Mod Rheumatol (2005) 15:153–162
DOI 10.1007/s10165-005-0383-0

REVIEW ARTICLE

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Treatment of early rheumatoid arthritis

Received: January 5, 2005 / Accepted: January 5, 2005

Abstract Recent advances in the understanding of the pathophysiology, aggressive treatment, and early detection of rheumatoid arthritis (RA) have changed the clinical, pathologic, and functional outcomes in patients with RA. Early aggressive treatment of RA has now become the norm in clinical practice rather than the use of the traditional pyramid approach of the last half of the twentieth century. Early treatment with monotherapy of traditional disease-modifying antirheumatic drugs (DMARDs) or biologics, combination traditional DMARD therapy and, especially, combination of biologic therapy and methotrexate, have revolutionized the treatment of RA, producing significant improvement in clinical, radiographic, and functional outcomes not seen previously. For the individual patient, we still cannot determine which medication or combination of medications will give the most complete response. There have been a number of recent, well-designed clinical trials that have tried to answer this question. Herein we review the evidence-based medicine that addresses these issues.

Key words Adalimumab · Anti-tumor necrosis factor · Combination therapy · Disease-modifying antirheumatic drugs (DMARD) · Early rheumatoid arthritis · Etanercept · Infliximab · Methotrexate

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting between 0.5% and 1% of the world's population, causing chronic pain, dysfunction, and disability.[1] Rheumatoid arthritis causes a significant economic burden on society. Direct average cost for the treatment of RA has been calculated to be $5919 per year in the United States and patients with poorer function have higher costs[2] with an overall economic burden of $20 billion in the United States. There are also significant indirect costs involved in terms of employer expenses, disability, and work loss. Patients with RA have 4–15 times higher disability rates compared with the general population. Work disability rates vary between 30% and 40% at 5 years, and a significant socioeconomic impact can be seen within the first year after disease onset.[3–6]

To establish a definite diagnosis of RA, four of the seven criteria established by the American College of Rheumatology (ACR) should be met with symptoms continually present for a minimum of 6 weeks.[7] Thus, RA can be diagnosed as early as 6 weeks if sufficient ACR criteria are met.[8] As patients with RA (particularly females) with extra-articular manifestations such as rheumatoid nodules, high levels of rheumatoid factor (RF) or anticyclic citrullinated peptide (anti-CCP) antibodies, and persistent elevation of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have a significantly lower expectation of survival than the normal, unaffected population and increased disability, with the most common causes of death being cardiovascular disease and infections,[5,9–11] the hope is that the earlier the disease can be diagnosed and treated effectively, the more likely it will be that the patient will have a normal life-span and less disability.

It is clear that radiographic joint damage occurs early in the disease course and is persistent and progressive, especially within the first 2 years of disease onset.[12–16] It has recently been shown that early, aggressive, effective treatment significantly reduces radiographic progression in RA.[17] Patients who are diagnosed with very early RA and are treated aggressively with disease-modifying antirheumatic drug (DMARD) therapy earlier have better clinical outcomes compared with patients who are treated later.[18] A brief delay in initiation of DMARD therapy results in more rapid joint destruction and loss of function in most patients.[19] This is the "therapeutic window of opportunity" in which early diagnosis of RA with early intervention with

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aggressive DMARD therapy can halt or significantly reduce disease progression.

Recent clinical trials have shown that aggressive therapy with traditional DMARDs may well control clinical symptoms but may not slow radiographic progression to the extent possible with a combination of a biologic, especially an anti-tumor necrosis factor alpha (TNF-α) and methotrexate (MTX). The premise that early and aggressive therapy, especially the combination of an anti-TNF-α and MTX produces the best clinical, radiographic, and functional outcomes, will be reviewed herein.

What serologic and imaging modalities predict a poor prognosis in RA?

Serologic markers

Rheumatoid factor (RF), the traditional serologic marker for RA, has a sensitivity of 60%–70% and a specificity of 80%–90% in patients who fulfill the ACR criteria for diagnosis and has been correlated with aggressive and erosive RA.[20,21] Anti-CCP antibodies have been shown to have a much higher specificity of 98% but a lower sensitivity of 68%–80% in patients with diagnosed RA. Anti-CCP antibodies can be seen two to three years before the development of clinical symptoms of RA. These antibodies are especially helpful in diagnosing RA in patients with early RF-negative arthritis. Anti-CCP antibodies have a high predictive value for erosive RA and are clearly a marker of poor prognosis.[22,23] The acute phase reactants ESR and CRP have been shown to have a strong correlation with radiographic damage and long-term functional disability[13,24] and persistent elevations of these acute phase reactants are also poor prognostic markers.

Radiographic markers of early RA

The single best prognostic marker for the development of erosions is the presence of erosions.[13,25] Since management decisions in RA may well be based on the presence or absence of joint erosions, as radiographic progression has been correlated with increasing disability over time,[26] it is important to detect erosions as early as possible.

Although erosions can be seen early in the course of disease as noted previously, there can be a delay of 6 months to 1 year before erosions can be seen on a plain radiograph. Use of newer techniques, such as magnetic response imaging (MRI), although not yet validated in RA, may well improve the capability of detecting erosive RA early. Magnetic response imaging scans have been reported to detect erosions as early as 4 months after the onset of disease[27–30] and seem to provide a more precise picture of what is happening in joints, given the fact that bone marrow edema, synovitis, tendonitis, and erosions can be seen in far greater detail. Although MRI may well have many advantages for early diagnosis, the disadvantages include high cost, extended procedure times, the availability of a skilled radiologist trained in reading joint MRIs, and the lack of validation of this procedure as yet.

Ultrasound has a well-established use, especially in academic clinics in Europe, and has been found to be superior in detecting synovitis early in disease compared with MRI,[31–35] Ultrasound has obvious advantages of being noninvasive, lacking nonionizing radiation, and low expense, which makes it a useful tool in assessing inflammation of the joints and joint damage. The disadvantage is that there is an extensive training period for readers of ultrasound and that the technique and interpretation is highly operator dependent. Long-term studies, however, are still required to validate the usefulness of MRI and ultrasonography in assessing RA patients whether for earlier diagnosis, progression of disease, or response to therapy.[36]

Clinical trial evidence for early, aggressive therapy of RA

Efficacy of traditional DMARDs either alone or in combination in early RA

Treatments of early RA with conventional DMARDs such as MTX, sulfasalazine (SSZ), hydroxychloroquine (HCQ), cyclosporine (CYC), and gold therapy have been shown to be beneficial with respect to improvement in the signs and symptoms, patient function, prevention of disability, cost-effectiveness, and reduction in X-ray progression to some extent.[37–39]

Early versus delayed use of SSZ or HCQ in early RA

The effect of early versus delayed treatment with DMARDs on disease outcome in patients with RA was investigated in an early arthritis clinic in which patients were seen within two weeks of referral.[19,40,41] A diagnosis of definite or probable RA was made by 4 weeks and therapy was started. There were two groups of patients: (1) those seen in the early 1990s when patients were treated as was customary for the time with the initial use of nonsteroidal anti-inflammatory drugs (NSAIDs) and then, after several months (median lag time for starting DMARD treatment approximately 120 days), HCQ or SSZ was introduced if the patient continued to have disease activity; and (2) those seen in the late 1990s when the treatment paradigm shifted to earlier institution of DMARDs and patients were treated with HCQ or SSZ by 4 weeks of referral. The primary outcome measures of the analysis were radiographic joint damage measured by the van der Heijde modified total Sharp score (mTSS)[42] and change in patient function as measured by the Health Assessment Questionnaire (HAQ).[43]

The median disease activity score (DAS)[44] improved in the early vs late treatment group from approximately 3.3 in both groups to 2.5 and 2.8, respectively ($P < 0.05$). The HAQ improved in both groups by 2 years but only modestly (P not significant). Radiographic joint damage assessed at 6

months was similar in both groups with a median mTSS of 3.5 in both. At 2 years, however, patients treated early had virtually no progression while those treated with DMARDs after a delay of approximately 4 months had a median mTSS of 10 ($P < 0.001$). Patients who were RF-positive and were in the delayed treatment group had a greater median increase in mTSS compared with the early treatment group.

The patients in both groups were followed for a total of 4 years to study progression of radiological joint damage.[19] There was less radiographic damage over this time in the early treatment group at 1.3 mTSS/year than the delayed group at 2.5 mTSS/year ($P = 0.03$). From year 1 to 4 the rate of progression was similar between the two groups. This study demonstrated that early treatment is effective in slowing radiographic progression but that it is never too late to interfere with progression, and thus modified the "window of opportunity" hypothesis to the "time of optimum therapy."[19]

Early, aggressive, sustained use of MTX, SSZ, HCQ, and prednisolone versus SSZ monotherapy in early RA

The Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) trial[45,46] also investigated the impact of the delay from the onset of symptoms to the institution of DMARDs as well as combination DMARD versus monotherapy DMARD in patients with early RA who had less than 2 years of disease duration, with the primary endpoint being the induction of ACR remission[47] (modified by allowing drug therapy and excluding fatigue) and the secondary endpoints being the number of patients obtaining an ACR50 (i.e., 50% response) by 2 years; the progression of radiographic joint damage was assessed using the Larsen method.[48] The patients were stratified by the presence of HLA-DRB1 alleles (the shared epitope) and were initially treated either with a combination of SSZ 500 mg twice a day, MTX 7.5 mg/week, HCQ 300 mg/day, and prednisolone 5 mg/day in the combination therapy group, or SSZ 1 g twice a day with or without prednisolone up to 10 mg/day in the monotherapy group. If the patient did not achieve 50% improvement then in the combination group the MTX could be adjusted up to 15 mg/week (by month 9) and the prednisolone to 10 mg/day, and in the monotherapy group the SSZ could be increased to 3 g/day. If the patient reached a remission in the combination group then the MTX and prednisolone could be tapered and discontinued. If the patient had an adverse event from one of the DMARDs, then a number of substitutions were allowed.

There was a median delay of approximately 6 months in the institution of DMARDs in either group. In both arms, patients were further divided into those with a short (<4 months) or long (>4 months) delay in institution of DMARDs.

At 2 years, 37% of the combination therapy arm was in remission compared with 18% of the single treatment arm ($P = 0.003$). In the single therapy arm, delay in initiation of therapy was highly significant in predicting less remission at 2 years.

The radiographic data showed an increase in the Larsen score in the single drug-treated arm from a score of 2 at baseline to 12 at 2 years compared with the combination-treated arm in which the Larsen score increased from a baseline of 2 to a score of 4 at 2 years. Thus there are two important conclusions reached from this study: (1) patients with early, active RA should be treated with combination DMARD therapy rather than monotherapy in order to increase their chances of obtaining clinical remission, and (2) combination DMARD therapy limits radiographic progression better than monotherapy but does not stop progression.

Induction therapy of combination SSZ, MTX, and prednisolone versus SSZ monotherapy in early RA

The Combinatietherapie Bij Rheumatoide Arthritis (COBRA) trial was undertaken to compare the early introduction of intensive combination DMARD therapy with DMARD monotherapy in patients with early RA who were DMARD naïve.[49,50] The trial was a multicenter, randomized, double-blind, controlled trial of 56 weeks' duration in which initial combination therapy included SSZ titrated up to 2 g/day by 3 weeks, MTX 7.5 mg/week for 40 weeks and then tapered to 0 over the next 6 weeks, and prednisolone initially 60 mg a day tapered to 7.5 mg a day by week 6 and then discontinued by week 34, was compared with SSZ monotherapy titrated to 2 g/day over 3 weeks and maintained for 56 weeks. The primary endpoint of the study was the "pooled index," which was a weighted score of five disease activity measures including tender joints count, physician global assessment of disease status, grip strength, ESR, and McMaster Toronto arthritis questionnaire,[51] and radiographic progression measured by the mTSS. Patients entered into the study had a median duration of RA of 4 months and active disease with the presence of ≥6 inflamed joints and at least two of the following three parameters: ≥9 tender joints, AM stiffness ≥45 min, and an ESR > 28.

Patients on combination therapy showed a significant improvement in disease activity early on, and at 28 weeks the efficacy as measured by the "pooled index" of the combination group was 1.4 versus 0.8 in the monotherapy group ($P < 0.0001$). However, by week 56, when the steroids and MTX had been discontinued, the difference in clinical efficacy was not different between the two groups (1.1 versus 0.9; P not significant), indicating that the improvement in clinical response required continuation of the combination therapy.

The analysis of radiographic progression showed that the mTSS increased significantly more in the SSZ monotherapy group in the first 28 weeks compared with the combination group (4 versus 1; $P < 0.0001$) and from week 28 to 56 (2.5 versus 1; $P = 0.04$). The differences in the rate of radiographic progression disappeared after week 56.

The patients were followed in an open study for a total of 5 years in order to examine differences in disease activity, radiologic damage, rate of radiographic progression, and

functional capacity between the two original groups, even though during the follow-up period the patients' RA medication could be adjusted as necessary by their own physician without protocol-defined changes.[50] Once treatment with corticosteroids and MTX was discontinued, there were no statistically or clinically significant differences between the original combination and the SSZ monotherapy treatment groups with respect to the HAQ score and disease activity at 5 years. In both groups the mTSS score increased significantly over time from about 5 to 25 in the combination group and from around 8 to 45 in the SSZ monotherapy group. After 5 years, the mean difference in the mTSS was approximately 35% lower in the combination-treated group in spite of the fact that both groups were treated similarly in the last 4 years of the study.

This study would seem to indicate that the aggressive use of intensive, short-term combination treatment in early RA patients induces a sustained decrease in the rate of radiologic joint damage but, unless aggressive therapy is maintained, significant clinical and radiographic progression continues.

Combination of MTX, CYC A and intra-articular (i.a.) corticosteroids versus SSZ monotherapy in early RA

A 48-week randomized study of 82 patients with RA of less than 12 months' duration of symptoms compared treatment with a combination of MTX (initially 7.5 mg/week titrated to 20 mg/week), CYC A (initially 1.5 mg/kg titrated to 4 mg/kg), and intermittent i.a. corticosteroids injected into all joints with synovitis versus SSZ (titrated up to 3 g/day) as well as i.a. corticosteroid injections as needed in the treatment of active "poor-prognosis" early RA.[52] "Poor-prognosis" RA was defined as patients who had a CRP $>$ 2 mg/dl, RF and HLA DRr1 or DR4 positivity, female sex, and HAQ $>$ 2. The primary endpoints were clinical improvement as assessed by ACR 20% and 50% response, as well as induction of remission as defined by the ACR criteria.[53] Secondary endpoints included the percentage of patients achieving a DAS28[54] and assessment of radiographic progression by mTSS.

Patients in the combination therapy group had a significantly more rapid improvement in the swollen and tender joint counts, CRP, ESR, and DAS28 scores in the first 12 weeks. At the primary endpoint of week 48, however, 58% of patients in the combination and 45% of patients in the SSZ monotherapy group achieved an ACR20 ($P = 0.36$) and 40% of the combination group versus 31% of SSZ obtained an ACR50 ($P = 0.57$). At 48 weeks 5 patients in the combination group and 4 in the SSZ group were in ACR remission.

Sixty-three percent of patients in the combination therapy group and 61% of the patients in the sulfasalazine monotherapy group had erosions at baseline. The mTSS increased 1.25 in the SSZ group and 1 in the combination group ($P = 0.28$) at week 48.

The results of this study would suggest that early aggressive therapy with the combination of aggressively dosed MTX, CYC, and i.a. corticosteroids could achieve a rapid reduction in disease activity when used as first-line therapy in patients with poor-prognosis RA compared with SSZ alone, but that continued therapy with this combination has no advantage over SSZ alone and that neither therapy effectively slowed radiographic progression sufficiently to prevent long-term disability.

Cyclosporine versus low-dose MTX in early RA

A randomized trial of CYC 3 mg/kg per day versus low-dose MTX 0.15 mg/kg per week in 103 patients was conducted to assess radiographic progression in patients with RA of less than 3 years' duration who were DMARD naïve.[55] Patients in both groups received daily prednisone at 7.5 mg. Patients had X-rays at baseline, year 1, year 2, and then every 6 months, which were scored by the Larsen method.

At 42 months 79% of the CYC and 82% of the MTX group ($P = 0.78$) had significant clinical improvement as measured by changes in AM stiffness, grip strength, tender and swollen joint counts, pain score, ESR, and CRP. Seventy-one percent of the patients in the CYC-treated group remained radiographically stable while 76% of patients in the MTX-treated group remained stable. This study would seem to indicate that the early treatment of active RA with a single DMARD may produce significant improvement in clinical parameters and slow radiographic progression.

Aggressive traditional DMARD mono or combination therapy guided by disease activity versus "routine" patient care

The Tight Control Of Rheumatoid Arthritis (TICORA) study was conducted to test the hypothesis that "tight" control of the clinical parameters of inflammation of RA can be achieved using standard DMARDs and that this will lead to improved clinical and radiologic outcomes in patients with early RA compared with routine outpatient care.[56] The study was a single blind, randomized controlled trial of 110 patients with RA of less than 5 years' duration, with median disease duration of 16 months, who were randomly assigned either into an intensive management group or a "routine" management group. The "tight control" group was seen monthly to review disease activity and have measurement of their disease activity as measured by DAS.[44] DAS scores of 3.6, 2.4, and 1.6 represented high, moderate, and low disease activity. If there were swollen joints they were injected with corticosteroids. Intramuscular (i.m.) steroids were given as "bridge therapy" during the first 3 months of a new DMARD. If the DAS was $>$ 2.4 after 3 months of a new DMARD, then there was a structured escalation of oral therapy by protocol. DMARD therapy was started with SSZ, then MTX plus SSZ plus HCQ, then MTX 25 mg/week, then SSZ 5 g/day, then the addition of prednisolone 7.5 mg/day, then MTX plus CYC, then leflunomide. No anti-TNF medications were used. The routine group was

seen every 3 months for review of their clinical status but no measure of DAS was performed and they were managed at the discretion of their attending rheumatologist for adjustment of their DMARDs and given i.a., i.m., and oral steroids without a predetermined protocol. The primary outcome measure was the difference in the two groups with respect to mean fall in DAS and the proportion of patients with EULAR good response;[57] DAS < 2.4 and fall in DAS from baseline by ≥ 1.2.

Sixty-seven percent of patients in the "tight control" group received combination DMARD compared with 6% in the routine treatment group. DMARDs given in the "tight control" group included MTX, SSZ, and HCQ with triple therapy in 51%, SSZ or MTX monotherapy in 30%, combination of MTX and CYC in 4%, and various other combinations of DMARDs in 15% of patients. Fifty-six percent of the "tight control" group finished on triple therapy; the mean MTX dose was 17.6 versus 13.6 mg/week in the routine group. i.a. steroid injections were given more frequently in the "tight control" group versus the routinely treated group.

EULAR good responses were seen in 80% of the "tight control" group versus 44% in the routine treatment group. Sixty-five percent of the "tight control" patients reached EULAR remission, 89% an ACR20, 82% an ACR50, and 70% an ACR70 versus 16%, 64%, 45%, and 18%, respectively in the routine treatment group ($P <$ 0.0001 for all comparisons). The mean DAS fell 3.5 versus 1.9 in the "tight control" and routine groups respectively ($P < 0.01$).

Radiographic outcomes were assessed in this study. There was progression of 8.5 Sharp units in the routine treatment group versus 4.5 units in the "tight control" group over the 18 months of the study ($P = 0.02$). Thus, the results of this study support the hypothesis that using intensive standard DMARD treatment in patients with early RA with therapy modified by a pre-determined therapeutic response (DAS) results in significant improvement in clinical outcomes but with only minimal slowing of radiographic progression.

Aggressively dosed monotherapy MTX versus monotherapy with etanercept

The Etanercept in Early Rheumatoid Arthritis (ERA) trial[58,59] was a randomized, double-blind trial which enrolled 632 patients with active RA (defined as ≥ 10 swollen and ≥ 12 tender joints, ESR ≥ 28 mm/h or CRP of > 2 mg/dl, and morning stiffness ≥ 45 min) of less than 3 years, duration (median 11 months) who had to have either a positive RF and/or evidence of ≥ 3 bone erosions in the hands and/or feet. Patients were treated with aggressively dosed MTX starting at 7.5 mg/week with weekly dose escalation to a maximum of 20 mg/week if there were any swollen or tender joints, etanercept monotherapy 10 mg s.c. twice per week (BIW), or etanercept monotherapy 25 mg s.c. BIW.

The primary endpoint was clinical effectiveness, which was predefined as an increased area under the curve (AUC) of the ACRn at 12 months (defined as the lowest of the percentage improvement in tender and swollen joint counts and the median of patient and physician global assessment of disease activity, patient assessment of pain, improvement in the HAQ, and improvement in the CRP) and an assessment of differences in radiographic progression as measured by the mTSS; the secondary endpoints were disease activity assessed by response in the ACR20, ACR50, and ACR70. Radiographs of the hands, wrists, and feet were obtained at baseline, 6, 12, and 24 months.

There was a much more rapid response to therapy in both etanercept groups compared with the MTX group with statistically significant differences in the ACRN, ACR20, and ACR50 within the first few months. By 12 months there was no statistically significant difference in the ACR20 (72% vs 65% etanercept 25 mg BIW vs MTX), ACR50 (approximately 40% in etanercept 25 mg BIW and MTX), and ACR70 (20% vs 20% etanercept 25 mg BIW vs MTX). There was no statistically significant difference in radiographic progression as measured by change in the mTSS at 1 year with a mTSS progression of 0.8 in the etanercept 25 mg BIW group versus 1.3 in the MTX group ($P = 0.11$). By 2 years there was a statistically and clinically significant difference in the ACR20 (72% etanercept versus 59% MTX) but no significant changes in ACR50 or ACR70 between the two groups (ACR50 49% in the etanercept 25 mg BIW group versus 42% in the MTX group, and ACR70 29% in the 25 mg etanercept BIW group versus 24% in the MTX group). Radiographic progression was significantly less in the 25 mg BIW etanercept treated group as compared with the MTX group at 24 months, with the mean change in mTSS of 1.3 units and 3.2 units in the etanercept and MTX groups, respectively ($P = 0.001$). There was no progression of radiographic damage in 63% of the 25 mg etanercept group compared with 51% of the patients treated with MTX ($P = 0.017$).

At baseline all patients in this study had moderate disability with mean HAQ scores of 1.4–1.5 units. At 2 years, 55% of the etanercept 25 mg BIW group improved their HAQ score by at least 0.5 units versus 37% of patients in the MTX group ($P < 0.001$) while improvement in HAQ $\geq$ 1.0 was seen in 29% of the etanercept 25 mg BIW group and 25% of the MTX group (P not significant).

The ERA study was very important as it showed that the aggressive use of MTX of up to 20 mg per week produces significant improvement in clinical symptoms, radiographic progression, and patient function which is similar to etanercept monotherapy at 1 year, and that these improvements are maintained in some patients up to 2 years. An individual patient was more likely to have significant improvement in clinical symptoms and function with less radiographic progression with etanercept 25 mg BIW monotherapy compared with aggressively dosed MTX, particularly at 2 years.[59]

Early versus delayed therapy of RA with an anti-TNF-α: effects on patient function

Patients treated in the ERA trial[58] with etanercept 25 mg BIW with disease duration of less than 3 years were compared with patients with long-standing RA also treated with etanercept monotherapy at 25 mg BIW[60] in order to assess whether early intervention with etanercept was more effective in reducing disability (HAQ scores) compared with late initiation of therapy in RA.[61] The patients from the ERA trial had median disease duration of 11 months while the established RA group had a mean disease duration of 12 years. Both the early and late RA groups had rapid improvement in the HAQ scores. At 1 month the HAQ scores of the early RA group had improved by 36% compared with 26% in the late RA group ($P = 0.0046$). At 3 years, the HAQ score improved by 56% in early RA group compared with 39% in the late RA group ($P = 0.0016$). Twenty-six percent of the early RA group compared with 14% of the late RA patients achieved a HAQ score of zero ($P = 0.0095$).

The importance of this study was the demonstration that early treatment of RA is much more likely to prevent disability, as measured by the HAQ, than delay in therapy. Patients with late RA do improve, thus it is "Never too early and never too late" to treat RA, but early therapy is more effective.

Traditional DMARD monotherapy versus step-up DMARD therapy versus combination of traditional DMARDs versus combination of MTX and an anti-TNF-α in early RA

There has been much debate in recent years as to whether monotherapy DMARD therapy, step-up DMARD therapy, initial combination of DMARDs, or the initial use of aggressively titrated MTX plus an anti-TNF-α would be more likely to accomplish control of the symptoms of RA, prevent radiographic progression, and preserve patient function. A randomized, single-blinded trial of 508 patients with less than a 2-year history of RA, termed the BeST trial, was conducted to assess the clinical and radiological outcomes in these four treatment groups.[62] Patients in all groups were started on therapy as discussed below with a change of therapy according to protocol if they did not reach a DAS remission (DAS < 1.6) at defined time points. Patient groups were as follows: (1) sequential monotherapy initially with MTX 15 mg/week, then MTX 25 mg/week, then SSZ 3 g/day, then leflunomide 20 mg/day, and then MTX 25 mg/week in combination with infliximab 3 mg/kg week 0, 2, 6 and then each 8 weeks if they had not reached a DAS remission; (2) step-up therapy initially with MTX as in group 1 and then the addition of SSZ followed by the addition of HCQ 400 mg/day, then the addition of prednisone 7.5 mg/day if they had not reached a DAS remission; (3) step-down therapy with MTX plus SSZ plus prednisone as in the COBRA trial, followed by MTX 25 mg per week plus SSZ plus prednisone, followed by MTX plus cyclosporine plus prednisone, followed by MTX plus infliximab 3 mg/kg as above, followed by MTX plus infliximab 6 mg/kg as above if they had not obtained a DAS remission; (4) initial therapy with MTX 25 mg/week plus infliximab 3 mg/kg, followed by increases of the infliximab to 6 mg/kg, then 7.5 mg/kg, then 10 mg/kg, then a switch to SSZ 2 g/day, then leflunomide if the patient had not reached a DAS remission. Patients in group 4, by protocol, had to discontinue infliximab if they reached a DAS remission and maintained this for 3 months. As the study has only been presented in abstract form, it is somewhat difficult to interpret the results. What is clear is that at both 1 and 2 years of therapy, patients in groups 3 and 4 had superior outcomes to patients in groups 1 and 2 in that they had more rapid improvement in clinical signs and symptoms, lower HAQ scores, and less radiographic progression (TSS increase of 2 in groups 1 and 2 versus 1 in groups 3 and 4; $P < 0.001$). It is difficult to understand whether there is a difference between group 3 and 4 as 72% of patients in group 4 never had to escalate therapy as opposed to 58% in group 3 and 33% and 30% of groups 1 and 2, respectively.

Thus, this study underscores the fact that the use of initial combination therapy is more effective then treatment with DMARD monotherapy or step-up DMARD therapy. What is not yet clear is whether COBRA therapy will be as effective as combination MTX and an anti-TNF-α over the long term with respect to clinical and radiographic progression.

Aggressive MTX versus combination aggressive MTX and an anti-TNF-α

The ASPIRE study was a randomized, double-blind trial conducted to compare the efficacy of combination therapy of MTX and infliximab with MTX monotherapy in patients with early RA with less than 3 years of disease.[63] One thousand and forty-nine patients with median disease duration of 7 months were randomized into three groups: (1) MTX plus placebo, (2) MTX plus 3 mg/kg infliximab, and (3) MTX plus 6 mg/kg infliximab. The MTX dose was escalated rapidly to 20 mg/week as in the ERA trial discussed above, and infliximab or placebo infusions then given at weeks 0, 2, 6, and then every 8 weeks. The primary clinical endpoint of the study was the ACR-n improvement from baseline to 54 weeks and the primary radiographic endpoint was the change from baseline to week 54 in the mTSS.[42] Secondary endpoints included improvement in the ACR20, 50, and 70 responses, DAS28, HAQ, and serum levels of acute-phase reactants.

The median improvement in the ACR-n at week 54 was 26%, 39%, and 47% in the MTX monotherapy, infliximab 3 mg/kg plus MTX, and infliximab 6 mg/kg plus MTX groups, respectively ($P < 0.001$ between MTX monotherapy group versus either of the infliximab groups). The ACR20 response at week 54 was 54%, 63% ($P = 0.028$), and 66% ($P = 0.001$) in the placebo plus MTX, MTX plus infliximab 3 mg/kg, and MTX plus infliximab 6 mg/kg groups, respectively; the ACR50 responses were 32%, 46%

($P < 0.001$), and 50% ($P < 0.001$) in the MTX plus placebo, MTX plus infliximab 3 mg/kg, and MTX plus infliximab 6 mg/kg groups, respectively, and ACR70 responses were 21%, 33% ($P = 0.002$), 37% ($P < 0.001$) in the MTX plus placebo, MTX plus infliximab 3 mg/kg, and MTX plus infliximab 6 mg/kg groups, respectively. The DAS28 improvement was −2.0 for MTX monotherapy, −2.7 for combination infliximab 3 mg/kg and MTX ($P = 0.003$), and −3.2 for combination infliximab 6 mg/kg and MTX ($P < 0.001$), with 31% of the 6 mg/kg group reaching remission versus 15% of the MTX monotherapy group ($P < 0.001$). Improvements in HAQ score from weeks 30 to 54 were statistically superior as well with either the 3 mg/kg group ($P = 0.03$) or the 6 mg/kg group ($P = 0.001$), with absolute decreases in the HAQ during this time period of 0.75, 0.784, and 0.792 in the three groups, respectively. The mean change in the van der Heijde modified TSS was 3.7, 0.4, and 0.5 ($P < 0.001$ for each comparison) in the in the MTX plus placebo, MTX plus infliximab 3 mg/kg, and MTX plus infliximab 6 mg/kg groups, respectively.

The ASPIRE study was the first study which conclusively showed that the combination of an anti-TNF-α in combination with aggressively dosed MTX is superior to aggressively dosed MTX alone in patients with early RA naïve to MTX with respect to clinical symptoms, radiographic progression and maintenance of function, and that the depth of response with the combination is impressive as more than 50% of patients who reached an ACR20 with the combination also reached an ACR70. This trial was also the first study that conclusively demonstrated that the combination of aggressively dosed MTX and an effective dose of an anti-TNF-α significantly slows radiographic progression when compared with aggressively dosed MTX monotherapy in early RA.

Aggressively dosed MTX versus anti-TNF-α monotherapy versus combination of aggressively dosed MTX and anti-TNF-α in early RA

The PREMIER trial was a 2-year double-blind, randomized controlled study of 799 patients with active, early RA (as demonstrated by the presence of ≥8 swollen joints, ≥1 erosion on X-rays of the hands or feet, or +RF and an ESR ≥28 or CRP ≥1.5 mg/dl) of less than 3 years' duration (mean duration 0.7 years) in which aggressively dosed MTX monotherapy was compared with adalimumab monotherapy and the combination of aggressively dosed MTX and adalimumab.[64] The primary clinical endpoint was the difference in ACR50 response between the three groups, while the primary radiologic endpoint was the difference in inhibition of radiographic progression between the three groups as measured by the mTSS.

The ACR20, 50, and 70 response for the MTX monotherapy, adalimumab monotherapy, and the combination of the two therapies at 1 year was 63/54/73%, 46/52/62%, and 28/26/42%, respectively, which was both clinically and statistically significant ($P < 0.001$) for the combination group versus either monotherapy. The primary clinical outcome of a superior ACR50 response with the combination was clearly met ($P < 0.001$ versus either monotherapy). Thus, not only was the combination group superior at the ACR20 level, but more than half the patients who achieved an ACR20 also achieved an ACR70 with the combination. The clinical responses were maintained at 2 years. In addition, 43% of patients treated with the combination of aggressively dosed MTX and adalimumab obtained a DAS28 remission at 1 year versus 23% in the adalimumab monotherapy group and 21% in the MTX monotherapy group ($P < 0.001$).

The TSS increased by 0.8 units in the combination group in the first 6 months compared with 2.1 units in the adalimumab monotherapy and 3.5 units in the MTX monotherapy groups ($P < 0.001$ versus either monotherapy). At 52 weeks the combination group progressed by 1.3 units versus 3.0 and 5.7 units in the adalimumab and MTX monotherapy groups, respectively ($P < 0.001$ versus either monotherapy). At 2 years, the combination group progressed by a total of 1.9 units versus 5.5 and 10.4 units in the adalimumab and MTX monotherapy groups, respectively ($P < 0.001$ versus either monotherapy). Thus there was an approximately 80% retardation of progression of radiographic damage in the combination group versus the MTX monotherapy at 2 years. This was the first study which conclusively demonstrated the effectiveness of the combination of aggressively dosed MTX and an anti-TNF-α versus either monotherapy with respect to clinical, functional, and radiographic outcomes.

Discussion

The goal of this review is to examine the evidence for the early treatment of RA. Evidence-based medicine utilizes the results of research to make informed decisions on treatment of diseases.[65] The "gold standard" of evidence-based research is the randomized double-blind placebo-controlled trial.[66] There has been recent discussion in the literature about whether patients who qualify for clinical trials represent the typical patient seen in the practice of rheumatology, as there may be a selection bias for more severe disease which would make it easier to demonstrate statistical improvements in clinical trials.[67–70] In one study it was shown that approximately 42% of new patients who were MTX naïve, 31% of all patients who were MTX naïve, and 16% of all patients in an early RA database would have met criteria for the ERA trial.[69] The question is whether all patients with early RA should be treated aggressively with the combination of aggressively dosed MTX and an anti-TNF-α or whether one of the other protocols discussed in this paper should be instituted first.

The initial challenge in treating early RA is identifying these patients and early referral to a rheumatologist for evaluation and treatment. This can best be accomplished by educating the primary care physician to be able to recognize the symptoms and physical findings associated with early RA. Guidelines which may be of value have been published

for the early recognition and referral of patients with inflammatory arthritis.[71] The experience in early arthritis clinics shows that rheumatologists are often correct in their early assessments.[8,72–74] There is an emerging role in the use of ultrasound and MRI to assist in the diagnosis of early RA. Anti-CCP antibodies add additional help in diagnosing early undifferentiated polyarthritis.

The studies reviewed demonstrate that early treatment results in better outcomes clinically, radiographically, and functionally. Clearly, an individual patient may have an excellent response to any of the treatment regimens discussed above and these studies have not shown how to tailor therapy for an individual patient with early RA. Advances in gene chip array technology and proteomics in the future may help guide individual therapy.

It is very clear, however, that the most effective therapy for the treatment of early RA is the combination of aggressively dosed MTX plus an appropriate anti-TNF-α. Many more patients treated with this combination (no matter which anti-TNF-α was employed) reach an ACR70, a DAS remission, and a marked decrease in HAQ, suggesting much more function and marked slowing of radiographic progression.

The TICORA and FIN-RA-CO studies demonstrated that aggressive use of DMARDs in combination can be very effective clinically but will not slow radiographic progression to the extent seen with the anti-TNF-α agents in combination with MTX. The COBRA and BeST trials showed that combination DMARDs are superior to DMARD monotherapy but that radiographic progression continues at a more rapid rate than a combination of MTX and an anti-TNF-α. The COBRA and BeST trial (the COBRA arm) both demonstrated some slowing of radiographic progression, but in both studies there was discontinuation of the combination which may have affected radiographic progression.

What we do not know is whether early intervention with anti-TNF therapy in combination with MTX is superior to combination DMARD which is maintained versus methotrexate monotherapy, which hopefully will be answered in future trials. Another unanswered question is whether aggressive treatment of very early RA will induce a remission that can be maintained when therapy is discontinued.

Conclusions

Current evidence strongly suggests that the combination of aggressively dosed MTX and a TNF-α inhibitor is the most effective combination in our current armamentarium to significantly improve clinical, radiographic, and functional outcomes in patients with early RA.

References

1. MacGregor A, Silman AJ. Rheumatology. 3rd ed. Phildelphia: Elsevier Science; 2003.
2. Yelin E, Wanke LA. An assessment of the annual and long-term direct costs of rheumatoid arthritis: the impact of poor function and functional decline. Arthritis Rheum 1999;42(6):1209–18.
3. Birnbaum HG, Barton M, Greenberg PE, Sisitsky T, Auerbach R, Wanke LA et al. Direct and indirect costs of rheumatoid arthritis to an employer. J Occup Environ Med 2000;42(6):588–96.
4. Albers JM, Kuper HH, Van Riel PL, Prevoo ML, van't Hof MA, van Gestel AM et al. Socio-economic consequences of rheumatoid arthritis in the first years of the disease. Rheumatology (Oxford) 1999;38(5):423–30.
5. Young A, Dixey J, Cox N, Davies P, Devlin J, Emery P et al. How does functional disability in early rheumatoid arthritis (RA) affect patients and their lives? Results of 5 years of follow-up in 732 patients from the Early RA Study (ERAS). Rheumatology (Oxford) 2000;39(6):603–11.
6. Young A, Dixey J, Kulinskaya E, Cox N, Davies P, Devlin J et al. Which patients stop working because of rheumatoid arthritis? Results of five years' follow up in 732 patients from the Early RA Study (ERAS). Ann Rheum Dis 2002;61(4):335–40.
7. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315–24.
8. van der Horst-Bruinsma IE, Speyer I, Visser H, Breedveld FC, Hazes JM. Diagnosis and course of early-onset arthritis: results of a special early arthritis clinic compared to routine patient care. Br J Rheumatol 1998;37(10):1084–8.
9. Young A. Short-term outcomes in recent-onset rheumatoid arthritis. Br J Rheumatol 1995;34 Suppl 2:79–86.
10. Chehata JC, Hassell AB, Clarke SA, Mattey DL, Jones MA, Jones PW et al. Mortality in rheumatoid arthritis: relationship to single and composite measures of disease activity. Rheumatology (Oxford) 2001;40(4):447–52.
11. Gabriel SE, Crowson CS, Kremers HM, Doran MF, Turesson C, O'Fallon WM et al. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. Arthritis Rheum 2003; 48(1):54–8.
12. Fuchs HA, Kaye JJ, Callahan LF, Nance EP, Pincus T. Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. J Rheumatol 1989;16(5):585–91.
13. Wolfe F, Sharp JT. Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. Arthritis Rheum 1998;41(9):1571–82.
14. Hulsmans HM, Jacobs JW, van der Heijde DM, van Albada-Kuipers GA, Schenk Y, Bijlsma JW. The course of radiologic damage during the first six years of rheumatoid arthritis. Arthritis Rheum 2000;43(9):1927–40.
15. van der Heijde DM, Van Leeuwen MA, Van Riel PL, van de Putte LB. Radiographic progression on radiographs of hands and feet during the first 3 years of rheumatoid arthritis measured according to Sharp's method (van der Heijde modification). J Rheumatol 1995;22(9):1792–96.
16. Bukhari MA, Wiles NJ, Lunt M, Harrison JB, Scott DG, Symmons DP et al. Influence of disease-modifying therapy on radiographic outcome in inflammatory polyarthritis at five years: results from a large observational inception study. Arthritis Rheum 2003; 48(1):46–53.
17. Stenger AA, Van Leeuwen MA, Houtman PM, Bruyn GA, Specrsra F, Barendsen BC et al. Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. Br J Rheumatol 1998;37(11):1157–63.
18. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. Rheumatology (Oxford) 2004;43(7):906–14.
19. van Aken J, Lard LR, le CS, Hazes JM, Breedveld FC, Huizinga TW. Radiological outcome after four years of early versus delayed treatment strategy in patients with recent onset rheumatoid arthritis. Ann Rheum Dis 2004;63(3):274–9.
20. van Boekel MA, Vossenaar ER, van den Hoogen FH, van Venrooij WJ. Autoantibody systems in rheumatoid arthritis: specificity, sensitivity and diagnostic value. Arthritis Res 2002;4(2):87–93.
21. Schellekens GA, Visser H, de Jong BA, van den Hoogen FH, Hazes JM, Breedveld FC et al. The diagnostic properties of rheu-

matoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum 2000;43(1):155–63.
22. Jansen LM, van Schaardenburg D, van der Horst-Bruinsma I, van der Stadt RJ, de Koning MH, Dijkmans BA. The predictive value of anti-cyclic citrullinated peptide antibodies in early arthritis. J Rheumatol 2003;30(8):1691–5.
23. van Gaalen FA, Linn-Rasker SP, van Venrooij WJ, de Jong BA, Breedveld FC, Verweij CL et al. Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. Arthritis Rheum 2004;50(3):709–15.
24. Devlin J, Gough A, Huissoon A, Perkins P, Holder R, Reece R et al. The acute phase and function in early rheumatoid arthritis. C-reactive protein levels correlate with functional outcome. J Rheumatol 1997;24(1):9–13.
25. Dixey J, Solymossy C, Young A. Is it possible to predict radiological damage in early rheumatoid arthritis (RA)? A report on the occurrence, progression, and prognostic factors of radiological erosions over the first 3 years in 866 patients from the Early RA Study (ERAS). J Rheumatol Suppl 2004;69:48–54.
26. Kirwan JR. Links between radiological change, disability, and pathology in rheumatoid arthritis. J Rheumatol 2001;28(4):881–6.
27. Benton N, Stewart N, Crabbe J, Robinson E, Yeoman S, McQueen FM. MRI of the wrist in early rheumatoid arthritis can be used to predict functional outcome at 6 years. Ann Rheum Dis 2004;63(5):555–61.
28. McQueen FM, Stewart N, Crabbe J, Robinson E, Yeoman S, Tan PL et al. Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals a high prevalence of erosions at four months after symptom onset. Ann Rheum Dis 1998;57(6):350–6.
29. McQueen FM, Stewart N, Crabbe J, Robinson E, Yeoman S, Tan PL et al. Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals progression of erosions despite clinical improvement. Ann Rheum Dis 1999;58(3):156–63.
30. McQueen FM, Benton N, Crabbe J, Robinson E, Yeoman S, McLean L et al. What is the fate of erosions in early rheumatoid arthritis? Tracking individual lesions using x rays and magnetic resonance imaging over the first 2 years of disease. Ann Rheum Dis 2001;60(9):859–68.
31. Taylor PC, Steuer A, Gruber J, Cosgrove DO, Blomley MJ, Marster PA et al. Comparison of ultrasonographic assessment of synovitis and joint vascularity with radiographic evaluation in a randomized, placebo-controlled study of infliximab therapy in early rheumatoid arthritis. Arthritis Rheum 2004;50(4):1107–16.
32. Ostergaard M, Wiell C. Ultrasonography in rheumatoid arthritis: a very promising method still needing more validation. Curr Opin Rheumatol 2004;16(3):223–30.
33. Rau R, Simianer S, Van Riel PL, van de Putte LB, Kruger K, Schattenkirchner M et al. Rapid alleviation of signs and symptoms of rheumatoid arthritis with intravenous or subcutaneous administration of adalimumab in combination with methotrexate. Scand J Rheumatol 2004;33(3):145–53.
34. McQueen F, Lassere M, Edmonds J, Conaghan P, Peterfy C, Bird P et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Summary of OMERACT 6 MR Imaging Module. J Rheumatol 2003;30(6):1387–92.
35. Ostergaard M, Peterfy C, Conaghan P, McQueen F, Bird P, Ejbjerg B et al. OMERACT Rheumatoid arthritis magnetic resonance imaging studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. J Rheumatol 2003;30(6):1385–6.
36. Backhaus M, Burmester GR, Sandrock D, Loreck D, Hess D, Scholz A et al. Prospective two year follow up study comparing novel and conventional imaging procedures in patients with arthritic finger joints. Ann Rheum Dis 2002;61(10):895–904.
37. Quinn MA, Conaghan PG, Emery P. The therapeutic approach of early intervention for rheumatoid arthritis: what is the evidence? Rheumatology (Oxford) 2001;40(11):1211–20.
38. Goldbach-Mansky R, Lipsky PE. New concepts in the treatment of rheumatoid arthritis. Annu Rev Med 2003;54:197–216.
39. Quinn MA, Green MJ, Marzo-Ortega H, Proudman S, Karim Z, Wakefield RJ et al. Prognostic factors in a large cohort of patients with early undifferentiated inflammatory arthritis after application of a structured management protocol. Arthritis Rheum 2003;48(11):3039–45.
40. Lard LR, Boers M, Verhoeven A, Vos K, Visser H, Hazcs JM et al. Early and aggressive treatment of rheumatoid arthritis patients affects the association of HLA class II antigens with progression of joint damage. Arthritis Rheum 2002;46(4):899–905.
41. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001;111(6):446–51.
42. van der Heijde DM. Plain X-rays in rheumatoid arthritis: overview of scoring methods, their reliability and applicability. Baillieres Clin Rheumatol 1996;10(3):435–53.
43. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23(2):137–45.
44. van der Heijde DM, van 't Hof M, Van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993;20(3):579–81.
45. Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela M et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 1999;353(9164):1568–73.
46. Mottonen T, Hannonen P, Korpela M, Nissila M, Kautiainen H, Ilonen J et al. Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. Arthritis Rheum 2002;46(4):894–8.
47. Pinals RS, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24(10):1308–15.
48. Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta Radiol Diagn (Stockh) 1977;18(4):481–91.
49. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350(9074):309–18.
50. Landewe RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46(2):347–56.
51. Tugwell P, Bombardier C, Buchanan WW, Goldsmith CH, Grace E, Hanna B. The MACTAR Patient Preference Disability Questionnaire – an individualized functional priority approach for assessing improvement in physical disability in clinical trials in rheumatoid arthritis. J Rheumatol 1987;14(3):446–51.
52. Proudman SM, Conaghan PG, Richardson C, Griffiths B, Green MJ, McGonagle D et al. Treatment of poor-prognosis early rheumatoid arthritis. A randomized study of treatment with methotrexate, cyclosporin A, and intraarticular corticosteroids compared with sulfasalazine alone. Arthritis Rheum 2000;43(8):1809–19.
53. Pinals RS, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24(10):1308–15.
54. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38(1):44–8.
55. Drosos AA, Voulgari PV, Katsaraki A, Zikou AK. Influence of cyclosporin A on radiological progression in early rheumatoid arthritis patients: a 42-month prospective study. Rheumatol Int 2000;19(3):113–8.
56. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364(9430):263–9.
57. van Gestel AM, Prevoo ML, van't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/

International League Against Rheumatism Criteria. Arthritis Rheum 1996;39(1):34–40.
58. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000;343(22):1586–93.
59. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum 2002;46(6):1443–50.
60. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130(6):478–86.
61. Baumgartner SW, Fleischmann RM, Moreland LW, Schiff MH, Markenson J, Whitmore JB. Etanercept (Enbrel) in patients with rheumatoid arthritis with recent onset versus established disease: improvement in disability. J Rheumatol 2004;31(8):1532–7.
62. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, van Zeben D, Kerstens PJS, Hazes JM, Zwinderman AH. Treatment strategies in early rheumatoid arthritis: clinical and radiological outcomes after 2 year follow-up of the BeST study (abstract). Proceedings of the American College of Rheumatology, San Antonio, USA; 2004.
63. St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004;50(11):3432–43.
64. Breedveld FC, Kavanaugh A, Cohen SB. Early treatment of rheumatoid arthritis (RA) with adalimumab (Humira) plus methotrexate vs. adalimumab alone or methotrexate alone: The PREMIER Study (abstract). Proceedings of the American College of Rheumatology, San Antonio, USA; 2004.
65. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996;312(7023):71–2.
66. Sackett DL. The competing objectives of randomized trials. N Engl J Med 1980;303(18):1059–60.
67. Pincus T, Sokka T. Clinical trials in rheumatic diseases: designs and limitations. Rheum Dis Clin North Am 2004;30(4):701–24, v–vi.
68. Pincus T, Sokka T. Should contemporary rheumatoid arthritis clinical trials be more like standard patient care and vice versa? Ann Rheum Dis 2004;63 (Suppl 2):ii32–9.
69. Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis. Arthritis Rheum 2003;48(2):313–8.
70. Sokka T, Pincus T. Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or american college of rheumatology criteria for remission. J Rheumatol 2003;30(6):1138–46.
71. Emery P, Breedveld FC, Dougados M, Kalden JR, Schiff MH, Smolen JS. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. Ann Rheum Dis 2002;61(4):290–7.
72. Wolfe F, Ross K, Hawley DJ, Roberts FK, Cathey MA. The prognosis of rheumatoid arthritis and undifferentiated polyarthritis syndrome in the clinic: a study of 1141 patients. J Rheumatol 1993;20(12):2005–9.
73. Tunn EJ, Bacon PA. Differentiating persistent from self-limiting symmetrical synovitis in an early arthritis clinic. Br J Rheumatol 1993;32(2):97–103.
74. Kim JM, Weisman MH. When does rheumatoid arthritis begin and why do we need to know? Arthritis Rheum 2000;43(3):473–84.