Combination Therapy for Rheumatoid Arthritis in the Era of Biologicals

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Abstract Early, aggressive disease management is critical for halting disease progression and joint destruction in patients with rheumatoid arthritis. Combination therapy with at least two disease-modifying antirheumatic drugs, such as methotrexate (MTX), sulfasalazine, or hydroxychloroquine, is often more effective than monotherapy in reducing disease activity. Biologic therapies represent more effective and tolerable treatment options that, when combined with MTX, have been shown to dramatically reduce inflammation, inhibit radiographic progression, and induce remission. Although several types of treatment strategies are used in clinical practice, the most aggressive approaches that target early disease have shown the most promise in reversing disease progression and reducing disease-related costs.

Key words combination therapy · disease-modifying antirheumatic drugs · joint destruction · rheumatoid arthritis · tumor necrosis factor antagonists

Introduction

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease that mainly affects the synovial joints. The disease has a worldwide prevalence of 1% and affects women and men disproportionately (~2:1, respectively) [1]. RA commonly affects people between the ages of 40 and 70 years, with incidence of the disease increasing with age [2].

The signs and symptoms and clinical course of RA can be extremely variable, ranging from mild, self-limiting arthritis to rapidly progressive disease that is associated with significant physical and psychosocial morbidity and premature mortality [2]. Joint destruction from synovitis can occur rapidly and early in the course of the disease. Erosion of the joints can be detected by magnetic resonance imaging as early as 4 months of symptom onset [3], and as many as 93% of patients will sustain radiographic damage within 2 years if left untreated [4]. Within 5–10 years of being diagnosed, one in two people with RA will be unable to work, and the remainder will have functional disability resulting in reduced earning capacity [5, 6].

Historically, RA has been treated using a multitiered “pyramid” strategy, beginning with symptom-relieving nonsteroidal anti-inflammatory drugs and/or corticosteroids, and subsequently with more potent disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX). However, the realization that radiographic progression and joint damage frequently occur early during the disease process [3, 4, 7, 8] has prompted calls for more aggressive treatment approaches, including the immediate use of DMARDs upon diagnosis and/or the combined use of multiple agents [9]. This is especially true for patients who present with multiple inflamed joints at the outset. In these patients, aggressive therapy at symptom onset is critical for reducing RA activity and for preventing disease progression and permanent structural damage. Lard et al. [10] have shown that a delay in initiating DMARD therapy by 4 months resulted in substantially more radiographic damage at 2 years compared with intervention within 15 days of referral. In addition, several combinations, including two or more traditional DMARDs, have been found to be more effective than monotherapy in reducing disease activity and slowing radiographic progression [11–17]. However, not all DMARD combinations have shown superiority over monotherapy and may, in fact, increase the incidence of adverse events and toxicity [18–21].

Advances in treatment and treatment strategies over the past decade have greatly revolutionized rheumatologic

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medicine and raised the bar for what is expected of RA treatments. Gone are the days where DMARD monotherapies of gold compounds, azathioprine, sulfasalazine, or hydroxychloroquine were routinely used in clinical practice. The advent of biologic agents offers safer, more effective, but more expensive therapeutic options for the management of RA over conventional DMARDs. Currently, two classes of biologic agents are approved for RA: tumor necrosis factor (TNF) inhibitors (etanercept, infliximab, and adalimumab) [22–24] and interleukin-1 receptor antagonists (IL-1Ra; anakinra) [25]. These agents neutralize specific cytokines that mediate the inflammatory process underlying RA pathogenesis and have been shown to significantly retard radiographic progression and improve the functional status of RA patients. Recent findings from clinical trials have demonstrated that more aggressive treatment approaches using biologic agents in combination with DMARDs, especially MTX, provided significantly greater benefits in controlling disease progression than DMARD therapy or biologic therapy alone [26–32].

In the new era of biologicals, combination therapy has shown great promise, and its utilization is expected to become a mainstay of RA therapy for years to come. This article describes evidence from randomized, controlled clinical trials of the efficacy of common combination therapies, including those with biologic agents, to control disease activity. The objective of this review is to evaluate strategies for combination therapy and of early, aggressive intervention, in terms of efficacy, safety, and cost effectiveness. Alternative treatment strategies are also reviewed.

Combination disease-modifying antirheumatic drug therapies

The major rationale for combination therapy is based on studies showing that incomplete control of inflammation in RA can lead to disease progression and unfavorable long-term outcome [17]. Therefore, by combining various agents with different mechanisms of action, it has become possible to target multiple inflammatory pathways that mediate the pathogenesis of RA, without necessarily increasing toxicity. Traditional approaches to combination therapy involve the use of DMARDs, such as cyclosporine, sulfasalazine, methotrexate, hydroxychloroquine, and leflunomide, in combination with each other or with non-DMARD agents.

Cyclosporine and methotrexate

The benefit of adding cyclosporine to stable MTX dosing was evaluated in patients with severe RA and an inadequate response to MTX [17]. Patients receiving cyclosporine plus MTX had a 25% improvement in both swollen ($P = 0.005$) and tender joint counts ($P = 0.02$) compared with MTX alone after 6 months of therapy. In addition, 48% receiving the combination achieved a 20% improvement in the American College of Rheumatology (ACR 20) response compared with 16% of patients receiving MTX alone. The combination of cyclosporine plus MTX also

elicited significant improvements in joint pain (23%, $P = 0.04$) and degree of disability (26%, $P < 0.001$) as measured by the Health Assessment Questionnaire (HAQ), compared with MTX alone. At least 25% improvement in tender joints was observed in 64% of patients receiving cyclosporine plus MTX, compared with 47% ($P = 0.033$) of patients receiving MTX alone. A greater proportion of patients in the combination group also achieved at least a 50% improvement in tender joints than MTX monotherapy (45% vs. 27%, respectively, $P = 0.023$). However, more patients receiving the combination withdrew because of adverse events (nine vs. five, respectively), and one patient died from potentially treatment-related causes. The incidence of adverse events, such as hypertrichosis, tremors, paresthesia, nausea, and mouth ulcers, was higher in the combination group.

Sulfasalazine, methotrexate, and prednisolone

In the Combinatietherapie Bij Reumatoide Artritis (COBRA) trial, triple therapy with sulfasalazine, MTX, and prednisolone was compared with sulfasalazine alone in patients with early (<2 years) RA [11]. Prednisolone was tapered off and discontinued after 28 weeks and MTX after 40 weeks. At 28 weeks, significantly more patients receiving combination therapy vs. sulfasalazine alone achieved ACR 20 (72 vs. 49%, respectively; $P = 0.006$) and ACR 50 (49 vs. 27%, respectively; $P = 0.007$) responses. Joint destruction progressed at a higher rate in patients receiving monotherapy compared with those receiving the triple combination. At 28 weeks, 13% of the sulfasalazine group vs. 31% ($P = 0.009$) of the combination group had stable radiographic damage scores [11]. However, the differences in clinical efficacy were no longer significant after the withdrawal of prednisolone. By week 56, radiographic damage scores were not significantly different between the two treatment groups.

Combination therapy was associated with significantly fewer withdrawals (8 vs. 29%; $P = 0.0008$) [11]; withdrawals as a result of lack of efficacy and adverse events were also lower in the group receiving combination therapy (8 vs. 25%) compared with sulfasalazine alone. However, combination therapy was associated with more frequent adverse events, such as infection, gastrointestinal complaints, and cardiovascular disorders.

Patients who participated in the COBRA trial were followed for an additional 4 years during which no treatment protocol was specified. At 5 years, patients in both groups had similar HAQ scores, but mean change per year in radiographic progression was 35% lower in patients receiving the combination treatment (Sharp scores 5.6 vs. 8.6; $P = 0.03$) [14]. These results suggest that the rate of progression established during early aggressive treatment was maintained despite a subsequent change in therapy.

Sulfasalazine, methotrexate, and hydroxychloroquine

In three trials evaluating the combination of sulfasalazine, MTX, and hydroxychloroquine, the triple combination was

superior to combinations involving two of the DMARDs and to individual agents alone.

O'Dell et al. [15] evaluated the efficacy and safety of the triple combination vs. MTX alone for a period of 2 years in patients unresponsive to at least one DMARD. At 9 months, significantly more patients receiving the combination therapy achieved a Paulus 50 response (77%) compared with sulfasalazine plus hydroxychloroquine (40%, $P = 0.003$) or MTX alone (33%, $P < 0.001$). This response was maintained for the remainder of the 2 years. Adverse events leading to discontinuations were highest (19%) in the MTX monotherapy group, followed by 9% in the sulfasalazine plus hydroxychloroquine group, and 10% in the triple therapy group.

In a second trial, O'Dell et al. [16] evaluated the benefits of the triple therapy compared with either MTX plus hydroxychloroquine or MTX plus sulfasalazine over a 2-year period in patients with duration of RA >6 months. Of the three regimens, the triple combination resulted in the greatest improvement, with an ACR 20 response of 78 vs. 60% ($P = 0.05$) and 49% ($P = 0.02$) for MTX plus hydroxychloroquine and MTX plus sulfasalazine, respectively. ACR 50 responses followed a similar trend for the triple combination group vs. the MTX plus sulfasalazine group ($P = 0.005$), but not between the triple combination and the MTX plus hydroxychloroquine ($P < 0.10$) treatment arm. Withdrawals as a result of treatment-related adverse events were similar in all three groups, with discontinuation rates of 7% in the triple combination group and 9% each in the MTX plus hydroxychloroquine and MTX plus sulfasalazine groups.

The Finnish Rheumatoid Arthritis Combination Therapy trial also provides data on the benefit of combination therapy in patients with early, clinically active RA (<2 years) [12]. In an open-label trial, patients were randomized to triple therapy or sulfasalazine, with or without prednisolone, for 2 years. Although treatment became unrestricted after 2 years, it was optimized toward the goal of remission. At 2 years, 40% of patients receiving combination therapy were in clinical remission, as defined by the ACR criteria [33], vs. 18% ($P < 0.009$) receiving monotherapy. However, by 5 years, remission rates were statistically insignificant between the groups (28 and 22%, respectively, $P = 0.41$).

Radiographic improvement was seen in the combination therapy as well. Median Larsen scores were 4 for the combination therapy group and 12 for the sulfasalazine (with or without prednisolone) group ($P = 0.005$) [12]. At 5 years, the damage was still significantly lower with the combination therapy ($P = 0.001$). During the first 2 years, discontinuations because of adverse events were comparable for both groups, with treatment withdrawals occurring 23 times in the combination group and 22 times in the sulfasalazine group. Gastrointestinal distress was the most commonly reported adverse event for both groups. There were no significant differences in the frequency of serious adverse events between the two groups during the period between years 2 and 5, with 9% reported in the combination group and 8% reported in the sulfasalazine group. Serious adverse events included multiple myeloma, pros-

tate carcinoma, pneumonia, nonspecific pain, myocardial infarction, and staphylococcal septicemia.

Leflunomide and methotrexate

In patients whose RA was insufficiently controlled with MTX alone, the addition of leflunomide provided significant clinical improvement [13]. At 24 weeks, 46% of patients receiving leflunomide plus MTX achieved an ACR 20 response, compared with only 20% for patients receiving MTX alone ($P < 0.001$). However, abnormal liver function was more common in the combination group than in patients receiving monotherapy. Elevated liver enzyme levels that were greater than three times the upper limit of normal occurred more frequently at any time during the study in the leflunomide plus MTX group than in the MTX group (3.8 vs. 0.8% for alanine aminotransferase levels and 1.5 vs. 0.8% for aspartate aminotransferase levels, respectively). However, all elevated levels exceeding 1.2 times the upper limit of normal in the leflunomide plus MTX group normalized to 1.2 times the upper limit of normal or less during the study or after week 24. It should be noted that mild elevations of liver enzymes are common and may be induced by alcohol consumption, but these elevations typically do not exceed two to three times normal values and are only temporary. In contrast, prolonged and highly elevated liver enzymes (more than three times the normal values) may lead to serious liver test abnormalities and irreversible liver damage.

Other adverse events occurring more frequently in the combination group were diarrhea (25%), nausea (16%), headache (10%), dizziness (8%), and alopecia (6%). Because both leflunomide and MTX are associated with an increased incidence of severe liver damage, close monitoring is required for patients receiving this regimen.

Combinations of biologic and disease-modifying antirheumatic drug therapies

Early studies evaluating biologic therapies examined their effects on patients with an inadequate response to DMARDs, particularly MTX. Adding a biologic agent to existing DMARD therapy was found to significantly improve RA signs and symptoms, halt radiographic progression, and induce remission, as measured by the disease activity scoring method [6, 13, 26–31]. In general, addition of biologic therapy was not associated with an increase in treatment-related adverse events.

There are two major types of TNF biologic inhibitors approved for RA: soluble TNF receptors (etanercept) [22] and monoclonal antibodies against TNF (infliximab and adalimumab) [23, 24]. The IL-1 receptor antagonist anakinra [25] provides an additional option for patients with RA who have had inadequate response to DMARD therapy.

Etanercept

A 24-week trial evaluated the addition of etanercept to MTX in patients with active disease despite MTX therapy

[32]. Clinical response, as measured by the ACR criteria, was achieved by more patients receiving combination therapy than in patients receiving monotherapy with MTX. At 24 weeks, significantly higher ACR 20/50/70 response rates were observed for patients receiving etanercept plus MTX compared with those receiving MTX alone ($P < 0.001$; Fig. 1). Injection site reactions occurred more often in patients receiving combination therapy (42%) vs. those receiving MTX alone (7%) [32]. However, all injection site reactions were mild (erythema with or without itching, pain, or swelling) and most resolved without treatment, with none of the patients requiring suspension

of etanercept therapy. No patients withdrew because of treatment-related adverse events.

More recently, the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) compared the combination of etanercept plus MTX with etanercept monotherapy or MTX alone in patients with active RA despite therapy with a DMARD other than MTX [28]. After 1 year of therapy, significantly higher ACR 20/50/70 response rates were observed for the combination group (85/69/43%) than the MTX (75/48/19%) or etanercept group (76/48/24%) ($P < 0.05$). In addition, the proportion of patients achieving remission [disease activity score

Trial Treatment Arms	ACR Responses		
	ACR 20 (%)	ACR 50 (%)	ACR 70 (%)
Weinblatt et al, 1999 (24-Week Response)³²			
Etanercept 25 mg BIW + MTX	71	39	15
MTX	27	3	0
TEMPO (2-Year Response)³⁵			
Etanercept 25 mg BIW + MTX	86	71	49
Etanercept 25 mg BIW	75	54	27
MTX	71	42	21
ASPIRE (54-Week Response)³⁹			
Infliximab 6 mg/kg + MTX	66	50	37
Infliximab 3 mg/kg + MTX	62	46	33
MTX	54	32	21
ATTRACT (2-Year Response)²⁹			
Infliximab 10 mg/kg + MTX (q8 weeks)	48	36	20
Infliximab 10 mg/kg + MTX (q4 weeks)	40	20	10
Infliximab 3 mg/kg + MTX (q8 weeks)	42	21	10
Infliximab 3 mg/kg + MTX (q4 weeks)	40	30	21
MTX	16	6	1
ARMADA (24-Week Response)³¹			
Adalimumab 80 mg eow + MTX	66	43	19
Adalimumab 40 mg eow + MTX	67	55	27
Adalimumab 20 mg eow + MTX	48	32	10
MTX	15	8	5
DE019 Study (52-Week Response)^{44,45}			
Adalimumab 40 mg eow + MTX	59	42	23
Adalimumab 20 mg eow + MTX	55	38	21
MTX	24	10	5
PREMIER (2-Year Response)⁴²			
Adalimumab 40 mg eow + MTX	-	59	47
Adalimumab 40 mg eow	-	37	27
MTX	-	43	28
Cohen et al, 2002 (24-Week Response)²⁶			
Anakinra 2 mg/kg daily + MTX	35	17	7
Anakinra 1 mg/kg daily + MTX	42	24	10
Placebo	23	4	0
990145 Study (24-Week Response)⁴⁶			
Anakinra 100 mg daily + MTX	38	17	6
Placebo	22	8	2

BIW = twice weekly; q8 weeks = every 8 weeks; q4 weeks = every 4 weeks; eow = every other week

Fig. 1. American College of Rheumatology response rates of biologic agents + methotrexate combination therapy vs. monotherapy: results from clinical trials of etanercept, infliximab, adalimumab, and anakinra.

(DAS) <1.6 [34] was similarly greater in the combination group (35%) vs. the MTX group (13%; $P = 0.05$) and etanercept group (16%; $P < 0.001$). The combination was also more efficacious than MTX or etanercept alone in improving functional disability (as measured by the HAQ) and retardation of radiographic progression [28]. At 52 weeks, 80% of patients receiving the combination showed no radiographic progression vs. 68 and 57% with etanercept and MTX monotherapy, respectively.

Comparable rates of ACR responses (Fig. 1) were sustained for up to 2 years favoring the combination of etanercept plus MTX, as were remission rates and HAQ improvement [35, 36]. When analyzed by disease duration, patients with early RA (<3 years duration) in the combination group had significantly higher mean percentage improvement in HAQ scores compared with MTX (62 vs. 42%; $P < 0.01$) [36]. The combination therapy group also showed significantly greater radiographic improvement compared with either monotherapy, with 78% of patients showing no radiographic progression vs. 68% of etanercept-treated patients and 60% of MTX-treated patients ($P < 0.05$) [37]. In several measures of disease activity (e.g., ACR 50 and DAS), etanercept monotherapy was significantly better than MTX after 2 years of therapy.

Discontinuations because of adverse events were comparable across all treatment groups (10% for the combination, 14% for MTX alone, and 11% for etanercept alone) at 1 year. Serious adverse events were reported in 8% of the combination group, 12% of the MTX group, and 11% of the etanercept group. Mild injection site reactions were more commonly reported for the combination (10%) and etanercept monotherapy (21%) groups than the MTX group (2%). No cases of tuberculosis, opportunistic infections, multiple sclerosis, or other central demyelinating diseases were reported. Three cases of carcinomas (one in each group) and one case each of breast cancer, rectal cancer, and melanoma in the etanercept group were reported. Etanercept monotherapy and combination therapy contin-

ued to be well tolerated at 2 years. No new safety findings were observed, and the combination therapy did not result in increased infections after 2 years of treatment.

The efficacy and safety of etanercept in early RA has also been evaluated in another post hoc analysis of patients with recent onset (mean duration of 1 year) vs. late disease (mean duration of 12 years) [38]. Patients with established RA had higher baseline HAQ scores ($P = 0.0004$) and C-reactive protein (CRP) levels ($P = 0.0005$) than patients with early disease. The improvements in HAQ scores were rapid in both groups (Fig. 2). However, the magnitude of the improvements in disability was greater in patients with early disease compared with patients with long-standing disease. The difference in mean percentage improvement was seen within 2 weeks of etanercept therapy ($P = 0.0074$) and was sustained throughout the duration of the study. At 3 years, more patients with early disease (26%) achieved a HAQ score of 0 than did patients with long-standing disease (14%; $P = 0.0095$). The minimal clinically important difference (MCID) from baseline in HAQ score, defined as a reduction of at least 0.22 units, was achieved by 66% of recent-onset RA patients vs. 52% for established RA patients ($P = 0.0094$) as early as week 2 and continuously increased over the observation period. At 3 years, 85% of the recent-onset RA group and 73% of the established RA group ($P = 0.0125$) achieved the MCID in HAQ.

Infliximab

The Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Early-Onset RA trial evaluated the efficacy of the combination of infliximab 3 or 6 mg/kg plus MTX and MTX alone in MTX-naïve patients with early active RA [39]. Although the differences between the number of ACR 20/50/70 responders in the combination groups were relatively small compared with the MTX group at 54 weeks ($P < 0.05$; Fig. 1), the number of patients showing radiographic benefit (defined as the

Fig. 2. Changes in the Health Assessment Questionnaire (HAQ) scores with etanercept treatment over 3 years in patients with early and long-standing rheumatoid arthritis. Scores range from 0 (no disability) to 3 (severely disabled). Adapted with permission from Baumgartner et al. [38].

change in van der Heijde modification of the total Sharp score) was significantly higher with either dose of infliximab plus MTX compared with MTX monotherapy ($P < 0.01$) [39]. Higher baseline erythrocyte sedimentation rate and CRP levels were associated with greater radiographic progression in patients receiving MTX but not in patients receiving combination therapy [40]. Withdrawals as a result of adverse events were more frequent in the infliximab plus MTX groups (10%) than the MTX group (3%). Mild infusion reactions were more commonly reported among patients receiving combination therapy (15–21%) compared with those receiving MTX alone (7%). Serious infections were also greater in the combination groups (5–6%) vs. MTX alone (2%), and four patients receiving infliximab therapy developed tuberculosis vs. none for MTX alone.

The addition of infliximab to existing MTX therapy was evaluated in another study, the Anti-TNF Therapy in Rheumatoid Arthritis (ATTRACT) trial [29, 30]. Patients were selected if they had an inadequate response to previous MTX treatment (at any previous dose of MTX). At 2 years, ACR 20/50/70 response rates were significantly higher for patients receiving infliximab plus MTX vs. those receiving MTX alone ($P < 0.001$; Fig. 1) [29, 30]. The addition of infliximab to existing MTX therapy also resulted in significant improvement in both HAQ scores (median improvement from baseline of 0.4 vs. 0.1 for MTX alone; $P \leq 0.006$) and SF-36 physical component summary scores (median improvement from baseline of 6.4 vs. 2.8 for MTX alone; $P \leq 0.011$). There were less joint damage progressions, as measured by the modified van der Heijde–Sharp scoring method, in patients receiving combination therapy (mean change from baseline in total radiographic score ranging from 1.14 to -0.42) than in patients receiving MTX alone (mean change from baseline of 12.59; $P < 0.001$) [30]. Significantly greater reductions in erosion score (mean change ranging from 0.50 to -0.57) and in joint-space narrowing score (mean change ranging from 0.77 to 0.10) from baseline to week 102 were also observed for the infliximab plus MTX group, compared with MTX alone (mean change in erosion score of 6.65 and in joint-space narrowing score of 5.91; $P < 0.001$). This was particularly pronounced among a subgroup of patients with early disease (≤ 3 years), in which the mean change from baseline in total erosion score for the infliximab plus MTX group (range 0.46 to -1.07) was greater than for the MTX group (mean change from baseline of 12.21; $P < 0.001$), thus indicating the benefits of early intervention [41].

After 52 weeks of therapy in the ATTRACT study, similar rates of discontinuations as a result of adverse events were observed across all groups (3–7% for infliximab plus MTX and 8% for MTX alone). Serious adverse events were also comparable between the various dosing groups of infliximab plus MTX (9–13%) and MTX alone (16%). The frequency of any infection requiring antimicrobials was significantly higher for the 10-mg/kg dose of infliximab (64–73%) than for MTX alone (40%). In addition, the frequency of mild infusion reactions was

higher in the infliximab plus MTX groups (16–20%) compared with MTX alone (10%). Antibodies to double-stranded DNA were reported in 16% of infliximab plus MTX-treated patients vs. none in the MTX group. One patient receiving the 10-mg/kg dose of infliximab developed drug-induced lupus syndrome. Between weeks 54 and 102 of the study, there was an increase of 13% in the percentage of patients with ANA in the infliximab plus MTX group and an increase of 5% in the percentage of patients with anti-dsDNA antibodies, compared with increases of 6 and 0%, respectively, for the MTX group. No additional cases of lupus-like syndrome were observed in the second year of the study, and only one patient experienced a lupus-like reaction during the entire study.

Adalimumab

The efficacy and safety of adding adalimumab to insufficient DMARD therapy was evaluated in three trials: the Anti-Tumor Necrosis Factor Research Study Program of the Monoclonal Antibody Adalimumab in Rheumatoid Arthritis (ARMADA) trial, the DE019 trial, and the PREMIER trial [31, 42–45].

In the ARMADA trial, addition of adalimumab 20, 40, and 80 mg every other week to existing MTX therapy was evaluated during the 24-week study (Fig. 1) [31]. Response to therapy was seen as early as 1 week after initiation of therapy, and the percentage of patients achieving a response increased from week 1 to 24 [31]. At week 24, significantly greater ACR 20/50/70 response rates were achieved by the groups receiving adalimumab plus MTX compared with those receiving MTX ($P < 0.001$). Clinical measures of improvements for fatigue (FACIT) and quality of life (SF-36) also favored adalimumab plus MTX over MTX alone. More patients in the adalimumab plus MTX group withdrew from the study because of adverse events (five patients) compared with the MTX group (two patients). The number of treatment-related adverse events was similar between the combination group and the MTX group. Higher rates of mild or moderate injection site reactions were reported for the adalimumab plus MTX group (15%) compared with the MTX group (3%). Antibodies to double-stranded DNA were reported in 3.9% of adalimumab plus MTX-treated patients vs. none in the MTX group.

The DE019 trial evaluated adalimumab 20 mg once a week and 40 mg every other week in combination with MTX in patients with an inadequate response to MTX [44, 45]. Similar to reported observations from the ARMADA trial, a significantly higher percentage of patients receiving adalimumab plus MTX achieved ACR 20/50/70 responses after 52 weeks of therapy, compared with patients receiving MTX alone (Fig. 1) [44, 45]. There was also significantly less radiographic progression (as measured by the change in Total Sharp Score) in the combination group than in the MTX monotherapy group (mean change ranging from 0.1 to 0.8 for combination group vs. 2.7 for MTX alone; $P \leq 0.001$). Similarly, reductions in HAQ scores were significantly greater in the combination group

than in the MTX monotherapy group (mean change ranging from -0.59 to -0.61 vs. -0.25 for MTX alone; $P \leq 0.001$). Discontinuations related to adverse events occurred in 10% of adalimumab-treated patients, compared with 7% for MTX-treated patients. However, significantly higher rates of serious infections were reported for the adalimumab combination group than for the MTX group (3.8 vs. 0.5%; $P \leq 0.02$). Rare cases of tuberculosis, histoplasmosis infection, herpes zoster, nonskin cancers, and central demyelinating illness were reported for adalimumab-treated patients. Injection site reactions were comparable for the adalimumab plus MTX (22–26%) and MTX monotherapy (24%) groups. At week 52, 12% of adalimumab-treated patients and 9% of MTX-treated patients were positive for ANA.

In a subsequent analysis, the effect of combination therapy was examined by disease duration [43]. Patients with early disease (<2 years) had a significantly greater benefit than patients with late disease (>2 years). In patients receiving adalimumab 40 mg every other week, ACR 20/50/70 responses were 70/59/41% in the group with early disease vs. 62/36/18% in patients with longstanding disease. HAQ improvement was also higher for combination-treated patients (0.79 vs. 0.57, respectively).

The PREMIER study compared the safety and efficacy of adalimumab 40 mg every other week plus MTX combination therapy with MTX alone or adalimumab alone in MTX-naïve patients with recent-onset RA [42]. At 2 years, ACR 50/70 responses were significantly higher in the combination group compared with either MTX ($P < 0.001$) or adalimumab ($P < 0.001$; Fig. 1). The proportion of patients achieving remission, as defined by a disease activity, 28-joint score of <2.6 , was also significantly higher in the combination group (50%) than the MTX or the adalimumab group (25% for both groups, $P < 0.001$). Radiographic outcomes were also significantly better in the combination group than the monotherapy groups after 2 years of therapy. The frequencies of adverse events were comparable among all three groups.

Anakinra

The benefits of adding anakinra to MTX therapy in patients with moderate to severe RA who had received MTX for ≥ 6 months was evaluated in a 24-week study [26]. At 24 weeks, ACR 20/50/70 response rates were significantly greater for patients receiving anakinra 1 and 2 mg/kg than for patients receiving MTX alone (Fig. 1). Anakinra was well tolerated. Withdrawals as a result of adverse events were higher in the 1- and 2-mg/kg anakinra plus MTX groups (14–15%) than MTX alone (4%). Mild and moderate injection site reactions were the most frequent adverse events reported for anakinra (63% for the 2-mg/kg group compared with 28% for the MTX control). Abdominal pain was reported more frequently for patients receiving anakinra plus MTX (6%) than for patients receiving MTX alone (1%). Five of 345 patients (1%) receiving anakinra plus MTX developed leukopenia. No serious infections were noted.

In the 990145 Study, patients with active RA despite current treatment with MTX received either anakinra 100 mg daily or MTX for 24 weeks [46]. Significantly greater proportions of patients receiving anakinra plus MTX compared with MTX achieved ACR 20 ($P < 0.001$), ACR 50 ($P < 0.01$), and ACR 70 ($P < 0.05$) responses (Fig. 1). These responses were achieved as early as 4 weeks after therapy. Safety profiles for anakinra were similar to those reported in the earlier trial, with more mild to moderate injection site reactions reported for anakinra than placebo (65 vs. 24%). The number of withdrawals because of injection site reactions was greater in the anakinra plus MTX groups (8%) compared with the MTX group ($<1\%$). Rates of serious adverse events were comparable (4% anakinra plus MTX vs. 3% MTX alone). Serious adverse events leading to study withdrawal included reported gangrene of a limb, fracture, and prostate cancer in the MTX group and interstitial lung disease and pulmonary fibrosis in the anakinra group. Rates of infectious events were comparable for both groups (33% anakinra vs. 26% MTX). The use of anakinra together with etanercept has also been studied. A significant increase in infection was seen in the combination group without any increased efficacy. As a result, this combination is not recommended for clinical use.

Cost and effectiveness of DMARDs vs. biologic therapies

Healthcare costs frequently rise as a function of disability. Expenses are projected to be three times higher in patients with a HAQ disability index score of 3 than in those with a score of 1 over a 5-year period (HAQ scale 0–3, 0 = no disability, 3 = severe disability) [47]. When estimating the cost effectiveness of a therapeutic regimen, all costs associated with the acquisition of the medication, with the frequent medical visits and laboratory testing, and with the treatment of adverse events must also be considered. For musculoskeletal diseases such as RA, indirect costs, including work absenteeism, lost productivity, unemployment, and underemployment, are additional considerations. When evaluating effectiveness, early and long-term outcomes must be included. Savings from avoiding surgery or long-term care and continued employment may make a drug with a high acquisition cost more cost-effective than one with a lower acquisition cost that does not provide the same level of joint damage control.

In a review of clinical trials, Mullan and Bresnihan [48] reported that no study evaluating traditional DMARDs either alone or in combination therapy has demonstrated a complete halting of progressive joint damage in the majority of patients with early RA. In contrast, therapy with traditional DMARDs, especially in combination with biologic therapy, has resulted in clinical remission as defined by DAS [28, 35, 49, 50] or ACR criteria [12] as well as a slowing of disease progression. Furthermore, studies evaluating biologic therapies have demonstrated a halting or inhibition of joint damage and its progression [28, 37, 45].

In a retrospective study of patients with RA receiving at least one course of DMARD therapy, the leading causes of therapy termination were adverse events (42%) and lack of efficacy (37%) [51]. Although MTX had a higher retention rate compared with other DMARDs ($P < 0.001$), as many as 50% of patients taking MTX discontinued because of lack of efficacy or toxicity within 5 years of therapy [51]. Other limitations include a delayed onset of action, constant monitoring because of multiple toxicities, and limited long-term sustainability [52].

Corticosteroids have been used as bridge therapy in combination therapy trials to control inflammation until DMARD therapy takes effect [11, 53]. However, corticosteroids are associated with an increased incidence of acute myocardial infarction, heart failure, diabetes mellitus, herpes, and osteoporosis [54–57]. Implementation of measures to prevent osteoporosis and close monitoring of the patient are critical during use of these agents.

TNF α antagonists overcome several of the limitations of DMARD therapies. They have a rapid onset of action, provide more consistent responses, and improve health-related quality of life significantly. Responses have been seen as early as 1 week after therapy initiation [31]. Recent trials such as TEMPO indicate that prevention of disease progression is sustained for as long as 2 years after initiation of therapy [28, 35, 50]. In long-term extensions of combination therapy trials including TNF α antagonists, inhibition of radiographic damage has been maintained for as long as 5 years [58].

Because traditional DMARD monotherapy rarely results in halting joint damage or long-term disease remission, it is hypothesized that the long-term costs of DMARDs associated with continued disease progression may be higher (e.g., loss of function, work disability, increased hospitalization costs, and surgery) than long-term treatment with a biologic agent for which drug acquisition costs are considerably higher. Using this rationale, combination therapy with biologic agents plus MTX may provide the most cost-effective approach currently available in the treatment of RA. Studies to address these and other economic outcome questions are in progress (Gibofsky et al. unpublished data).

Treatment strategies for management of rheumatoid arthritis

Several treatment strategies, such as the “step-up,” “parallel,” “step-down,” and sequential or “sawtooth” have been used to optimize patient outcomes (Table 1).

Step-up therapy

“Step-up” or “add-on” therapy is the addition of one or more drugs to existing therapy. It may be the most common strategy used to evaluate new therapies. Newer DMARDs, such as leflunomide, and TNF α and IL-1 receptor antagonists were first evaluated in patients who had active disease despite MTX treatment [26, 27, 30–32].

Table 1 Strategies for combining therapies for the treatment of rheumatoid arthritis

Strategy
Step-up Addition of one or more drugs to insufficient existing therapy Newer therapies are often evaluated using this strategy
Parallel Simultaneous use of more than one therapy Has been used as early intervention to prevent disease progression
Step-down [62] Treatment is initiated with a combination of rapid-acting anti-inflammatory agents, such as prednisolone, and slower-acting second-line drugs Anti-inflammatory agent is eliminated after slower medications take effect If inflammation is not controlled within 1 month, aggressive combination therapy is initiated
Sawtooth [64] DMARD therapy is started as early as possible Patient receives one or more DMARDs throughout the course of the disease Disease progression is closely monitored Therapy is changed when the predetermined ceiling for disease progression has been reached

DMARDs = disease-modifying antirheumatic drugs.

Addition of study drug was significantly better than existing therapy or MTX monotherapy.

In the Tight Control for Rheumatoid Arthritis (TICORA) trial in patients with disease duration of <5 years, patients receiving intensive disease management step-up therapy showed significant improvement in disease activity, radiographic progression, functional status, and quality of life compared with patients receiving routine care [50]. Intensive management included assessment of DAS monthly, intra-articular corticosteroid injections into amenable swollen joints, and changes in dosage, therapeutic agent, or the addition of agents if DAS indicated sustained moderate to high activity. Routine care included a visit every 3 months with no formal disease activity assessment. Alternative monotherapy was provided to patients with active synovitis and treatment failure. Intensive management resulted in a significantly greater percentage of patients achieving remission (DAS score < 1.6) than in those receiving routine care (65 vs. 16%, $P < 0.0001$) at 18 months.

Parallel strategy

Combination therapy with simultaneous use of more than one drug has been employed as an aggressive approach to slowing disease progression [15, 16, 28]. In one study by O'Dell et al. [15] evaluating a combination of sulfasalazine, MTX, and hydroxychloroquine vs. MTX alone or a combination of sulfasalazine and hydroxychloroquine, the triple combination was more effective than the other two regimens at 9 months, and efficacy was sustained over the remainder of the 2-year study. In a second trial, the triple therapy resulted in better treatment outcomes than the combinations of MTX plus hydroxychloroquine or MTX plus sulfasalazine [16].

In the TEMPO trial, the combination of etanercept plus MTX was superior to either etanercept or MTX monotherapies [28]. At 1 year, clinical remission (DAS < 1.6) was achieved by more patients receiving combination therapy than either monotherapy [28] and was sustained for 2 years [35]. At week 76, a substantially greater proportion of patients receiving etanercept (82%) or the combination (87%) were satisfied with their therapy compared with patients receiving MTX alone (69%) [59]. Similar proportion of patients (87% for the combination, 82% for etanercept, and 69% for MTX) indicated that they would retake their medication. The results of the PREMIER trial recently demonstrated the superiority of the combination of adalimumab + MTX over either adalimumab or MTX alone [69].

However, not all combinations show superior efficacy compared with monotherapy [19, 60]. Combination therapy with sulfasalazine and MTX was not more effective than either therapy alone [19]. A 5-year follow-up study also showed no benefits from this combination of DMARDs [60]. The combination of etanercept and anakinra showed no benefit over etanercept monotherapy [61]. Serious infections, such as pneumonia, cellulitis, and herpes zoster, as well as the incidence of neutropenia occurred more frequently in the group receiving the combination therapy; however, no cases of tuberculosis or opportunistic infections were reported. The frequency of mild injection-site reactions was more than 50% higher with combination therapy than etanercept alone.

Step-down strategy

Wilske and Healey [62] initially proposed the “step-down bridge” concept in which aggressive treatment is initiated with a combination of rapid-acting anti-inflammatory medications and slower-acting second-line drugs. This strategy would provide early control of inflammation before the slower-acting medications take effect. The investigators suggest initiating treatment with prednisone (10 mg/day) monotherapy. If inflammation is not controlled after 1 month, a combination of DMARDs should be added to the existing prednisone. Once the inflammation is controlled, medications are sequentially withdrawn.

The COBRA trial employed the step-down strategy in patients with early RA (median duration 4 months) [11, 14]. Therapy was initiated with sulfasalazine, prednisolone, and MTX. Prednisolone and MTX were tapered and eliminated by 28 and 40 weeks, respectively. Patients receiving the early combination therapy had a rapid relief of clinical symptoms and sustained significant reduction in the rates of new joint erosion over a period of 5 years [11, 14].

In another trial evaluating the long-term effects of etanercept plus MTX in patients with inadequate response to MTX, 56% of patients were able to reduce or discontinue concomitant corticosteroid use, and 62% were able to decrease or discontinue the dosage of MTX after 3 years in the extension study [63]. Reduction of the MTX dose was not associated with a decrease in ACR response scores [63].

Sawtooth strategy

DMARD monotherapies often lose their effectiveness over time and are associated with toxicities that limit long-term use. Fries [64] proposed the “sawtooth” strategy, which involves either substituting or adding a DMARD to the existing therapy when existing therapy starts to wane or when the existing therapy is discontinued because of toxicity. The strategy combines early DMARD use with continued long-term DMARD use, with switching to prevent disability or when adverse events warrant a change. Regular quantitative monitoring of disability ensures a sequential change in the DMARD when the predetermined ceiling is reached.

Sokka et al. [65] compared the progression of joint damage from two prospective studies of DMARD therapy in patients with early RA. In the earlier study, the majority of patients received DMARD monotherapy. In the later study, patients were treated continually and serially with DMARDs after the first year using the “sawtooth” strategy. After 8 years, progression of joint damage was significantly ($P = 0.001$) higher in patients receiving monotherapy than in those receiving combination therapy. In another study using the “sawtooth” strategy [66], the number of patients achieving remission as defined by the ACR criteria increased over time from 20% at year 1 to 32% at year 5. However, almost one in four patients did not respond to this approach.

Comparing strategies

The four strategies discussed were recently compared in the BeST study, a randomized trial of newly diagnosed (<2 years) DMARD-naïve patients [67]. In this study, the comparators were as follows: (1) “step-up” therapy, from MTX to sulfasalazine, then the addition of hydroxychloroquine; (2) “parallel” treatment with infliximab 3 mg/kg plus MTX; (3) “step-down” therapy, whereby prednisone is tapered off from the triple combination of MTX + sulfasalazine + prednisone; and (4) “sawtooth” therapy starting with MTX, then sulfasalazine, followed by leflunomide. The “step-down” approach and “parallel” combination therapy resulted in significantly greater and more rapid reduction in HAQ and less radiographic damage than “sawtooth” (sequential monotherapy) or “step-up” therapy (Table 2). Early treatment with infliximab plus MTX resulted in less radiographic damage than “sawtooth” monotherapy or “step-up” therapy. Almost one out of two patients receiving infliximab plus MTX therapy showed no radiographic progression at 1 year. When asked about their treatment experience, the majority (>75%) of patients in these groups said that their health status and treatment regimen were acceptable for the next year, and more than 80% of those receiving infliximab plus MTX said they would prefer to continue on this therapy [68].

Disease activity scores continued to improve over the second year [49]. Most of the patients (93%) in the group receiving step-down therapy had discontinued prednisolone, and 74% in the group receiving infliximab plus MTX discontinued infliximab because their DAS scores were

Table 2 Percentage of patients expressing preference after 1 year of therapy

Patient preference	Sequential monotherapy (N = 78)	Step-up therapy (N = 79)	Step-down therapy (N = 101)	Infliximab + methotrexate (N = 99)
Initial treatment improved general health much or very much (%)	56	60	50	75
Finds current health status and treatment acceptable for the next year (%)	87	86	75	87
Objects to taking prednisone (%)	15	22	49	11
Would now choose the treatment that was received following randomization (%)	36	30	41	81

Adapted with permission from De Vries-Bouwstra et al. [68].

≤2.4. Furthermore, at 2 years, more than one in four patients receiving sequential monotherapy had switched to infliximab [49].

Conclusions

In clinical trials evaluating combination therapy, early aggressive therapy with two or more agents, such as a DMARD and a biologic agent, has been shown to slow the progression of RA. Combinations of two or more DMARDs or a DMARD and a biologic agent are often superior to monotherapy for improving the clinical signs and symptoms of the disease in addition to reducing the rate of joint damage in patients with early RA. Although they slow disease progression and may even result in clinical remission, combinations of conventional DMARDs do not always result in inhibition of joint destruction, as evidenced by continued radiographic progression over the long term. DMARDs are slower acting than corticosteroids or biologic therapy and are associated with an increased incidence of therapy discontinuations because of adverse events and lack of efficacy. Corticosteroids have been used as bridge therapy to reduce inflammation until DMARDs become effective. Although effective at inhibiting synovitis and radiographic progression, long-term corticosteroid use in the treatment of RA has been associated with an increased incidence of acute myocardial infarction, heart failure, diabetes, and osteoporosis.

Agents targeting TNF overcome some of the limitations of DMARD therapy. They have a relatively rapid onset of action and long-term sustained effects. TNF antagonists inhibit radiographic progression by effectively reducing synovitis. These agents have been shown to halt disease progression when used as monotherapy or in combination with MTX for the treatment of early RA and in patients with long-standing disease inadequately controlled with DMARD therapy alone. The major issue, however, in this time of limited resources is cost benefit or cost effectiveness. Whereas TNF inhibitors are more expensive medications than traditional DMARD therapies, they may be more cost-effective in the long-term because of their safety profiles and their ability to reduce the burden of illness. However, the effects of TNF antagonists on indirect costs, such as absenteeism, await further investigation.

In conclusion, clinical trials of combination therapy with DMARDs or DMARD plus biologic combinations

have demonstrated that an aggressive approach to RA early in the disease process, coupled with careful monitoring of patient response and appropriate optimization of the treatment regimen, can lead to favorable long-term outcomes. Data from trials, such as the TEMPO, BeST, ARMADA, and PREMIER studies, have greatly raised expectations for treatment outcomes. Current biologic treatments, as well as those that are now in development, are likely to dramatically alter the natural history of RA and make severe RA a rarity in clinical practice.

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References

- Gabriel SE (2001) The epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am* 27:269–281
- Lee DM, Weinblatt ME (2001) Rheumatoid arthritis. *Lancet* 358:903–911
- McQueen FM, Stewart N, Crabbe J et al (1998) 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* 57:350–356
- Fuchs HA, Kaye JJ, Callahan LF et al (1989) Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. *J Rheumatol* 16:585–591
- Felts W, Yelin E (1989) The economic impact of the rheumatic diseases in the United States. *J Rheumatol* 16:867–884
- Weinblatt ME (2004) Rheumatoid arthritis: more aggressive approach improves outlook. *Cleveland Clin J Med* 71:409–413
- van der Heijde DM (1995) Joint erosions and patients with early rheumatoid arthritis. *Br J Rheumatol* 34(Suppl 2):74–78
- van der Heijde DM, van Leeuwen MA, van Riel PL et al (1995) 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* 22:1792–1796
- Stenger AA, Van Leeuwen MA, Houtman PM et al (1998) Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. *Br J Rheumatol* 37:1157–1163
- Lard LR, Visser H, Speyer I et al (2001) Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med* 111:446–451
- Boers M, Verhoeven AC, Markusse HM et al (1997) Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 350:309–318
- Korpela M, Laasonen L, Hannonen P et al (2004) Retardation of joint damage in patients with early rheumatoid arthritis by initial

- aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. *Arthritis Rheum* 50:2072–2081
13. Kremer JM, Genovese MC, Cannon GW et al (2002) Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 137:726–733
  14. Landewe RB, Boers M, Verhoeven AC et al (2002) COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. *Arthritis Rheum* 46:347–356
  15. O'Dell JR, Haire CE, Erikson N et al (1996) Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 334:1287–1291
  16. O'Dell JR, Leff R, Paulsen G et al (2002) Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 46:1164–1170
  17. Tugwell P, Pincus T, Yocum D et al (1995) Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. The Methotrexate-Cyclosporine Combination Study Group. *N Engl J Med* 333:137–141
  18. Dougados M, Combe B, Cantagrel A et al (1999) Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. *Ann Rheum Dis* 58:220–225
  19. Haagsma CJ, van Riel PL, de Jong AJ et al (1997) Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. *Br J Rheumatol* 36:1082–1088
  20. Proudman SM, Conaghan PG, Richardson C et al (2000) 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* 43:1809–1819
  21. van den Borne BE, Landewe RB, Goei The HS et al (1998) Combination therapy in recent onset rheumatoid arthritis: a randomized double blind trial of the addition of low dose cyclosporine to patients treated with low dose chloroquine. *J Rheumatol* 25:1493–1498
  22. Enbrel® (etanercept) [package insert] (2004) Thousand Oaks, CA: Amgen Inc. and Wyeth-Ayerst Pharmaceuticals
  23. Remicade® (infliximab) [package insert] (2003) Malvern, PA: Centacor Inc.
  24. Humira® (adalimumab) [package insert] (2003) North Chicago, IL: Abbott Laboratories
  25. Kineret® (anakinra) [package insert] (2002) Thousand Oaks, CA: Amgen Inc.
  26. Cohen S, Hurd E, Cush J et al (2002) Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 46:614–624
  27. Furst DE, Schiff MH, Fleischmann RM et al (2003) Adalimumab, a fully human anti tumor necrosis factor- α monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: Results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol* 30:2563–2571
  28. Klareskog L, van der Heijde D, de Jager JP et al (2004) Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 363: 675–681
  29. Maini R, St Clair EW, Breedveld F et al (1999) Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial, AT-TRACT Study Group. *Lancet* 354:1932–1939
  30. Maini RN, Breedveld FC, Kalden JR et al (2004) Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum* 50:1051–1065
  31. Weinblatt ME, Keystone EC, Furst DE et al (2003) Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 48:35–45
  32. Weinblatt ME, Kremer JM, Bankhurst AD et al (1999) A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 340:253–259
  33. Pinals RS, Masi AT, Larsen RA (1981) Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum* 24:1308–1315
  34. Prevoo ML, van Gestel AM, van T'Hof MA et al (1996) Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. *Br J Rheumatol* 35:1101–1105
  35. Klareskog L, van der Heijde D, de Jager JP et al (2004) Clinical outcomes of a double-blind study of etanercept and methotrexate, alone and combined, in patients with active rheumatoid arthritis (TEMPO trial), year 2 results [Abstract]. *Ann Rheum Dis* 63
  36. van der Heijde D, Klareskog L, Pedersen R et al (2004) Assessment of functional status among patients with active rheumatoid arthritis in a double-blind trial of etanercept and methotrexate, alone and combined (TEMPO trial) [Abstract]. *Arthritis Rheum* 50
  37. van der Heijde D, Landewe R, Klareskog L et al (2005) Presentation and analysis of data on radiographic outcome in clinical trials: experience from the TEMPO study. *Arthritis Rheum* 52:49–60
  38. Baumgartner SW, Fleischmann RM, Moreland LW et al (2004) Etanercept (Enbrel) in patients with rheumatoid arthritis with recent onset versus established disease: improvement in disability. *J Rheumatol* 31:1532–1537
  39. St Clair EW, van der Heijde DM, Smolen JS et al (2004) Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 50:3432–3443
  40. Smolen J, van der Heijde DM, Emery P et al (2003) Methotrexate naive early rheumatoid arthritis (RA) patients with higher baseline ESR and CRP derive greater radiographic benefit from initiating treatment with a combination of infliximab and methotrexate [Abstract]. *Arthritis Rheum* 48
  41. Breedveld FC, Emery P, Keystone E et al (2004) Infliximab in active early rheumatoid arthritis. *Ann Rheum Dis* 63:149–155
  42. Breedveld FC, Kavanaugh AF, Cohen SB et al (2004) Early treatment of rheumatoid arthritis (RA) with adalimumab (Humira) plus methotrexate vs. adalimumab alone or methotrexate alone: the PREMIER study [Abstract]. *Arthritis Rheum* 50
  43. Keystone EC, Haraoui B, Bykerk VP (2003) Role of adalimumab in the treatment of early rheumatoid arthritis. *Clin Exp Rheumatol* 21:S198–S199
  44. Keystone EC, Kavanaugh A, Sharp J et al (2002) Adalimumab (D2E7), a fully human anti-TNF monoclonal antibody inhibits the progression of structural joint damage in patients with active RA despite concomitant methotrexate therapy [Abstract]. *Arthritis Rheum* 46
  45. Keystone EC, Kavanaugh AF, Sharp JT et al (2004) Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 50:1400–1411
  46. Cohen SB, Moreland LW, Cush JJ et al (2004) A multicentre, double blind, randomised, placebo controlled trial of anakinra

- (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. *Ann Rheum Dis* 63:1062–1068
47. Fries JF (1999) Safety, cost and effectiveness issues with disease modifying anti-rheumatic drugs in rheumatoid arthritis. *Ann Rheum Dis* 58(Suppl 1):I86–I89
  48. Mullan RH, Bresnihan B (2003) Disease-modifying anti-rheumatic drug therapy and structural damage in early rheumatoid arthritis. *Clin Exp Rheumatol* 21:S158–S164
  49. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Zeven DV et al (2004) Treatment strategies in early rheumatoid arthritis: clinical and radiologic outcomes after 2 year follow-up of the BeST Study [Abstract]. *Arthritis Rheum* 50
  50. Grigor C, Capell H, Stirling A et al (2004) Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 364:263–269
  51. Aletaha D, Smolen JS (2002) Effectiveness profiles and dose dependent retention of traditional disease modifying antirheumatic drugs for rheumatoid arthritis. An observational study. *J Rheumatol* 29:1631–1638
  52. Cannella AC, O'Dell JR (2003) Is there still a role for traditional disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis? *Curr Opin Rheumatol* 15:185–192
  53. Mottonen T, Hannonen P, Leirisalo-Repo M et al (1999) Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial, FIN-RACo trial group. *Lancet* 353:1568–1573
  54. Wolfe F, Michaud K (2004) Prednisone but not biologics or DMARDs is associated with increased risk of myocardial infarction in persons with RA [Abstract]. *Ann Rheum Dis* 63
  55. Wolfe F, Michaud K (2004) Rates and risk factors for herpes zoster in patients with rheumatoid arthritis [Abstract]. *Ann Rheum Dis* 63
  56. Wolfe F, Michaud K (2004) Corticosteroids increase the risk of diabetes mellitus in RA and contribute to the risk of myocardial infarction and heart failure [Abstract]. *Ann Rheum Dis* 63
  57. van Everdingen AA, Siewertsz van Reesema DR, Jacobs JW et al (2003) Low-dose glucocorticoids in early rheumatoid arthritis: discordant effects on bone mineral density and fractures? *Clin Exp Rheumatol* 21:155–160
  58. Genovese MC, Martin RW, Fleischmann RM et al (2003) Etanercept (Enbrel) in early erosive rheumatoid arthritis (ERA trial): clinical and radiographic data [Abstract]. *Arthritis Rheum* 47(Suppl)
  59. Singh A, Van der Heijde D, Klareskog L et al (2004) Assessment of treatment satisfaction among patients with active rheumatoid arthritis in a double-blind trial of etanercept and methotrexate, alone and combined (TEMPO trial) [Abstract]. *Arthritis Rheum* 50(Suppl)
  60. Maillefert JF, Combe B, Goupille P et al (2003) Long term structural effects of combination therapy in patients with early rheumatoid arthritis: five year follow up of a prospective double blind controlled study. *Ann Rheum Dis* 62:764–766
  61. Genovese MC, Cohen S, Moreland L et al (2004) Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 50:1412–1419
  62. Wilske KR, Healey LA (1989) Remodeling the pyramid—a concept whose time has come. *J Rheumatol* 16:565–567
  63. Kremer JM, Weinblatt ME, Bankhurst AD et al (2003) Etanercept added to background methotrexate therapy in patients with rheumatoid arthritis: continued observations. *Arthritis Rheum* 48:1493–1499
  64. Fries JF (1990) Reevaluating the therapeutic approach to rheumatoid arthritis: the “sawtooth” strategy. *J Rheumatol*, Suppl 22:12–15
  65. Sokka TM, Kaarela K, Mottonen TT et al (1999) Conventional monotherapy compared to a “sawtooth” treatment strategy in the radiographic progression of rheumatoid arthritis over the first eight years. *Clin Exp Rheumatol* 17:527–532
  66. Mottonen T, Paimela L, Ahonen J et al (1996) Outcome in patients with early rheumatoid arthritis treated according to the “sawtooth” strategy. *Arthritis Rheum* 39:996–1005
  67. De Vries-Bouwstra JK, Goekoop-Ruiterman YPM, Van Zeven D et al (2004) A comparison of clinical and radiologic outcomes of four treatment strategies for early rheumatoid arthritis: results of the BEST trial [Abstract]. *Ann Rheum Dis* 63
  68. De Vries-Bouwstra JK, Goekoop-Ruiterman YPM, Kerstens PJSM et al (2004) Patient preferences for treatment of newly diagnosed rheumatoid arthritis [Abstract]. *Ann Rheum Dis* 63
  69. Breedveld FC et al (June 8–11, 2005) Presented at: EULAR Annual Meeting; Vienna, Austria. Abstract OP0013