
Combination therapy in early rheumatoid arthritis

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ABSTRACT

The course of rheumatoid arthritis (RA) is determined early and the goals in early RA are to prevent radiologic joint degradation and to achieve optimal clinical and biological remission. Achieving these goals means that many RA patients may be candidates for combination disease-modifying therapy. We review data from randomized clinical trials regarding the impact of these treatment strategies as the initial therapy in early RA. It appears likely that the place of combination therapy will increase in the coming decades, even in very early RA patients, where the ultimate goal is persistent remission.

Rationale for early aggressive step-down therapy in early rheumatoid arthritis

Accumulating evidence indicates that the course of rheumatoid arthritis (RA) is determined early and that optimal management of RA requires a swift diagnosis and immediate aggressive treatment (1). Several randomized clinical trials have shown that conventional single-drug therapy with disease-modifying anti-rheumatic drugs (DMARDs) and glucocorticoids can alter the clinical course of RA, and retard radiographic progression (2-7). However, even therapy with methotrexate, the currently considered most effective DMARD, rarely leads to true remission, even when it is used with low-dose prednisone (8-11). Contemporary goals in early RA are to prevent radiologic joint damage and to achieve optimal clinical and biological remission, or "no evidence of disease" (8-11). Achieving these goals means that many, if not most, RA patients may be candidates for combination therapy. Furthermore, in most patients the consequences of RA seem to be considerably more severe than the side effects of contemporary DMARDs (12). Early, rather than late, institution of therapy with DMARDs has been sug-

gested to be more effective in the prevention of joint (13, 14). Radiographic damage is seen in more than 70% of patients with rheumatoid arthritis within the first 2 years of disease (15-17) and rates of radiologic progression are often highest in early disease, particularly without treatment. The "window of opportunity" theory reflects this vision of a narrow time-frame between reversible inflammatory synovitis and irreversible joint damage (18). Thus, a more favorable course of the disease (by clinical and radiological evaluation) has been reported with very early DMARD therapy; Lard *et al.* compared a median delay before initiation of DMARD of 15 days with a median delay of 123 days and found lower 2-year disease activity scores and less radiologic joint damage after 2 years in the early treatment group (19). Other studies concur with these results (20, 21). These data support the rationale for early aggressive treatment of RA. This is the principle behind the "step-down strategy" as opposed to the "pyramid strategy": a combination of DMARDs is begun initially at a high dose, followed by tapering, withdrawal of one or more agents, or both once remission is obtained (22). In fact "step-down" has always been used for flares; for example, it is usual to prescribe a short higher-dose corticosteroid therapy to treat a flare.

Published reports on combination therapy in early arthritis

Several reports have shown the beneficial effects of combination treatment with DMARDs on the outcome of patients with RA, as measured by disease activity and joint damage, but these studies were not focused on early RA and will not be described here (23-28). Three major randomized controlled trials have been published reporting combination therapies in early arthritis. We briefly summarize the main results of these clinical trials.

1. Methotrexate, sulfasalazine and prednisolone

The COMBInatietherapie Bij Reumatoïde Artritis (COBRA) trial is a randomized double-blind controlled trial comparing step-down combination therapy with sulfasalazine monotherapy in patients with early RA who had never taken DMARDs (29). COBRA combination therapy involved step-down prednisolone (initially 60 mg/day, tapered in 6-weekly steps to 7.5 mg/day, then stopped after week 28), low-dose methotrexate (MTX) (7.5 mg/week, then tapered and stopped after week 40), and sulfasalazine (SSZ) (2 gram/day). After approximately 6 months, all patients were placed on SSZ alone. The trial included 155 patients (combination treatment: $n = 76$; SSZ alone: $n = 79$) with early active RA satisfying RA ACR criteria (30) of < 2 years duration and with no prior treatment with DMARDs or corticosteroids, except hydroxychloroquine. Median duration of the disease was 4 months. The study length was 56 weeks.

Results from the initial 56-week study indicated that COBRA combination therapy was more efficacious than SSZ monotherapy with respect to suppressing disease activity at week 28 (the difference in clinical response between the treatment arms was lost at week 58). Moreover, radiologic progression during the first 18 months was significantly slower in the COBRA group than in the SSZ monotherapy group. The median change in joint damage determined as a modified Sharp score after 12 months was 2.0 in combination-DMARD patients compared with 8.0 in the sulfasalazine treatment group ($p = 0.004$) (29).

Patients who took the drug combination had fewer side effects of therapy, lower total medical costs, and more frequent capacity to remain employed compared with patients who received SSZ only. In the SSZ group, significant differences in the progression of joint damage were observed between the subgroup of patients with the shared epitope DR4 at the HLA-DR locus compared with the patients who were negative for the shared epitope. How-

ever, in the combination treatment group, no significant differences in joint damage were observed between the subgroups positive or negative for the shared epitope (31). The authors concluded that early and aggressive treatment is especially effective in a subgroup of patients with shared epitope positivity, although the trend is similar for shared epitope-negative or rheumatoid factor-negative patients, but less pronounced. These results are consistent with those of a study by O'Dell *et al.* (32), who observed significantly better clinical improvement, as measured by joint tenderness and swelling, in shared epitope positive patients with longstanding disease who were treated with the triple-DMARD combination of methotrexate, sulfasalazine and hydroxychloroquine compared with shared epitope positive patients who received methotrexate alone.

According to the results of a 5-year follow-up of patients in the COBRA trial (33), blinded treatment was continued until week 80 whenever possible. During the follow-up period, the treating rheumatologists were allowed to select therapy with no limiting rules. In both groups, the radiographic damage scores according to the Sharp method increased significantly over time; however, the mean change per year was 35% lower in the COBRA group (5.6 points versus 8.6 in the SSZ group; $p = 0.03$). After adjustment for differences in treatment and disease activity during follow-up, the difference between groups in the rate of radiologic progression was 3.7 points per year. In conclusion, the initial 6-month cycle of intensive combination treatment including high-dose corticosteroids resulted in sustained suppression of the rate of radiologic progression over 5 years.

2. Methotrexate, sulfasalazine, hydroxychloroquine and prednisolone

In the FIN-RACo (FINnish Rheumatoid Arthritis Combination therapy) trial, recent-onset (< 2 years duration) active RA patients who were DMARD-naïve were recruited for a multicenter, parallel-group, randomized study to compare the efficacy and

tolerability of combination DMARD therapy (simultaneous sulfasalazine, methotrexate, hydroxychloroquine and prednisolone) with those of single-DMARD therapy (initially, SSZ 1 gram twice daily with or without low-dose prednisolone) (34). Median duration of symptoms was 6 months. The main end point was the induction of remission, according to the ACR preliminary criteria for remission (35). One hundred ninety-five patients began therapy, 97 with combination DMARD therapy and 98 with single-drug therapy. Combination therapy was initiated with SSZ 500 mg twice daily, MTX 7.5 mg/week, hydroxychloroquine 300 mg/day, and prednisolone 5 mg/day, but the protocol allowed flexible subsequent dose adjustments to mimic clinical practice (final doses were SSZ 1-2 gram/day, MTX 7.5-15 mg/week, hydroxychloroquine 300 mg/day). Oral prednisolone (5-10 mg/day) was prescribed for 63 patients in the single-DMARD therapy group, according to the clinicians' decisions. SSZ as single-drug therapy was replaced with MTX monotherapy due to inefficacy or intolerance in 51 of the 98 original single-treatment patients. The combination strategy induced more remissions than the single drug strategy, 37% versus 18% at 2 years ($p = 0.003$) (34). Clinical improvement (ACR 50 criteria) was achieved after 1 year in 75% of patients with combination therapy, and 60% with single-drug therapy ($p = 0.028$), while at the 2-year visit ACR 50 results were 71% vs. 58%, respectively ($p = 0.058$). Radiographic progression was significantly lower in the combination therapy group. The frequency of adverse events was similar in both groups.

Furthermore, a delay of more than 4 months from the onset of symptoms to institution of therapy decreased the capacity of the traditional single-drug strategy to induce remission in early RA, whereas delay to therapy (or any other variable) did not influence prediction of remission with combination-DMARD therapy (36).

3. Methotrexate and sulfasalazine

This study investigated the potential

clinical benefit of a combination therapy on 205 recent-onset (< 1 year) active RA patients in a multicenter cohort who had not been treated with DMARDs previously (37). Patients had to be rheumatoid factor positive and/or HLA-DR 1 or 4 positive. Patients were randomized to 3 treatment groups: SSZ 2-3 gram/day (n = 68), MTX 7.5-15 mg/week (n = 69), or combination SSZ + MTX (n = 68). The study lasted 1 year. The mean changes in the DAS were -1.15, -0.87, and -1.26 in the SSZ, MTX, and SSZ + MTX groups, respectively (p = 0.019). However, the number of ACR responders and radiographic progression in the 3 groups did not differ significantly. Adverse effects were more frequent in the combination-DMARD group, but tolerability remained acceptable.

The results at 5 years for 146 of the initial 205 RA patients were presented in another report (38). Patients were followed and treated by their own rheumatologists, who freely introduced therapy, after the end of the 1-year study. At the end of the 5 years of follow-up, the patients receiving single or combined treatment were similar for mean DAS, HAQ, and radiographic scores.

In this study, combined therapy with MTX and SSZ during the first year did not influence the long-term inflammatory status, disability or structural progression; a clinically relevant superiority of the combination therapy was not seen.

Which DMARDs should be combined?

Discussions of combination therapy are directed at which molecules to use. Two separate one-year studies of combination therapy with MTX and SSZ seemed to offer no benefits compared to either drug used as monotherapy (3, 39). In a meta-analysis published in 1990 (40), no significant difference between MTX and SSZ monotherapies was evidenced, but this is in contrast to several studies showing that low-dose methotrexate given weekly is more effective than monotherapy using traditional disease-modifying drugs, with acceptable toxicity (41-43). Other

work indicated that methotrexate was continued for much longer than other DMARDs in clinical care, suggesting that it had greater efficacy (44). These data suggest that short-term clinical trials are not sufficient to evaluate long-term efficacy, perhaps explaining the lack of differences between MTX and SSZ in some studies. Thus associations of methotrexate plus another DMARD should be strongly considered (45).

On the other hand, DMARD combinations so far proven to be superior to single DMARDs have initially also included a corticosteroid component. Landewé *et al.* suggested that the use of intensive, short-term combination treatment in patients with early rheumatoid arthritis (RA) according to the COBRA schedule (33) induces a sustained reduction of the rate of radiological progression. Since this trial compared a combination of MTX, sulfasalazine and prednisolone to SSZ alone, it is difficult to assess whether the long-term beneficial effects were due to MTX, prednisolone, or both.

Low-dose corticosteroids also appear to provide considerable clinical benefit to many, if not most, patients with RA and are widely used. Recently, van Everdingen *et al.* presented new insights concerning corticosteroid therapy in early RA (46). The authors included 81 patients presenting active RA of < 1 year duration, not previously treated, between 1992 and 1995. They randomly assigned 41 patients to placebo and 40 patients to 10 mg/day prednisone in monotherapy, over 2 years. The active group showed significantly greater clinical improvement than the placebo group, particularly over the first 6 months, and use of additional therapies was significantly less common in the prednisone group. After month 6, radiographic scores showed significantly less progression in the prednisone group than in the placebo group. However, the prednisone group also experienced more adverse events (body weight increase, hyperglycemia, and new vertebral fractures). This study suggests a place for low-dose prednisone in combination with DMARDs in early active RA. Some authors suggest that 10 mg is a high

rather than low dose of prednisone, and generally begin and maintain treatment with 3-5 mg per day (47).

The new drugs approved for rheumatoid arthritis – leflunomide, IL-1 inhibitors, and anti-TNF – expand the possible combination therapy options with two or more DMARDs; more information on combination regimens in very early disease and long-term safety will emerge with time. Thus, methotrexate is certainly an essential DMARD in any combination therapy; benefits and risks of long-term low dose corticosteroids must be carefully weighed, and the exact place of the newest agents will necessitate further studies.

Conclusion

The concept of combination therapy in early RA is certainly appealing in view of what is known of the natural history of this disease; yet there are few data from randomized trials regarding the impact of these treatment strategies in early RA. Until recently, it was recommended that a combination therapy with DMARDs should be considered only in patients with residual inflammation after maximum doses of single agents (3). There have been few studies published of results of combination-DMARDs as initial therapy in early RA but their results are beneficial, and further studies with large numbers of patients and lasting 5 years or more are needed to determine the long-term effectiveness, toxicities and optimum clinical use of DMARD combinations in early RA. At this time, combinations of disease modifying anti-rheumatic drugs are used in at least some RA patients by almost all rheumatologists (10, 22, 48); it appears likely that the place of combination therapy will increase in the coming decades, even in very early RA patients, where the ultimate goal is persistent remission.

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