Pharmacological Management of Early Rheumatoid Arthritis — Does Combination Therapy Improve Outcomes?

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ABSTRACT. Treatments for rheumatoid arthritis (RA) have involved a variety of single agent and combination therapies with one paramount goal, to slow disease progression and bone destruction. However, data indicate that not all drug combinations are equally efficacious in all patients with RA, and toxicity levels can be difficult to manage. In addition to these concerns, studies are difficult to compare because of methodologic differences and differing drug doses and schedules, for example. To more accurately discern how to best manage early RA, and because treating RA within 3 months of diagnosis appears crucial for improved outcomes, this review summarizes studies that compared combination to monotherapies in early RA, while attempting to consider factors that could complicate the results. These reports utilized disease modifying antirheumatic drugs (DMARD) with known efficacy among patients with RA, but more importantly a number also used varying levels of glucocorticoids as well. Collectively, these data are beginning to shed light on how to best treat early RA, suggesting that DMARD work best when given very early. (J Rheumatol 2002;29 Suppl 66:20–26)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
COMBINATION THERAPY
TREATMENT
DISEASE MODIFYING ANTIRHEUMATIC DRUGS

Rheumatoid arthritis (RA) is a destructive inflammatory disease affecting roughly 1% of the population in the industrialized world, with prevalence rates that may exceed 5%, depending upon one's ethnic background. Aside from the serious economic impact of this debilitating disease — which has been found to be similar to that for coronary artery disease[1] — approximately 90% of RA patients with aggressive disease become disabled within 20 years of onset[1,2]. The mortality of RA among patients with extraarticular symptoms or severe disease matches that for triple artery coronary artery disease or stage IV Hodgkin's lymphoma[1], illustrating the seriousness of this disease and the importance of early, aggressive treatments.

Although a variety of factors including genetic predisposition, female sex, immune response, hormonal interactions, viral infections, and psychological stress have been associated with RA, the cause of this disease remains unknown[3]. However, it is clear that clinically significant joint damage is most rapid within the first 2 years of disease onset and that inflammatory changes also occur at an accelerated rate early in the pathogenesis of RA[4]. Moreover, because the etiology of RA itself is not known, drug treatment strategies are largely empirical[4]. Issues further complicating the evaluation of different treatment strategies include variations in study design, outcome assessments, and confounding and overlapping drug effects.

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INTERPRETING RA STUDIES IS NOT STRAIGHTFORWARD

Recently, a number of detailed reviews of combination therapy in RA have been published[4-8]. From these reports it is becoming evident that although the use of simultaneous antirheumatic drugs appears efficacious, the reality is that such dosing schedules may only be as useful as monotherapy. While investigators agree that clinical advantages favoring combination therapy are beginning to emerge, not all combinations of disease modifying antirheumatic drugs (DMARD) are either effective in or tolerated by different patients[5]. Despite this finding, it is reasonable to infer that the early and sustained suppression of disease activity should be the main goal of therapy for RA — such an approach helps to prevent joint damage and ongoing functional decline. However, the open question is how to achieve this goal. Further, the joints of RA patients are most vulnerable early in disease progression, emphasizing the need for early and aggressive treatment.

Studies that evaluated the use of methotrexate (MTX) and sulfasalazine (SSZ) with or without hydroxychloroquine (HCQ) in early RA suggested that combined therapy was superior to monotherapy; however, many of these reports also included corticosteroids as part of the combined DMARD therapy, thereby confounding the interpretation of the effects of the agents being studied[6].

STUDY DESIGN KEY TO INTERPRETATION

Aside from overlapping drug effects, the specific methodology utilized in a clinical trial has a direct bearing on the type and validity of data derived from the trial. For many years, physicians have been dissatisfied with the "pyramid" approach to RA treatment, which entails beginning with low toxicity nonsteroidal antiinflammatory drugs and progressing to more potent and hence more toxic antirheumatic drugs as therapeutic responses are sought[9]. Because of the disease progression associated with such an approach, many rheumatologists now employ various combination strategies early in the disease course as a way of enhancing efficacy and hopefully mitigating concomitant toxicity[10].

Potentially useful combination strategies. Although it is not the goal of this discussion to exhaustively compare the differing methodologies associated with RA therapy, a brief overview of the alternative methods will be presented. As discussed by Boers[10], 5 fundamental combination strategies can be employed. These include:

- parallel administration
- step-up administration
- step-down (or bridge) dosing
- sawtooth dosing, and
- parallel/switched dosing

Parallel administration describes the use of usually 2 drugs simultaneously, continuing throughout the study. Step-down therapy, while similar to the parallel method, requires that simultaneously administered agents be stopped over time, either on the basis of protocol or treatment responses. Conversely, step-up therapy begins as monotherapy, with additional agents being added sequentially over time. In this case, newly added drugs are administered to aid in achieving a desired response after failure of initial DMARD. Sawtooth dosing profiles are begun as a step-down approach; however, this protocol allows for the readministration of stopped agents to manage disease flares. The parallel/switch approach among combination therapies permits the switching of one agent to another while continuing the other component(s).

Overall, future trials are needed to more precisely evaluate which approach to RA treatment is best. These trials need to address key issues that (1) identify the optimal combinations of DMARD to use, (2) define the best time to begin dosing of each component, and (3) individualize combination therapies[6] in a disease known for heterogeneous responses between patients.

EARLY RA — HOW EARLY IS EARLY?

The key to successful therapy for RA is early intervention, a crucial aspect of disease management because most patients exhibit joint destruction within the first 2 years of symptom onset[2]. Although strategies for early referral of newly diagnosed disease have been proposed[2], continued awareness of the importance of early treatment cannot be overlooked. Moreover, combination therapy could be used in patients with early disease if proven more effective than DMARD monotherapy and individuals with persistent aggressive disease can be clearly identified[5].

Accurately diagnosing RA in its very early phase is difficult[11]; however, clinical experience in Europe and the United Kingdom now indicates that early RA (eRA) can be diagnosed when symptoms persist for 12 weeks or more[2]. Thus, the presence of untreated rheumatoid symptoms for more than 12 weeks' time signifies the need for intervention in order to mitigate a poor prognosis. As noted by Emery, *et al*, the strongest predictor of persistent disease was disease duration of more than 12 weeks[2,11]. Thus, a delay in treatment implies that improvements in longterm outcomes are less likely[2].

Table 1 summarizes a series of controlled trials that compared combination therapies to various monotherapies in eRA, highlighting the main outcomes of these studies along with the reported toxicity levels. As shown, patients included in these studies exhibited symptoms of RA for up to 2 years' time, with mean symptom durations as short as 3 months or as long as 13 months; median values were within this range as well. Despite the attempt at selecting patients with early disease, the clinical reality of identifying patients with RA within 12 weeks of symptom onset is difficult, owing to delays in patients seeking medical care and to the time involved in making a complete diagnosis[2]. Such challenges further complicate the interpretation of study results.

Separately, and because it is critical to treat RA early, data reported by Bathon, *et al*[12] are also encouraging among patients with eRA. Although not a study of combination therapy, these authors compared the administration of twice weekly subcutaneous etanercept (10 or 25 mg) to weekly oral MTX (mean 19 mg per week) to evaluate the efficacy in reducing the level of disease activity and joint damage. Among the 632 patients studied, etanercept decreased symptoms and slowed joint damage more rapidly than did MTX (data not shown)[12].

RECENT COMPARATIVE STUDIES OF COMBINATION THERAPY

Clinical trials designed to study the pharmacologic effects of various drug dosing schedules and combinations on eRA have been summarized[4,8]. As presented in Table 1, parallel, step-down, and tailored/flexible dosing strategies have been employed in a number of the studies that included patients who presented with eRA. In addition to these data, Felson, *et al* published a metaanalysis that investigated the efficacy and toxicity of combination therapy in RA as well[13].

Among the 7 studies summarized in Table 1, four utilized combined SSZ and MTX with[14,15] or without[16,17] high dose prednisolone, one used SSZ + MTX + HCQ with prednisolone[18], and 2 used a combination of MTX + cyclosporin

Table 1. Selected randomized trials comparing combination treatment strategies in early rheumatoid arthritis. Data compiled from Mottonen, *et al*[4], Quinn, *et al*[8], Landewé, *et al*[15], and Marchesoni, *et al*[20]. (Continued opposite.)

Study	No. of Patients and Selection Criteria	Symptom Duration at Baseline	Study Duration (mo)	Drugs Compared	Corticosteroid Use During Trial
Boers, 1997[14] COBRA Trial	155, 21% erosive, DMARD naive	Median 4 mo (≤ 2 yrs)	13	SSZ + MTX + Prd vs SSZ	Combi: Prd 60 mg/day tapered to 7.5 mg and stopped after 28 wks. Single: not allowed
Landewé, 2002[15] COBRA Extension Trial	148, 21% erosive, DMARD naive	Median 4 mo	5 yr followup	SSZ + MTX + Prd vs SSZ	Combi: Prd 60 mg/day tapered to 7.5 mg and stopped after 28 wks. Single: not allowed
Dougados, 1999[16]	205, DMARD naive	Mean 13 mo (diag. RA < 1 yr)	12	MTX + SSZ vs MTX vs SSZ	Not reported
Haagsma, 1997[17]	105, DMARD naive	Mean 3 mo (≤ 1 yr)	12	MTX + SSZ vs MTX vs SSZ	Not allowed
Mottonen, 1999[18]	195, DMARD naive	Mean 8 mo (< 2 yrs)	24	Combi– Mainly SSZ + MTX + HCQ + Prd vs single DMARD ± Prd	Combi: up to 10 mg/day Single: 0 to 10 mg/day
Proudman, 2001[19]	82, poor prognosis, DMARD naive, 62% erosive	Median 8 mo (< 1 yr)	11	Combi: MTX + CSA + mPrd injections in all inflamed joints vs single SSZ + injections	Apart from i a injections in both groups, 1 × 120 mg mPrd on failure to respond
Marchesoni, *et al*, 2000[20]	42	Mean 10 mo	12	CSA + MTX vs MTX	Not reported

COBRA: *Combinatietherapie Bij Reumatoide Artritis*; DMARD: disease modifying antirheumatic drug; MTX: methotrexate; SSZ: sulfasalazine; HCQ: hydroxychloroquine; CSA: cyclosporin A; Prd: prednisolone; mPrd: methylprednisolone; Pl: placebo; Combi: combination therapy group; Single: single therapy group; ia: intraarticular; ACR RA: American College of Rheumatology list of criteria for RA, 1987; DAS: Disease Activity Score; EMS: early morning stiffness; HAQ: Health Assessment Questionnaire; PGA: patient global assessment; PhGA: physician global assessment; RI: Ritchie Index: Rx: treatment; STJC: swollen, tender joint count; VAS: visual analog scale; XR: radiographic progression. ACR20/50/70: fulfilling ACR 20%/50%/70% response criteria.

A (CSA) with or without corticosteroids (methylprednisolone)[19,20]. In each study, the combination therapies were compared with single DMARD, with 2 studies using low dose steroids in conjunction with the single agent.

Regardless of the DMARD combination chosen, but with the exception of the 5 year extension study reported by Landewe, *et al*[15], few clinically significant improvements in disease progression, joint degradation, or remission rates were reported for the combined treatments versus monotherapy (Table 1). Trends favoring the use of a combination approach to eRA therapy were reported in 4 of these studies[14,16,18,20]; however, these data suggest that additional longer term studies are needed to confirm the initial findings. In addition, the reported toxicities for the combination treatments were largely similar to those for the monotherapy treatments. The metaanalysis by Felson (data not shown) also reported no statistically significant benefit for combination therapy over monotherapy in RA (trials in early RA were not evaluated), and toxicity was higher than that reported with single agents[13]. Finally, it was commonly found that when combination therapy tended to be better, it was confounded by additional factors: high dose prednisolone[14,15] as part of the combination therapy or insufficient dose of comparative DMARD[21], while similar results were seen when such confounding factors were not present[16,17].

Additive versus sequential therapy. The studies mentioned above included DMARD naive patients with eRA (note: Marchesoni, *et al*[20] did not report prior medication usage). Separate studies in patients who did not respond to SSZ, for example, have also been reported. One such study by Haagsma, *et al*[22] involved 40 RA patients randomized to MTX (n = 18) or MTX + SSZ (n = 22) after not achieving an adequate response to SSZ alone. This 24 week parallel open trial compared the efficacy and toxicity of these 2 treatment strategies and showed that the change from baseline in the disease activity score (DAS) was –1.0 for the MTX arm versus –2.6 for the MTX + SSZ arm ($p < 0.001$). Combination therapy resulted in other improvements as well, including fewer swollen joints, fewer painful joints, improved Ritchie Articular Index, and perceived improvements in general health, pain, and morning stiffness, among others. No significant differences in toxicity levels were reported between the treatment arms[22]. Although this was a small study, the results suggest that combining MTX with the previously ineffective drug SSZ yielded superior clinical responses relative to switching to MTX alone. Thus, additive combination therapy may prove to be useful in a subset

Table 1. Continued

Combination	Main Outcome	Toxicity
Step-down	STJC, HAQ, pain VAS, ESR and PhGA improved with comb. Rx at 28 wks ($p < 0.05$), but not significant at 56 wks. Reduction in XR at 28, 56 + 80 wks ($p < 0.05$)	Total withdrawals (efficacy + toxicity) 8% vs 29% ($p = 0.0008$)
Step-down	Radiologic progression was suppressed by an initial 6 mo course of intensive combination treatment that included high dose steroids. The progression was sustained after therapy was stopped	Not reported
Step-down bridge	Similar efficacy of all groups for STJC, HAQ, EMS, CRP/ESR, and XR	Combination slightly more adverse events
Parallel with dose adjustment	Similar efficacy of all groups for DAS, STJC, HAQ, RI, ESR, and pain VAS. No significant difference in tolerability	Similar
Tailored steps with flexible dose adjustment	No significant difference in STJC, HAQ, ESR, PGA, PhGA at 24 mo. More patients in remission with combination treatment ($p < 0.05$) and at ACR 50 at 24 mo	Similar
Parallel with dose adjustment; flexible selection of joints, fixed injection dose/joint	No significant difference in ACR 20/50, remission rates or XR at 48 wks. Greater reduction in STJC only in combination treatment group ($p < 0.05$)	Fewer withdrawals in combination arm; CSA doses limited due to increases in serum creatinine levels
Parallel	No significant differences in ACR 20, 50, or 70; possibility of improved prevention of structural joint damage with combination regimen	Overall safety and tolerability good for both groups

of nonresponding patients; however, additional large randomized controlled trials are needed to validate these findings[22].

A separate larger study by Dougados, *et al* evaluated the safety and efficacy of leflunomide (LEF) in RA patients (M. Dougados, RELIEF study, personal communication). LEF is a newly introduced DMARD whose active metabolite inhibits dihydroorotate dehydrogenase, thereby blocking the cell cycle of activated lymphocytes[5] as well as transcription of nuclear factor κB[23]. Lymphocyte cell cycle inhibition results in decreased immune function of lymphocytes and an inhibition of antigen processing[5]. In the RELIEF study (Rheumatoid arthritis Evaluation of LEF further Insights into its EFficacy) 778 patients were given open label LEF for 24 weeks. Of these patients, 672 responded to therapy. The responders were continued on study drug for an additional 24 weeks while nonresponders (n = 106) were randomized to either placebo + SSZ (n = 50) or LEF + SSZ (n = 56) for 24 weeks as well. Thirty-four percent of SSZ treated patients responded to therapy verus 44.6% of those treated with combination drugs ($p = 0.179$), and similar levels of adverse events were reported for both treatment groups: 46% for the combination and 34% for SSZ alone. Although an insufficient number of patients were randomized to study drug in the second phase of the study to adequately evaluate response rates, the data suggest a possible benefit of adding SSZ to LEF in patients who do not adequately respond to this drug. Overall, LEF + SSZ may be a reasonable alternative for RA patients refractory to LEF monotherapy. Although small, the trend of this study suggests that additive combination therapy may prove useful in patients who do not respond to SSZ.

EMERGING DATA — DO COMBINED DMARD OR GLUCOCORTICOIDS ALTER DISEASE PROGRESSION?

As evidenced by the above studies, the inclusion of glucocorticoid drugs in eRA trials cannot be overlooked. Although potential benefits were reported for combinations of MTX + SSZ, the use of concomitant steroids, particularly during the early stages of the trials, may have contributed to the favorable effects seen for these combination treatments, an observation that has been supported by others (see Garrood and Scott[6]). Moreover, Bingham and Emery point out that while the role of steroids in combination therapy is not well defined, it appears likely that the administration of a new DMARD would be more efficacious if the patient's inflammatory burden has first been reduced with steroids[5].

Despite the potential for improvements in outcome, longterm high dose steroid use is hampered by unacceptable levels of side effects and a loss of efficacy at low doses[24]. Recently, Boers summarized a group of trials that employed steroids in eRA; overall, the results were impressive in that steroids yielded good symptomatic improvements, disease remission, and sustained suppression of RA (see Boers' Table 1)[24]. According to Boers, the following issues must be considered concerning the use of steroids in RA, especially eRA:

• the "classical" view that steroid use only yields short symptomatic benefit at the expense of unacceptable toxicity levels is not based on scientific evidence
• new evidence in RA suggests that steroids are potent disease modifying antirheumatic drugs
• judicious dosing of steroids, especially if new anti-osteoporosis agents are used, yields an acceptable level of side effects

Although these views can be refuted, Boers further emphasizes the need for additional research aimed at identifying dosing regimens and combinations, at evaluating longterm efficacy and toxicity, and at defining the role of these agents in prophylactic treatments against toxicity[24].

Combinatietherapie Bij Reumatoide Artritis (COBRA) trial results. The data presented in Table 1 for the COBRA trial indicate that combination therapy with SSZ + MTX + prednisolone yielded statistically significant improvements in radiographic disease progression relative to SSZ alone ($p < 0.05$), with significantly fewer patients withdrawing from the study due to adverse toxicity levels ($p = 0.0008$). Although combination therapy rapidly improved disease activity, improvements were also seen with monotherapy, albeit to a lesser degree. Moreover, once prednisolone was discontinued, the between-group differences became insignificant[4]. Thus, these initial data would imply that combination therapy in a step-down regimen offers only a small transient benefit over monotherapy. Interestingly, however, longer term followup for the COBRA study population has recently yielded new data, possibly leading toward improved outcomes for eRA patients treated aggressively.

According to a 5 year followup study of the COBRA trial[15], an initial 6 month combination DMARD regimen that includes high dose steroids suppressed radiologic progression in these eRA patients, regardless of subsequent DMARD therapy. This effect was sustained among those treated after combination therapy was completed[15]. Because this followup trial began after one year of combination treatment, the analyses of the longterm outcomes began after one year's time. Thus, as shown in Table 2 at one year, the combination treated patients exhibited significantly better scores for radiologic damage (reported as the Sharp damage score; see Methods[14]) and similar disease activity levels. The mean change per year for these variables was greater with combined treatment than with SSZ alone, with the mean rate of change in radiographic damage being calculated at 35% lower for combined therapy (5.6 points) versus monotherapy (8.6 points; $p = 0.03$). Based on this rate difference, additional analyses revealed that radiologic destruction eventually ceased among the combination-treated patients and did not resume after the trial was completed. This reduced rate of progression was further analyzed, and, as shown in Table 3, the rate of radiologic change over time remained suppressed with combination (COBRA) therapy compared with SSZ monotherapy.

Table 2. Longterm outcomes in the COBRA followup study[5]. Outcome measures for radiologic damage and functional ability were the Sharp score and HAQ score, respectively. Change scores are longitudinal (time) trends per group, estimated using generalized estimating equations (GEE). Data compiled from Landewé, *et al*[15].

	Score at 1 Year†	Mean Change per Year	p
Radiologic damage			
SSZ	17 (5.8, 29)	8.6 (6.2, 11)	0.001
COBRA	6.5 (2.0, 21)	5.6 (4.3, 7.1)	0.001
Disease activity DAS28			
SSZ	4.3 ± 1.6	–0.13 (–0.24, –0.02)	0.021
COBRA	3.7 ± 1.4	–0.02 (–0.12, –0.08)	0.629
Time-averaged DAS28			
SSZ	4.8 ± 1.3	–0.17 (–0.23, –0.11)	0.001
COBRA	4.2 ± 1.2	–0.07 (–0.11, –0.03)	0.001
Functional ability			
SSZ	0.72 ± 0.60	0.01 (–0.03, 0.05)	0.647
COBRA	0.69 ± 0.61	0.01 (–0.03, 0.05)	0.745

† Values for the Sharp score are the cross-sectional median (25th, 75th percentiles); other values are the mean ± SD. SSZ: sulfasalazine; COBRA: Combinatietherapie Bij Reumatoide Artritis; DAS28: 28 joint disease activity score.

Table 3. Radiologic progression by time, with adjustment for confounders. Adjusted for baseline variables (age, sex, disease duration at baseline, DAS28 at baseline, Sharp score at baseline, rheumatoid factor status at baseline, HLA–DR4 status) and longitudinal variables (SSZ use, prednisolone use, MTX use, prednisolone + MTX use, use of combination therapy with DMARD, time averaged DAS28). Data compiled from Landewé, *et al*[15].

Time	No. of Patients/ No. of Observations	True Progression Rate, Points/Year, (SD)	
		SSZ	COBRA
From 0.5 yrs	148/798	9.3 (1.3)	5.7 (0.8)
From 1.0 yrs	146/679	8.6 (1.2)	5.6 (0.7)
From 1.5 yrs	141/523	8.4 (1.2)	5.1 (0.7)
From 2.0 yrs	141/394	8.3 (1.3)	4.9 (0.7)

SSZ: sulfasalazine; COBRA: Combinatietherapie Bij Reumatoide Artritis.

The authors also reported that these observations support the concept that the rate of radiologic degradation is "set" very early in the pathogenesis of RA. More important, however, early and aggressive pharmacologic intervention may actually "reset" this progression rate provided that intervention is given within a narrow time frame now known as the "window of opportunity," a concept previously reported by others[25]. According to this study, a time frame of 12 to 24 months after diagnosis of RA appears to be the interval within which aggressive therapy is to be started in order to limit future radiologic degradation. Although this concept remains unproven, this study brings to light the possibility that the initial high dose oral prednisolone may have suppressed disease activity to such a low

level early in treatment that the rate of radiologic damage was altered or reset. This concept is confirmed by newer studies[26,27]; however, in these studies, monotherapy was sufficient to achieve many good results if started in very early arthritis. Because radiologic damage begins in the joint with the cytokine-associated activation of macrophage- and fibroblast-like cells as well as osteoclasts, drugs that can interrupt these inflammatory processes or alter the physiologic changes that result in joint destruction could likely influence outcome. Once reset, the rate of radiologic progression is dramatically lowered over time, persisting for years after the cessation of therapy[15,26,27].

All these results suggest 2 differing concepts in RA management, (1) that DMARD therapy works best very early, and (2) longterm associations between DMARD use and radiologic progression cannot be studied in observational studies where patients were not randomized to treatments, illustrating the need for additional randomized trials in RA and reinforcing that past studies may not be easily interpreted because of design issues. Further, the use of high dose steroids early in therapy may yield potential longterm benefits by reducing the rate of radiologic bone degradation. Future large, randomized trials are anticipated to confirm these results.

SUMMARY AND CONCLUSIONS

Initial data show that combination therapy for early RA is no better than monotherapy. However, despite many studies confirming this finding, new 5 year followup data now indicate that aggressive high dose steroids, given in conjunction with DMARD early on, may play an important role in slowing and even stopping bone destruction in patients with RA. However, these findings await confirmation. Importantly, these followup data also illustrate that study design is critical for proper interpretation of outcomes and that randomized trials offer the most robust means of comparing complex therapeutic regimens among patients known to respond differently to separate therapies.

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