP improved the specificity to 96%.[35] Additionally, anti-CCP may be helpful in making the diagnosis of RA in RF-negative patients. RFs are present in other autoimmune diseases, infections (particularly hepatitis C virus) and malignancies. In addition to autoantibody testing, nonspecific markers of inflammation are also seen in early RA, and these include elevations in the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Therefore, although laboratory tests are helpful in guiding a diagnosis, they are by no means absolute.

One final hurdle in early diagnosis deserves mention and that is getting the patients with early inflammatory arthritis into specialist rheumatology care. For example, stoic patients may not recognise the need to see a physician when they have joint pain or swelling. Alternatively, inflammation may be insidious and evolve gradually, delaying referral to a rheumatologist. Finally, there is a shortage of rheumatologists, and patients may be placed on waiting lists or not receive a scheduled appointment for 2–3 months. Educational campaigns targeted at patients and primary care doctors, in addition to the development of early arthritis clinics, may improve early referral as well as access to rheumatology care.

In summary, early diagnosis is critical, but there remain challenges, including a large differential diagnosis, poor performance of the ACR diagnostic criteria in early RA, inaccuracy of clinical examination to detect mild synovitis, lack of absolute diagnostic laboratory tests, inability of conventional radiography to detect early bony changes and limited access to specialist rheumatology care (table II). In recognition of these challenges, efforts are being made to enhance early diagnostic ability by developing new predictive models. Advances in imaging, such as MRI and ultrasonography have led to improvements in our ability to detect synovitis and erosive disease earlier and more accurately. In addition, newer and more specific serological tests, such as the anti-CCP, are now available and continued research is ongoing to find determinants, such as genetic typing, that will augment early diagnosis. Finally, physician education and patient access issues are garnering more attention with the development of practical solutions.

2. Pathogenesis of Rheumatoid Arthritis (RA)

Although a complete review of the pathogenesis of RA is beyond the scope of this article, it is important to briefly discuss important immune effectors to understand more fully some of the therapeutic targets. For an excellent and more in depth review, readers are referred to the article by Choy and Panayi.[36] The normal inflammatory process is usually tightly regulated with both activators and

Table II. Challenges to the early diagnosis of rheumatoid arthritis (RA)

Inflammatory polyarthritis has a large differential diagnoses
ACR criteria performs poorly in early RA
Mild synovitis can be difficult to perceive by physical examination
Absolute or definitive laboratory tests are lacking
Conventional radiography inadequately detects erosions in their earliest stages
Barriers exist for early patient access to rheumatology care

ACR = American College of Rheumatology.

inhibitors of inflammation working in concert with each other. When chronic inflammation develops, there is an imbalance, resulting in cellular damage. In patients with RA, this manifests with cartilage, bone and ultimately joint destruction. CD4+ T cells appear to be one of the fundamental cells in both cell-mediated and humoral immune responses in RA. Genetic studies of RA have identified a strong link between RA and a region in the class II MHC called the 'shared epitope' (SE), including HLA-DRB1*0404 and DRB1*0401.[37] The main role of the MHC class II molecules is to present antigenic peptides to CD4+ cells. This genetic link and the primary role played by CD4+ cells in RA, strongly suggests that RA may be caused by an unidentified arthritogenic antigen, such as a viral or endogenous protein.[38]

Antigen-activated T cells then stimulate the release of interleukin (IL)-1, IL-6 and TNFα by macrophages, and stimulate the secretion of matrix metalloproteinases by chondrocytes and synovial fibroblasts (figure 1). Concurrently, activated CD4+ cells also express osteoprotegerin ligands that stimulate osteoclastogenesis, and stimulate B cells to produce immunoglobulins (including RF), which may form immune complexes and activate complement.

IL-1 and TNFα are key cytokines that drive the inflammation in RA. Both are potent stimulators of mesenchymal cells (synoviocytes, osteoclasts and chondrocytes) to release matrix metalloproteinases and inhibit the production of tissue inhibitors of metalloproteinases by synovial fibroblasts.[39] These dual actions lead to joint destruction. TNFα also stimulates the development of osteoclasts, which degrade bone.[40]

The antigen or antigens responsible for this cascade of events are unknown; however, it is accepted that once initiated, the process occurs in a parallel, rather than a sequential fashion. The fact that cytokines are redundant and pleiotropic with multiple and overlapping functions makes the whole immune response difficult, at times, both to comprehend and to predictably inhibit. While the above explanation seems cumbersome and by no means complete, it exemplifies the premise that RA is a process of many inflammatory and proliferative pathways activated in parallel; therefore, it makes sense that effective therapy may include multiple agents targeted at individual aspects of the immune response.[41,42]

3. Treatment of Early RA

3.1 Disease-Modifying Antirheumatic Drug (DMARD) Monotherapy

During the 1990s, the treatment of RA was radically transformed. Before then, patients were initially treated with NSAIDs. The use of DMARDs was only employed later, if patients continued to be symptomatic or had evidence of joint destruction (erosions on radiographs). In 1996, van der Heide et al.[5] published an open, randomised, clinical trial comparing functional disability, pain, joint score and ESR at 6 and 12 months, and 12 month radiographic progression in 238 patients with a recent (≤1 year) onset of RA. Patients received delayed or immediate introduction of therapy with hydroxychloroquine, methotrexate or intramuscular gold. Corticosteroids were used in both groups in a similar percentage of patients. The results showed a statistically significant advantage for the immediate DMARD group at 12 months in all measures except for radiographic progression. This finding confirmed what most rheumatologists already believed, that early institution of DMARD therapy provides the best outcomes.

Traditional DMARDs include methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, ciclosporin (cyclosporine), azathioprine, penicillamine (D-penicillamine) and gold (oral or intramuscular). These agents all share several features, including a slow onset and poorly understood mechanism of action.[43] A meta-analysis of blinded clinical trials published in 1990 suggested that the relative potencies of most (methotrexate, sulfasalazine, intramuscular gold, penicillamine) are similar, with hydroxychloroquine and oral gold somewhat less potent.[44] This meta-analysis did not

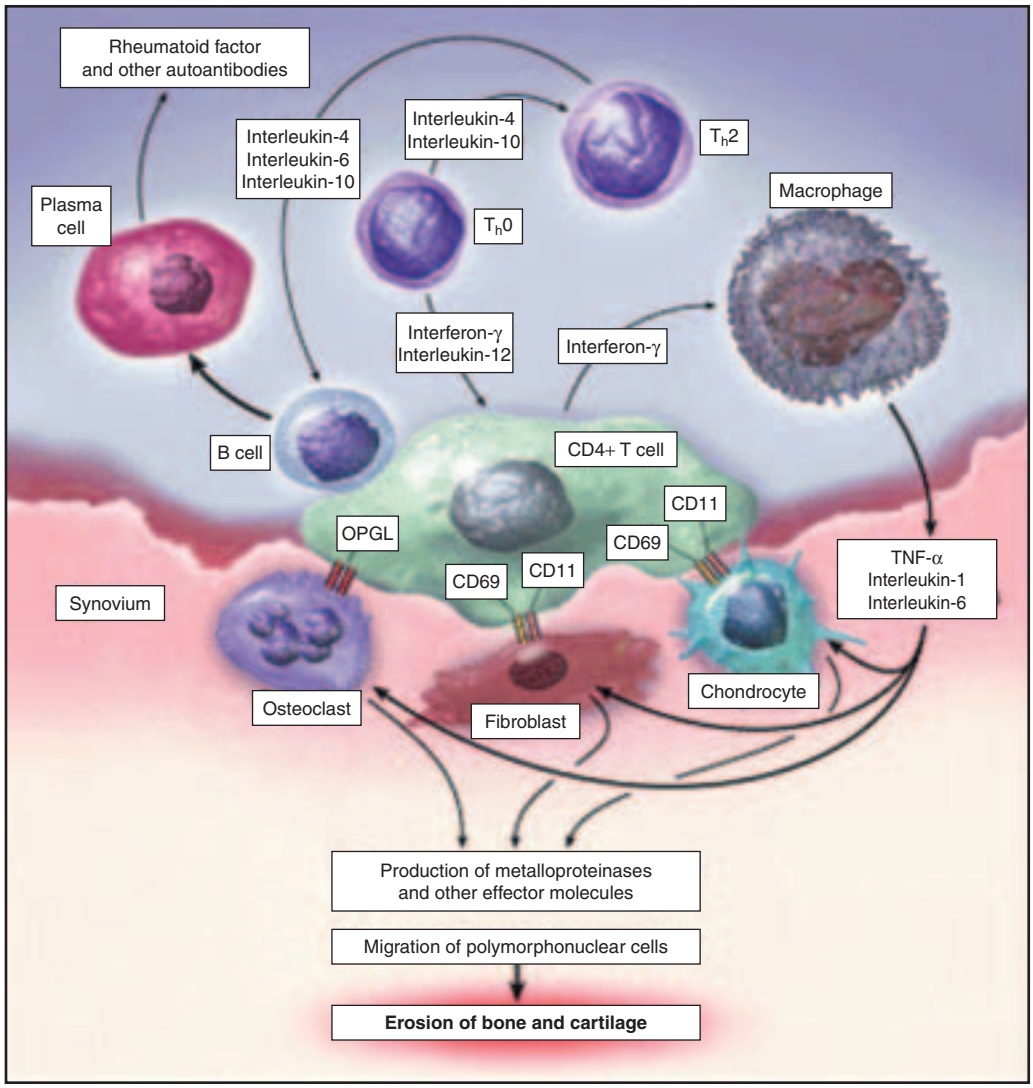

Fig. 1. Cytokine signalling pathways involved in inflammatory arthritis (reproduced from Choy and Panayi,[36] with permission from Massachusetts Medical Society. Copyright © 2001. All rights reserved). **OPGL** = osteoprotegerin ligands; **T_h** = T helper cell; **TNF**α = tumour necrosis factor-α.

include leflunomide, as it had not yet been approved by the US FDA for the treatment of RA.

Subsequent observational trials have clearly established methotrexate as the DMARD that is most likely to give a durable, long-term response.[45,46] Methotrexate has been shown to be efficacious in both open and placebo-controlled trials.[47-49] Furthermore, most toxicity can be monitored by routine blood tests[50] and folic acid supplementation can prevent some toxicity without interfering with efficacy.[51] Unfortunately, methotrexate monotherapy rarely induces remission, with only one-third of patients improved by 50% after 2 or 4 years.[9,52]

Sulfasalazine was the first DMARD developed to specifically treat RA and has been in use since 1942.[53] Hydroxychloroquine is well tolerated and

with appropriate administration, retinal toxicity is rare (<6.5 mg/kg/day).[54] Leflunomide is a synthetic DMARD with an efficacy similar to sulfasalazine and moderate doses of methotrexate for both suppression of inflammation and inhibition of radiographic progression.[55,56] Finally, although not considered a traditional DMARD, minocycline has been shown to be efficacious in patients with early seropositive RA compared with placebo and hydroxychloroquine.[57-59] The mechanism of action of minocycline in RA is complex and is likely to include inhibition of matrix metalloproteinases, an immunological effect and possibly nonspecific antibacterial effects.[58]

The use of corticosteroids in the treatment of RA deserves mention. Systemic corticosteroids are frequently employed in RA for their ability to provide rapid symptom relief. Furthermore, corticosteroids are disease modifying as a result of their ability to effectively suppress inflammation and retard radiographic progression.[60] However, long-term high-dose therapy is limited by the adverse-effect profile.

One fundamental concern with the use of the aforementioned DMARDs is to monitor for toxicity. The adverse-effect profiles of these agents are well known after years of use, and adverse effects occur at an estimated frequency of 0.1–5%, depending on the medication. The ACR has developed guidelines for monitoring drug therapy in RA, and a special article published in 1996 and revised in 2002, describes toxicity profiles, risk factors, strategies to prevent toxicity and recommendations for prudent monitoring.[61,62]

3.2 DMARD Combination Therapy

While the use of DMARD monotherapy has markedly improved RA outcomes, remission frequently does not occur with one agent alone and combinations of DMARDs are employed for enhanced efficacy. The premise behind combination therapy is that the use of multiple agents, each targeting a different aspect of the immune response, will have additive or synergistic properties and may reduce overall toxicity. Methotrexate is included in most regimens, and is frequently referred to as the anchor, ace or cornerstone. Combination DMARD therapy can be employed using three approaches: (i) step-up therapy starts with one DMARD and adds sequential DMARDs; (ii) parallel therapy starts and continues multiple DMARDs; and (iii) step-down therapy initiates a combination DMARD regimen then subsequently withdraws agents (in essence, induction therapy).

3.2.1 Outcome Measures

Multiple instruments have been developed for use in clinical trials to assess both current disease activity and improvement criteria, and should be reviewed before any discussion of the individual trials. The disease activity scale (DAS) is commonly used to measure current disease activity.[63] The DAS is reported as a single number reflecting multiple measures including the number of tender and swollen joints, markers of inflammation (ESR or CRP), and patient global assessment of health.

Improvement in disease activity is commonly measured by the ACR preliminary improvement criteria, which was developed for its discriminative validity against placebo.[64,65] The ACR preliminary definition of improvement consists of changes in joint tenderness and swelling, patient self-assessment of pain and disability, physician and patient global assessments, and acute phase reactant value (ESR or CRP).[64] The ACR improvement is reported as a percentage. For example, an ACR 20 response indicates at least a 20% improvement in five of the seven variables, which must include joint tenderness and swelling. ACR criteria of 50% and 70% improvement are also used. The Paulus improvement is a measure similar to the ACR improvement, but excludes pain and disability.[65]

Measures of both current disease activity and improvement in disease activity include the simple index[66] and the European League Against Rheumatism (EULAR) response.[67] The simple index comprises six variables: morning stiffness, tender and swollen joints, ESR, and a baseline change in pain and function. The EULAR response criteria are based on a change in the DAS, and patients are grouped as good, moderate or nonresponders.

3.2.2 Trials of Combination DMARD Therapy

Combination DMARD therapy has been shown to be more effective than monotherapy in established RA for measures such as disease activity and radiographic progression.[9,10,68] Subsequently, there have been multiple trials looking at combination therapy in early RA, and while some show only a trend in benefit, most show statistically significant improvements.[6-8,69,70]

Dougados et al.[69] studied 205 patients with active RA and a disease duration of <1 year (mean 2.9 months), who were randomised to receive sulfasalazine 2000–3000 mg/day versus methotrexate 7.5–15 mg/week versus sulfasalazine plus methotrexate for 52 weeks. No corticosteroids were allowed. The primary endpoint was the mean change in the DAS. Patients were also evaluated by EULAR and ACR criteria, and radiographic progression was tracked. The results showed a statistically significant change in the primary endpoint (DAS) with combination therapy versus methotrexate monotherapy ($p < 0.001$), but only a positive trend favouring combination therapy over sulfasalazine monotherapy ($p = 0.09$). No statistically significant changes were seen between combination therapy and ACR or EULAR criteria or radiographic endpoints; however, there was a trend in favour of the combination group in these secondary endpoints.

Haagsma et al.[70] studied combination therapy with sulfasalazine 2000–3000 mg/day versus methotrexate 7.5–15 mg/week versus methotrexate plus sulfasalazine in 105 patients with RA and disease duration of <1 year (mean 2.9 months). No corticosteroids were permitted. The primary endpoint was the mean change in the DAS over 52 weeks. The mean change in the DAS was −1.6 for sulfasalazine, −1.7 for methotrexate and −1.9 for sulfasalazine plus methotrexate. This was not a statistically significant change but there was a modest trend seen in favour of the combination group.

One of the first trials clearly showing a significant benefit for early intervention was the COBRA (Combinatietherapie Bij Reumatoide Artritis) trial.[6] 155 patients with RA for <2 years duration (median 4 months) were randomly assigned to receive treatment with combination prednisolone 60 mg/day plus methotrexate 7.5 mg/week plus sulfasalazine 2 g/day versus sulfasalazine 2 g/day alone. A step-down approach was used so that by week 40, the treatment in each group was the same, with the combination group having tapered and stopped prednisolone by week 28 and methotrexate by week 40. At week 28, the combination group had improved significantly more than the sulfasalazine-only group, with ACR 20 responses of 72% versus 49% and ACR 50 responses of 49% versus 27%, respectively ($p < 0.0001$). Clinical improvements converged after week 28; however, the benefits of combination therapy as shown by radiography persisted at least to year 5 of the study.[71]

The Finnish Rheumatoid Arthritis (Fin-RA) combination therapy trial group compared combination DMARD therapy with methotrexate 7.5–15 mg/week plus sulfasalazine 1–2 g/day plus hydroxychloroquine 300 mg/day plus low-dose prednisolone 5 mg/day monotherapy with sulfasalazine with or without prednisolone.[8] Patients ($n = 199$) with RA of <2 years' duration (mean 8 months) were randomised to each group with the primary endpoint of disease remission by ACR preliminary criteria.[72] After 2 years, 37% of the combination group and 18% of the monotherapy group were in remission ($p = 0.003$). Furthermore, when looking at all the variables, the only factor that predicted remission was whether they had received combination therapy in the beginning, with an odds ratio of 2.7. In addition, patients who received combination therapy were less likely to have C1–C2 subluxation 5 years later.[73]

Although not specifically aimed at patients with early RA, Calguneri et al.[7] followed 180 patients with RA (average disease duration of 2.3 years) who were not already receiving DMARDs. Patients were randomised to treatment with monotherapy methotrexate 7.5–15 mg/week, hydroxychloroquine 200 mg/day or sulfasalazine 1–2 g/day versus double therapy (methotrexate plus hydroxychloroquine or methotrexate plus sulfasalazine) versus triple therapy (methotrexate plus hydroxychloroquine plus sulfasalazine). The primary outcome was >50% improvement in composite criteria (based on the modi-

fied Paulus criteria). After 2 years, significant improvements were seen in all patients treated; however, the number of patients with >50% improvement in the composite criteria was significantly greater after triple therapy (88%) than after double therapy (73%) or monotherapy (49%) [$p < 0.001$]. Radiographic scores were improved or unchanged in 69% of patients receiving triple therapy, 64% receiving double therapy and 25% of those receiving monotherapy ($p = 0.001$ for double vs monotherapy and triple vs monotherapy; $p = 0.210$ for double vs triple therapy).

3.3 Biological Therapy

Despite marked therapeutic gains with the use of traditional DMARDS, remission is still not achieved in many patients. This fact, coupled with enhanced understanding of the immunological basis of the inflammation in RA has led to the development of specific biological response modulators for the treatment of RA. These agents, referred to as biologics, target cytokines such as TNFα. There are currently three anti-TNFα agents available for the treatment of RA: infliximab, adalimumab and etanercept.

Infliximab is a neutralising chimeric monoclonal IgG against TNFα that is effective and well tolerated in the treatment of established RA as monotherapy and in combination with methotrexate.[74-76] Current recommendations are for combination therapy, as methotrexate promotes immunological tolerance to infliximab (methotrexate decreases the formation of human antichimeric antibodies). Adalimumab is a monoclonal fully humanised antibody targeting TNFα and has been shown to be effective as monotherapy as well as when used in combination with methotrexate.[77-79] Etanercept is a recombinant fusion protein, consisting of two soluble TNF receptors linked to the Fc portion of a human IgG1, which binds to and inactivates TNFα. Etanercept improves the inflammatory symptoms of established RA alone and in combination with methotrexate.[80,81] Intense interest has centred on how these new agents fit into the therapeutic armamentarium for early RA.

Currently, anti-TNF therapy has an acceptable adverse-effect profile; the most common adverse effects are injection site reactions (etanercept, adalimumab), infusion reactions (infliximab) and minor upper respiratory infections. These agents should be withheld in the setting of acute or ongoing infection. Reactivation of tuberculosis has gained widespread attention and all patients for whom a biologic is going to be prescribed should have screening with a purified protein derivative (PPD) skin test. The risk of reactivation of tuberculosis seems to be higher in the monoclonal antibody agents (infliximab and adalimumab), but no direct comparative trials have been carried out.[82] Disseminated histoplasmosis has also been seen with the use of these agents.[83] There are reports of the development of pancytopenia, aplastic anaemia, demyelinating syndromes, worsening of congestive heart failure and drug-induced SLE.[84-87] Finally, at this time, there does not appear to be a significantly increased risk of overall malignancy with the use of TNF inhibitors in patients with RA, but there may be an association with the development of lymphoma.[88,89]

Geborek et al.[89] compared two groups of RA patients for their risk of lymphoma based on treatment with anti-TNFα therapy. Patients receiving biologics had an increased risk of lymphoma with a relative risk (RR) of 11.5 (95% CI 3.7, 26.9), but also had more severe RA. This issue is confounding as there is good evidence that the risk of lymphoma is related to RA severity.[90] However, this trend was seen after adjustment for disease severity with an RR of 5 (95% CI 0.9, 26.2). This is an area that deserves more study because the biological agents are relatively new, and judicious surveillance is warranted for both solid tumours and haematological malignancies.

3.3.1 Trials with Biological Agents

Biological agents were initially studied in patients with established RA who had not responded to traditional DMARDs, and were used as additive therapy. More recently, interest has shifted to treatment in early RA to see how these agents perform in comparison with traditional DMARDs.

The first study looking at this question was the ERA (Enbrel Early Rheumatoid Arthritis) trial.[11] This was a randomised controlled trial looking at 632 methotrexate-naive patients with seropositive or erosive RA of <3 years' duration (average disease duration of 11–12 months). Patients were randomised to monotherapy with methotrexate, starting at 7.5 mg/week and escalating to 20 mg/week versus monotherapy with etanercept 10 or 25mg twice weekly, and were followed for 1 year. Stable dosages of NSAIDs and prednisone (≤10 mg/day) were allowed. Outcome measures included percentage improvements in disease activity according to the ACR criteria, the area under the curve (AUC) for the percentage of ACR improvement (ACR-N),[64,91] and progression of bony erosions and joint space narrowing using the Sharp scale.[92,93] The results showed that etanercept 25mg was superior to methotrexate for early improvements in ACR 20, 50 and 70 during the first 6 months ($p < 0.05$), but this difference disappeared by 12 months. There was a decrease in progression of erosions in the etanercept 25mg group compared with the methotrexate group at both 6 months ($p = 0.001$) and 12 months ($p = 0.002$). There was no difference in the progression of joint space narrowing at 6 and 12 months, and although the total Sharp score was improved in the etanercept group at 6 months ($p = 0.001$), this difference was not seen at 12 months.

At the completion of the study, 512 patients continued to receive the therapy to which they had been randomised for up to 1 additional year.[94] After 2 years, more patients in the etanercept 25mg group had attained an ACR 20 than in the methotrexate group ($p = 0.005$); however, there was no difference for ACR 50 or 70. Although etanercept was numerically superior to methotrexate in the ACR 20, both agents were effective in reducing disease activity. All radiographic endpoints (joint space narrowing, erosions, total Sharp score) showed less progression in the etanercept 25mg group versus the methotrexate group ($p = 0.001$).

In summary, both etanercept and methotrexate are effective as monotherapy in early RA, and the results are sustained for at least 2 years. Therapy with etanercept has some advantages, including superiority in early clinical improvement, which is believed to be the result of the rapid action of etanercept compared with methotrexate. When evaluated at 2 years, etanercept did have a significantly greater clinical response as measured by ACR 20. Furthermore, etanercept is at least equivalent to methotrexate in preventing overall structural damage and is superior to methotrexate in preventing erosions. Follow-up has shown that those who initially received etanercept had sustained improvements in radiographic progression, an effect that was not seen in a group who switched from methotrexate to etanercept in the open-label portion of the trial,[95] suggesting a 'window' of opportunity for early therapy with etanercept.

The next major published trial addressed whether combination therapy with a biologic plus methotrexate would be more effective than either agent alone in established RA. The TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study was a randomised, double-blinded, trial comparing monotherapy with etanercept versus methotrexate versus combination therapy with etanercept plus methotrexate, in patients with established RA (mean duration of disease 6.3–6.8 years).[96] Results showed that the combination therapy was statistically better than either methotrexate or etanercept monotherapy for all primary outcomes, and the AUC for the ACR-N was comparable with the results of the ERA trial for each group.[11] Follow-up data from the TEMPO trial have shown that after 2 years, combination therapy results in statistically superior efficacy for clinical endpoints when compared with monotherapy. Also, the radiographic outcomes persist with patients receiving combination therapy and continuing to show a decreased modified Sharp score from baseline and a negative rate of progression.[97]

As illustrated in section 3.2.2, combination DMARD therapy has been shown to be more effective than monotherapy in early RA,[6-8] and biological therapy plus methotrexate is more effective than either as monotherapy in established RA;[81] thus, further studies were completed that studied biologi-

cal agents in combination with methotrexate in early RA.

In the ASPIRE (Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group) trial, 1049 methotrexate- and biologic-naive patients with RA of <3 years' duration (mean duration of disease 0.8–0.9 months) were randomised to receive methotrexate 20 mg/week plus placebo versus methotrexate plus infliximab 3 mg/kg versus methotrexate plus infliximab 6 mg/kg.[98] Infliximab is not routinely used as monotherapy. Methotrexate dosage was rapidly escalated to 20 mg/week and infliximab or placebo infusions were given at weeks 0, 2, 6 and then every 8 weeks for 46 weeks. Prednisone ≤10 mg/day and NSAIDs were allowed and continued at baseline dosages. The primary endpoints included the ACR-N for clinical signs and symptoms, the van der Heijde[99] modification of the total Sharp score (vdH-S) for radiographic changes from baseline to week 54, and changes in the Health Assessment Questionnaire (HAQ) scores from week 30–54 for physical function. Although there were no differences in the primary outcomes between combination groups (infliximab at 3 or 6 mg/kg), the combination groups did show significant improvement in all primary outcome measures when compared with methotrexate plus placebo (ACR-N: $p < 0.001$; changes in vdH-S: $p \leq 0.001$; HAQ improvement: $p = 0.01$) Unfortunately, there was a significantly higher incidence of serious infection in the combination groups, including pneumonia, and four patients developed tuberculosis: two who were not screened with a PPD before enrollment and two who had a negative PPD. In summary, combination therapy in early RA with methotrexate plus infliximab at 3 or 6 mg/kg is more effective than monotherapy with methotrexate, but there is an increased risk of serious infections.

The PREMIER study group recently published data on combination therapy with methotrexate plus adalimumab.[100] In this trial, 799 methotrexate- and biologic-naive patients with early RA of <3 years' duration (mean duration of disease 0.7–0.8 years) were randomised to receive monotherapy with methotrexate (rapid escalation to 20 mg/week) or adalimumab (40mg every other week) or the combination of both. The trial lasted 2 years and the primary outcomes were the ACR 50 response and the inhibition of radiographic progression, as measured by the mean change in the total Sharp score. The results showed that combination therapy at 52 weeks was superior to either monotherapy group in achieving the ACR 50 (combination 62%, methotrexate 46%, adalimumab 41%; $p < 0.001$ for combination vs each monotherapy) and this difference persisted to week 104 of the study. At 1 year, combination therapy resulted in less radiographic progression than either monotherapy group ($p = 0.002$ combination vs adalimumab; $p < 0.001$ combination vs methotrexate). Further analysis showed that this difference persists at 2 year follow-up ($p < 0.001$ for combination vs either monotherapy).[101] There were no significant differences in adverse events between treatment groups. The PREMIER study further highlights that combination therapy with a biologic and a DMARD can outperform either agent alone in early RA.

The Dutch BeSt (Behandel-Strategieen), or 'treatment strategies' trial in RA compared four different approaches to treatment in early RA.[102] In this trial, 508 RA patients with a disease duration of <2 years (median disease duration 23 weeks) were randomised to the following four groups: group 1 received sequential DMARD monotherapy (methotrexate was the initial DMARD), group 2 received step-up DMARD combination therapy (methotrexate then add sulfasalazine then add hydroxychloroquine), group 3 received parallel combination DMARD therapy with high-dose prednisone (methotrexate + sulfasalazine + prednisone 60 mg/day and then tapered) and group 4 received parallel combination therapy with a DMARD and a biologic (methotrexate + infliximab). Each patient was assessed at 3-month intervals and the medical regimen was adjusted according to the trial protocol if disease activity was not adequately controlled, allowing for the flexibility commonly seen in clinical practice and in accordance with the evidence that tight disease control

leads to better outcomes.[103] The protocol also allowed for tapering the regimen to a minimum of one DMARD for patients who had an adequate clinical response maintained for at least 6 months. Similarly to the COBRA trial,[6] patients in group 3 were started on high-dose prednisone that was tapered to 7.5mg over the first 7 weeks of the trial.

The primary endpoints were functional ability as measured by the Dutch HAQ and radiographic progression using the Sharp/van der Heijde radiographic joint score. The results showed that initial combination therapy including high-dose prednisone (group 3) or infliximab (group 4) resulted in a more rapid and sustained functional improvement, when compared with groups 1 or 2 (6 months: $p < 0.001$ groups 1 and 2 vs groups 3 and 4; 1 year: $p = 0.009$ groups 1 and 2 vs groups 3 and 4). There were no differences between group 1 and group 2 or between group 3 and group 4. At 1 year, patients in groups 3 and 4 also had less progression of radiographic joint damage than groups 1 or 2 ($p = 0.003$ group 1 vs group 3; $p < 0.001$ group 1 vs group 4; $p = 0.007$ group 2 vs group 3; $p < 0.001$ group 2 vs group 4).

It should be noted that there was a marked improvement in all groups at the end of the first year, with 32% of all patients achieving clinical remission. Although there were statistically significant differences between groups 1 and 2 versus groups 3 and 4 in the primary outcome variables, at 1 year these differences were smaller, indicating that some patients do well on less therapy and do not need initial combination therapy. Furthermore, many patients in group 3 (78%) and group 4 (50%) were able to discontinue prednisone and infliximab, respectively, and maintain clinical remission, suggesting that certain patients respond to induction therapy.

Future trials should be designed to answer several pivotal questions. First, more data are needed regarding the direct comparison of combinations of DMARDs with biological therapy in early RA. Secondly, data on the efficacy of step-up therapy compared with parallel combination therapy in early RA are warranted.

3.3.2 Induction Therapy

Clinical trials (section 3.3.1) suggest that intensive, early combination therapy may intervene in the RA disease process during a 'window of opportunity', when rapid suppression of inflammation decreases or resets disease progression for years to come. Induction therapy using a rapid step-down approach could potentially improve outcomes, decrease patient exposure to toxic medications and lower costs, all of which are appealing ideas in RA. The COBRA trial suggests that high-dose corticosteroids may be one appropriate agent for induction.[6] The BeSt trial confirms the use of corticosteroids and also suggests that biological agents, such as infliximab, may be used in an early combination regimen and then tapered with lasting results.[102]

An additional study examining infliximab induction in a group of early RA patients with poor prognostic indicators compared monotherapy (methotrexate) with step-down therapy (12 months of infliximab plus methotrexate), with maintenance methotrexate and the addition of sulfasalazine and hydroxychloroquine if needed.[104] The results showed that those who received induction with infliximab had significant improvements in measures of function (HAQ and RA Quality of Life questionnaire) 1 year after infliximab therapy was discontinued. Differences in clinical measures of disease were seen at 1 year but converged after discontinuation of therapy. Further study in this area is warranted because it may lead to better long-term outcomes, as well as less cumulative drug toxicity and cost containment.

4. Discussion

Most of the studies discussed demonstrate that aggressive therapy with combinations of conventional DMARDs or biologics plus methotrexate in early RA leads not only to clinical improvement but also to decreased structural damage (table III). Except for TEMPO, the aforementioned trials focus on early RA patients for whom delineation of the optimal therapy is critical because it can prevent long-term morbidity (pain, joint destruction and disability) and decrease mortality. The patients selected for

Table III. Relevant clinical trials in early rheumatoid arthritis (RA)

Study	Subjects	Therapy	Results	Comments
Dougados et al.[69]	205 early RA patients (<1y duration)	SSZ vs MTX vs SSZ + MTX	52wk DAS change: SSZ −1.15 MTX −0.87 SSZ + MTX −1.26 ($p = 0.09$ SSZ vs combo) ($p < 0.001$ MTX vs combo)	
Haagsma et al.[70]	105 early RA patients (<1y duration)	SSZ vs MTX vs SSZ + MTX	52wk DAS change: SSZ −1.6 MTX −1.7 SSZ + MTX −1.9 ($p > 0.05$)	
Boers et al.[6] (COBRA)	155 early RA patients (<2y duration)	SSZ vs SSZ + prednisolone (high dose off by wk 28) + MTX (off by wk 40)	28wk pooled index:[a] combo did better to wk 28 ($p < 0.0001$), then no difference; 1y vdH-S:[b] combo superior to mono ($p < 0.0001$)	Suggests that induction with prednisolone may be effective
Mottonen et al.[8] (Fin-RA)	199 early RA patients (<2y duration)	SSZ ± prednisolone vs MTX + SSZ + HCQ + prednisolone	2y remission by ACR preliminary criteria: SSZ: 18% Triple: 37% ($p = 0.003$)	The only variable predicting remission was early triple therapy, OR = 2.7
Calguneri et al.[7]	180 RA patients (average duration 2.36y)	Mono: HCQ, SSZ, MTX vs double therapy: MTX + HCQ or MTX + SSZ vs Triple therapy: MTX + SSZ + HCQ	2y 50% modified Paulus criteria Triple (88%) Double (73%) Mono (49%) ($p < 0.001$ for triple vs mono or double)	
Bathon et al.[11] (ERA)	632 early RA patients (<3y duration)	MTX (mean 19 mg/wk) vs etanercept 10mg vs etanercept 25mg	1y ACR 20: etanercept 25mg (72%) MTX (65%) $p = 0.16$; 1y ↑TSS:[b] etanercept 25mg (0.57) MTX (1.06) $p = 0.001$	
St Clair et al.[98] (ASPIRE)	1049 early RA patients (<3y duration)	MTX vs MTX+ infliximab 3 mg/kg vs MTX + infliximab 6 mg/kg	54-wk % ACR-N: MTX −3 mg/kg (38.9%) MTX −6 mg/kg (46.7%) MTX (26.4%) $p < 0.001$ for both combo vs MTX; 54-wk change in vdH-S:[b] MTX −3 mg/kg (0.4) MTX −6 mg/kg (0.5) MTX (3.7) $p < 0.001$ for both combo vs MTX	Infliximab groups had higher risk of serious infections
Breedveld et al.[100] (PREMIER)	799 early RA patients (<3y duration)	MTX vs adalimumab vs adalimumab + MTX	2y ACR 50: Combo (59%), adalimumab (37%) MTX (43%) $p < 0.001$ for combo vs either mono; Change in TSS:[b] combo (1.9), adalimumab (5.5) MTX (10.4) $p < 0.001$ for combo vs either mono	

Continued next page

Table III. Contd

Study	Subjects	Therapy	Results	Comments
Goekoop-Ruiterman et al.[102] (BeSt)	508 early RA patients (<2y duration)	4 groups: 1. sequential mono DMARD (MTX first DMARD) vs 2. step-up combo DMARD (MTX, add SSZ, add HCQ) vs 3. parallel combo DMARD (MTX + SSZ + prednisone 60 mg/day with taper) vs 4. parallel combo DMARD/ biological agent (MTX + infliximab)	1y D-HAQ groups 1 and 2 (1.0) groups 3 and 4 (0.6) $p < 0.001$; Median increase in vdH-S group 1 (2.0) group 2 (2.5) group 3 (0.5) group 4 (0.5) $p = 0.003$ group 1 vs 3 $p < 0.001$ group 1 vs 4 $p = 0.007$ group 2 vs 3 $p < 0.001$ group 2 vs 4	Allowed flexibility used in clinical practice. Induction with prednisolone or infliximab was effective

a 1y pooled index summarises the change in five measures: tender joint count, independent assessor visual analogue scale, grip strength, ESR (Westergren's method), McMaster Toronto arthritis questionnaire.

b The TSS and vdH-S are measures of radiographic progression.

ACR = American College of Rheumatology; **ACR-N** = the percentage of ACR improvement; **ASPIRE** = Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group; **BeSt** = the Dutch Behandel-Strategieen study; **COBRA** = Combinatietherapie Bij Reumatoide Artritis trial; **combo** = combination therapy; **DAS** = disease activity scale; **D-HAQ** = Dutch Health Assessment Questionnaire; **DMARD** = disease-modifying antirheumatic drug; **ERA** = Enbrel Early Rheumatoid Arthritis trial; **Fin-RA** = Finnish Rheumatoid Arthritis combination therapy trial group; **HCQ** = hydroxychloroquine; **mono** = monotherapy; **MTX** = methotrexate; **OR** = odds ratio; **SSZ** = sulfasalazine; **TSS** = Total Sharp Score; **vdH-S** = van der Heide modification of the TSS; ↑ indicates increase.

these early trials were methotrexate and biologic naive, and most had not taken other conventional DMARDs. This is important, as many of the completed trials in established RA examined populations of patients who have not responded to conventional therapy such as methotrexate, and this may represent a distinct subgroup within the RA population.

Although these trials argue for the use of combination DMARD therapy in early RA, concern has arisen over rapid combination DMARD implementation.[105,106] First, not all trials have shown a statistically significant benefit. If designed well, negative trials should carry the same weight as positive trials. It is noteworthy that the two aforementioned trials that did not show a strong benefit in all primary outcome measures (Dougados et al.[69] and Haagsma et al.[70]) did not include corticosteroids in the regimen and it is well accepted that corticosteroids have a disease modifying effect. Despite a reluctance to initiate combination DMARD therapy, most rheumatologists in clinical practice would favour using combination therapy in patients with early RA, in whom monotherapy does not quickly produce the desired effect.

Further complicating the interpretation of clinical trials in early RA is that direct comparisons between studies are difficult because of differing protocol designs (step-up vs step-down vs parallel), inclusion criteria (definition of early RA and duration of disease), therapeutic regimens and primary outcomes. Furthermore, these studies tell us that 'groups' of patients treated with combination therapy do better than with monotherapy; however, as seen in the BeSt study,[102] there are some individuals who achieve remission on monotherapy and others who clearly need early and aggressive combination therapy. One of the most challenging aspects of treating early RA is deciding in which category the individual RA patient resides.

4.1 Predictors of Response

It is widely accepted that there are several clinical and laboratory predictors of RA severity, such as an increased number of swollen and tender joints, nodules and elevated markers of inflammation (ESR and CRP). RF and anti-CCP antibodies are also major predictors of increased severity of radiographic erosions, especially when in high titre.[107,108] IgA RF may be a more specific predictor than IgG or IgM, and levels may change with treatment.[109] Furthermore, a baseline HAQ score of ≥1 and disease persisting for ≥12 weeks suggest a poor-

er outcome.[110] However, these prognostic variables for disease severity do not predict which patient will require more aggressive initial therapy.

Thus, despite intense interest, little evidence exists for alternative clinical or laboratory markers that can predict which therapeutic strategy is appropriate for an individual patient. One area of promising research has been in the genetics of RA, specifically, the SE, which portends an increased risk of severe disease, especially with dual copies.[111] O'Dell et al.[112] looked at the SE status in a cohort of patients with existing RA, and found that patients who were SE positive were more likely to achieve a 50% clinical improvement if treated with combination therapy (methotrexate + sulfasalazine + hydroxychloroquine) over methotrexate alone, but there was no difference in outcomes if patients were SE negative.

Lard et al.[113] looked at treatment response and SE status in previously studied groups of early RA patients, including a cohort from the COBRA trial.[6] The results showed that the association between HLA class II alleles and joint destruction can be abrogated by early and aggressive DMARD therapy, and that combination therapy is better than monotherapy. Thus, SE status may potentially be one way to guide treatment selection; however, further studies need to be conducted to better understand this phenomenon. Routine measurement of the SE is also expensive. Meanwhile, the search continues for a properly validated model that can predict which early RA patients are at greatest risk for poor long-term outcomes that can be changed in a differential way by the selection of therapy.

4.2 External Validity of Studies

The studies discussed here were all randomised, controlled clinical trials, which by the nature of the trial design should have the best internal validity; however, the patients recruited to most of these studies had very active disease and may not be representative of the general RA population, which questions the external validity of the findings. Although patients with early severe disease may be exactly the ones who need aggressive therapy and are most often the group recruited for study, these findings may not be generalisable to the patients seen in most rheumatology practices in the US. Sokka and Pincus[114] looked directly at this question by evaluating 232 early RA patients (duration of disease: <3 years) in a private rheumatology practice to see if they would meet inclusion criteria for the ERA trial. They found that inclusion criteria were met by 11 of 36 patients (31%) who had not taken methotrexate, 8 of 19 patients (42%) who were at their first visit and had not taken methotrexate, and 37 of 232 of the entire cohort (16%). The same trend was found in a survey of 123 practicing rheumatologists who reported that among early RA patients, 85% had <15 swollen/tender joints at presentation and <4% had >20 swollen/tender joints.[115] In the majority of the early RA trials, patients had >15 tender and 15 swollen joints. This leaves a substantial group of patients who may have less severe disease and thus respond well to less aggressive therapy. Future studies will need to include this group of patients.

5. Conclusion

Over the past decade, a substantial increase in the understanding of the pathobiology of RA has led to a marked improvement in pharmacological and biological therapeutic options, and the demonstration that early treatment is critical has shifted the treatment paradigm to early aggressive intervention. These facts coupled with an improved ability to make an early diagnosis should translate into better long-term outcomes for patients with RA.

Despite improvements, questions remain and ongoing research is needed to further stratify therapeutic regimens, incorporate the role of new biological agents currently in the research pipeline, understand the role of induction therapy, and search for the existence of biological or other markers that can help predict response and thus guide therapeutic decisions for individual patients.

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