Treatment strategies in recent-onset rheumatoid arthritis : the best study

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Chapter 2

Combination therapy in rheumatoid arthritis

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ABSTRACT

It has become clear that early suppression of rheumatoid arthritis disease activity is important in preventing progressive joint destruction and functional decline. To achieve this goal, many rheumatologists today advocate a more aggressive approach, using combinations of classical disease-modifying antirheumatic drugs–often including methotrexate–or new drugs. But, evidence on what should become our new approach is still scarce. During the last 2 years, the combination of methotrexate, sulphasalazine, hydroxychloroquine and prednisolone has been demonstrated to be more beneficial than monotherapy in patients with early rheumatoid arthritis. In addition, the superior efficacy of the combination of new tumor necrosis factor-α blocking agents plus methotrexate to methotrexate alone in patients with longstanding disease is very promising. Most studies of combination therapy focus on the efficacy of a combination compared with monotherapy, rather than on the efficacy of a treatment strategy. Although these studies of combination therapy provide useful information about the possible synergistic action of combinations of drugs, many questions remain unanswered and studies evaluating different treatment strategies are needed before a new approach can be suggested.

INTRODUCTION

During the past two decades, the therapeutic approach to patients with rheumatoid arthritis (RA) has changed markedly. Traditionally, nonsteroidal anti-inflammatory drugs were anchored at the base of the treatment pyramid. The application of the few available disease modifying antirheumatic drugs (DMARDs) was considered only after long-term (3-6 months) failure to suppress disease activity, because these drugs were thought to be more toxic than beneficial. This conventional pyramid approach was first challenged in the late 1980s [1]. Long-term follow-up studies showed RA to be a disease characterized by poor outcome, with progressive joint destruction, severe functional decline, disability and premature mortality in most patients [2-4]. Joint destruction was demonstrated to begin early in the course of disease, frequently during the first 2 years [5], underscoring the benefit of early treatment with DMARDs. Nonsteroidal anti-inflammatory drugs and DMARDs were demonstrated to have the same toxicity profile [6-8]. This knowledge led to a more aggressive treatment approach with early, continual, and serial use of disease-modifying agents, advocated by Fries as *the sawtooth strategy* [9]. Sokka and Hannonen [10] and Sokka *et al*. [11] reported the functional outcome of patients treated using this strategy for 8.5-13 years to be better preserved compared with historical data. However, long-lasting remission in RA is still exceptional, and even then progression of joint damage is hard to prevent. Through the efforts of Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT), rheumatologists have sharpened description of the outcome of disease in terms of disease activity, response criteria for drug efficacy, and functional loss. Radiologic damage as an outcome measurement has become increasingly refined and important.

Analogous to the way oncologists combine drugs, rheumatologists started to test combinations of moderately-acting DMARDs with different mechanisms of action, hoping to achieve addition or even synergy without increase in toxicity compared with the same agents used sequentially. In 1989, a step-down bridge model was proposed; this model used a combination of rapid-acting and slow-acting antirheumatic drugs to achieve early, sustained, and safe control of inflammation and to prevent joint damage and functional decline [1]. The earliest studies of combination therapy showed only a modest advantage, often with higher toxicity [12;13]. A meta-analysis of clinical trials published in 1994 concluded that combination therapy should not be recommended for widespread use [14]. However, most of these studies were small, nonrandomized trials, and the combinations used were potentially more toxic. During the last decade, the perception of combination therapy has become much more positive. Many questions still remain unanswered, however [15]. Should combination therapy be started initially, or only after failure to control disease activity with the most effective single DMARDs?

The importance of early treatment of patients with RA has become clear during the last decade. Long disease duration, previous DMARD use, female sex and worse Steinbrocker functional class were demonstrated to reduce the likelihood of treatment response [16]. Furthermore, delayed introduction of DMARDs was shown to lead to more damage [17]. As confirmed by later studies, early introduction of DMARDs results in a significantly better outcome compared with delayed application [18·] [Lard *et al*.,

Table 1. Controlled clinical trials on combination therapy published in 1999 or 2000.

Study	Study design	Patients, *n*	Treatment comparison	Disease duration
Dougados *et al*. [18], 1999	Double blind randomized	209	MTX + SASP vs MTX or SASP + placebo	2,3-2,4 mo
Möttönnen *et al*. [21·], 1999	Open randomized	195	MTX + SASP + HCQ + Pred vs MTX / other DMARD(+ /- Pred)	7,3-8,6 mo
Çalgüneri *et al*. [22], 1999	Open randomized	180	MTX + SASP + HCQ vs MTX + SASP or MTX + HCQ vs MTX or SASP or HCQ	2,2-2,5 yr
Drosos *et al*. [24] 2000	Open randomized	102	MTX + pred vs CSA + pred	2,1-2,2 yr
Proudman *et al*. [25], 2000	Open randomized	82	MTX+CSA+i.a.steroids vs SASP	8,4-8,9 mo
Keyszer *et al*. [26], 1999	Observational matched cohort	112	MTX + CYC + CQ vs MTX	12,6-12,7 yr
Rau [27], 1999	Observational	223	MTX + parenteral gold vs MTX	7,7-9,6 yr
Weinblatt *et al*. [28··], 1999	Double blind randomized	89	MTX + etanercept vs MTX + placebo	13 yr
Lipsky *et al*. [30··], 2000	Double blind randomized	428	MTX + infliximab vs MTX + placebo	9-12 yr
McKown *et al*. [33], 1999	Double blind randomized	190	DMARD(s) + oral type II collagen vs DMARD(s) + placebo	12,8-13,9 yr
Taylor *et al*. [34], 1999	Double blind randomized	36	DMARD(s) + synacthen vs DMARD(s) + placebo	6,6-8,1 yr

CYC, cyclophosphamide; CSA, cyclosporin-A; DMARD, disease-modifying antirheumatic drug; HCQ, hydroychloroquine; IA, intra-articular; MTX, methotrexate; ND, no difference; SASP, sulfasalazine.
*No previous DMARDs/DMARD-naïve.

Table 1. Continued.

Number of previous DMARDs	Length of follow-up	Clinical efficacy of combination vs monotherapy	Radiographic efficacy of combination vs monotherapy	Toxicity of combination vs monotherapy
*	52 wk	Trend better	Trend better	Significantly more
*	2 ys	Significantly better	Significantly better	Signifanctly less
*	2 yr	Significantly better	Significantly better	ND
*	48 mo	ND	ND	ND
*	48 wk	Significantly better first 3 mo, then no difference	ND	ND
4-6	1 yr/end of treatment (13-57,5 mo)	ND	Not determined	ND
Unknown	12-108 mo	ND	Not determined	ND
2,7-2,8	24 wk	Significantly better	Not determined	ND
2,5-2,8	54 wk	Significantly better	Significantly better	ND
Unknown	6 mo	ND	Not determined	ND
1,3-1,5	6 mo	Trend worse	Not determined	ND

unpublished data]. Studies of combination therapy in patients with chronic RA still provide useful information about possible beneficial combinations and are of special value for patients who failed to respond to all available agents; however, emphasis is on studies with combination therapy in patients with early RA (Table 1).

EARLY RHEUMATOID ARTHRITIS

The latest studies of combination therapy in DMARD-naive patients with a disease duration of less than 2.5 years are discussed here in a chronological order.

Methotrexate and sulfasalazine compared with single components

Dougados *et al*. [19] conducted a double-blind, randomized trial with 52 weeks follow-up. A total of 209 patients with a disease duration of about 3 months received the combination of methotrexate plus sulfasalazine or either methotrexate or sulfasalazine alone. The American College of Rheumatology and European League Against Rheumatism response rates tended to be higher in patients treated with the combination of methotrexate and sulfasalazine compared with monotherapy. However, no statistically significant difference in the number of responders between groups could be demonstrated. Statistically significant improvement was seen in the combination group compared with monotherapy only for the variable disease activity score. Analysis of radiographic progression was performed on the 73% of patients who completed the study. There was a trend in favor of a lower progression rate in the combination group compared with both monotherapy groups, but no statistically significant difference could be demonstrated. Mild to moderate adverse events occurred significantly more often in patients treated with the combination of methotrexate and sulfasalazine; however, premature discontinuations caused by adverse events were equally distributed among the treatment groups. As in earlier studies, no evident beneficial effect of this combination compared with monotherapy was demonstrated [20].

Methotrexate, sulfasalazine, hydroxychloroquine and prednisolone versus disease-modifying antirheumatic drug monotherapy

In an open, randomized trial with 2-year follow-up, Möttönen *et al*. [21·] compared combination therapy with monotherapy in 195 patients with a mean disease duration of about 8 months. Patients were randomized for treatment with either a combination of methotrexate 7.5 to 15 mg/wk plus sulfasalazine 1 to 2 g/d plus hydroxychloroquine 300 mg/d plus prednisolone 5 to 10 mg/d, or therapy with a single DMARD combined with oral prednisolone up to 10 mg/d, if necessary. In the single drug treatment group, patients started with sulfasalazine 2 to 3 g/d, which was successively replaced by methotrexate 7.5 to 15 mg/wk, azathioprine 2 mg/kg/d, or another effective DMARD in case of adverse events or a clinical response of less then 25% at 6 months evaluation. After 1 and 2 years

of treatment, a significantly greater clinical improvement was seen in the combination group. Moreover, in the combination group, significantly less radiographic progression occurred compared with the group of patients treated with a single DMARD. An equal number of adverse events was seen in both groups, although more liver enzyme elevations occurred in the monotherapy group. This study demonstrated the superiority of the combination of methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone compared with monotherapy.

Monotherapy versus combination therapy with two or three disease-modifying antirheumatic drugs

Çalgüneri *et al*. [22] performed an open randomized trial in which 180 newly diagnosed, DMARD-naive patients with RA were treated with a combination of two or three DMARDs or monotherapy. Mean disease duration at the start of the study was more than two years. Patients in the monotherapy group were randomized for treatment with methotrexate 7.5 to 15 mg/wk, sulfasalazine 1 to 3 g/d, or hydroxychloroquine 200 mg/d. Patients receiving a combination of two DMARDs were randomized to treatment with methotrexate plus sulfasalazine or with methotrexate plus hydroxychloroquine. These groups were compared to a group of patients receiving the combination of all three drugs. Concomitant use of nonsteroidal anti-inflammatory drugs was allowed, and all patients received prednisolone 1 to 2 mg/d. All patients had a significantly better clinical outcome at the end of the 2-year follow-up period than at baseline. More patients in the groups combining two or three DMARDs fulfilled the American College of Rheumatology criteria for remission compared with monotherapy. Combination of three DMARDs was more effective than combination of two DMARDs. In patients treated with a single DMARD, statistically significant radiographic progression was seen compared with baseline, which was not seen in the two and three DMARD combination groups. No difference in the number of adverse events between the treatment groups was observed.

Consistent with the results of the study described previously [21·], the combination of methotrexate, sulfasalazine, and hydroxychloroquine was demonstrated to be superior to single drug therapy in patients with early RA.

Methotrexate and prednisolone versus cyclosporin A and prednisolone

Supplementary to the results of an open randomized trial with 24-month follow-up [23], in 2000 *Drosos et al*. [24] published the 48-month results. A total of 102 DMARD-naïve patients with a median disease duration of 2 years were treated with either methotrexate 0.15 mg/kg/wk or cyclosporin A 3 mg/kg/d. All patients concomitantly received prednisolone 7.5 mg/d tapered to the minimum possible dose. Significant clinical improvement compared with baseline was seen in both groups, but statistically significant difference between the groups could not be demonstrated in either clinical efficacy or radiographic progression. The total number of adverse events was equal in

both groups; however, more hypertension was seen in patients treated with cyclosporin A and more nausea and liver enzyme elevations in patients treated with methotrexate. Both methotrexate and cyclosporin A combined with prednisolone are effective in the treatment of patients with RA.

Methotrexate, cyclosporin A, and intra-articular corticosteroids versus sulfasalazine

In an open randomized clinical trial, Proudman *et al.* [25] compared the efficacy of the combination of methotrexate, cyclosporin A and intra-articular corticosteroids with single therapy with sulfasalazine. Eighty-two patients with a mean disease duration of about 9 months were randomized to receive either combination therapy or monotherapy. In the combinationgroup, all active joints, including all small joints, were injected with corticosteroids, whereas in patients receiving sulfasalazine monotherapy, painful joint effusions were aspirated and injected with corticosteroids only when clinically indicated. During the first 3 months, a greater and more rapid reduction in clinical parameters of disease activity was seen in the combination group, but after 24 and 48 weeks the difference between the two groups was no longer statistically significant, except for joint swelling. More premature discontinuations caused by lack of efficacy were seen in the group of patients treated with sulfasalazin. The dose of cyclosporin A was reduced in 22.5% of patients because of elevated creatinine and in 22.5% of patients because of hypertension. There were no differences in radiographic deterioration between the treatment groups. Apart from the more rapid relief of clinical symptoms in the combination group, no evident beneficial effect of combination therapy over monotherapy was seen.

LATE RHEUMATOID ARTHRITIS

Compared with the drug combinations tested in patients with early RA, the combinations tested in patients with chronic RA are more heterogeneous. Besides studies of combinations of classic DMARDs, many studies evaluate the efficacy of a new drug or possible new DMARD that might be added to the existing therapy with classic DMARDs. Accordingly, we subdivided the studies described in this section into three different categories. Within these categories, studies are discussed in chronological order.

Combinations of classic DMARDs

Methotrexate, cyclophosphamide and chloroquine versus methotrexate

From a database with records of 1800 patients, Keyszer *et al.* [26] prospectively selected 56 patients with active RA who failed to respond to at least four DMARDs and previously had insufficient response to methotrexate. All of these patients were treated with the combination of methotrexate 15 mg/wk, cyclophosphamide 50 mg three times a week, and chloroquine 250 mg/d. Treatment efficacy was assessed every 6 months.

If a reduction of 50% or more in the number of swollen joints was seen compared with baseline, or if a patient reached the Steinbrocker criteria stage I or II, treatment was continued. Data were compared with the results of the previous methotrexate therapy in the same group, and with a matched patient cohort consisting of 56 patients identified from the same database who were receiving methotrexate for the first time. Baseline characteristics differed between the two groups: In the combination group, more swollen joints and a higher modified Lansbury index were seen, and patients had failed significantly more DMARDs. In both groups, results after 1 year and at the end of treatment were compared with baseline values. Significant improvement of the number of swollen joints was seen in both groups. An effect on the erythrocyte sedimentation rate was seen only in the matched cohort receiving methotrexate for the first time and during the previous methotrexate therapy in the combination group. In the matched cohort of patients receiving methotrexate for the first time, effective therapy could be given longer than in the combination group (57.5 *vs* 19 months). However, in the combination group, the duration of effective therapy was longer than the previous methotrexate therapy in the same group (13 months). The number of premature discontinuations caused by side effects was the same in both groups. The combination of methotrexate, cyclophosphamide, and chloroquine can be valuable to patients with refractory RA.

Gold and methotrexate versus methotrexate

Rau [27] published the results of an observational, nonrandomised study to compare the efficacy of methotrexate alone with the combination of methotrexate and gold. A total of 223 patients with a median disease duration of about 8 years were followed up for 12 to 108 months (mean 34). These patients represented all patients who started treatment with methotrexate between 1980 and 1987. Whether a patient was treated with methotrexate alone or in combination with gold was based on the judgement of the physician. As expected, more swollen joints, a higher level of C-reactive protein, more radiographic progression and a trend toward longer disease duration were seen at baseline in the combination group. At the end of evaluation, there was a significant clinical improvement compared with baseline in both treatment groups. No difference in clinical efficacy or toxicity was found between the groups. Only slightly more withdrawals caused by side effects were observed in the single-therapy group than in the combination group. Taking into account that the patients in the combination group had higher disease activity at baseline, treatment with the combination of methotrexate and gold is at least as effective as monotherapy.

Combinations of classic DMARDs and new drugs

Tumor necrosis factor-α blocking agents and methotrexate versus methotrexate

In a trial performed by Weinblatt *et al.* [28··], 89 patients with a mean disease duration of 13 years who had active RA despite treatment with methotrexate were randomized for blind treatment with methotrexate together with placebo or etanercept. Patients were

followed up for 24 weeks. A greater and more rapid improvement of clinical parameters was seen in patients treated with etanercept compared with placebo. The number of both adverse and serious adverse events was equal among the treatment groups. However, mild injection site reactions were reported more often in the group of patients treated with etanercept (42%) than in the group treated with placebo (7%). Seventy-nine of the patients were followed up in an open study of etanercept and methotrexate [29]. Continued clinical efficacy was seen after 6 to 18 months of treatment, despite dose reduction or cessation of methotrexate and prednisolone in a considerable number of patients. Methotrexate could be stopped in 25% of patients and prednisolone in 38% of patients. A 66% dose reduction of methotrexate was achieved in 65% of patients and a 72% reduction of prednisolone in 67% of patients.

This year the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) study group, represented by Lipsky *et al.* [30··] and Maini *et al.* [31··], published the results of both the 30-week and the 54-week follow-up of a large randomized study comparing the efficacy of methotrexate and placebo with methotrexate and anti-tumor necrosis factor-α (TNF-α). A total of 428 patients with a median disease duration of 9 to 12 years who had active RA despite methotrexate therapy were randomized for treatment with methotrexate and either placebo or infliximab in one of four dose regimen: 3 or 8mg/kg every 4 or 8 weeks. The combination of methotrexate and infliximab was significantly better for all clinical outcome parameters compared with methotrexate alone. Infliximab 3mg/kg every 8 weeks seemed to be less effective than the other doses of infliximab, but this difference was statistically significant only for the American College of Rheumatology 50% criteria. The radiographic progression was greater in patients treated with methotrexate and placebo than in patients treated with methotrexate and infliximab. In the latter group, no progression of radiographic damage was seen compared to baseline. The number of adverse and serious adverse events was equally distributed among the treatment groups. Patients treated with infliximab had slightly more upper respiratory tract infections and headache; also, more antibodies against double-stranded DNA and antinuclear antibodies were seen, but without clinical implications so far.

Last year, the results of the 102-week follow-up were published in abstract form [32]. A sustained clinical benefit was seen in patients treated with infliximab, and there was no radiographic progression compared with baseline. The evident superiority of the combination of methotrexate and TNFα-blocking agents to methotrexate monotherapy in patients with late RA gives hope for future treatment.

Combinations of classic disease-modifying antirheumatic drugs and possible new disease –modifying antirheumatic drugs

Addition of oral type II collagen or placebo to existing rheumatoid arthritis therapy

Mc. Kown *et al.* [33] conducted a double-blind, randomized Phase II trial to evaluate the efficacy of the addition of oral type II collagen to the existing therapy of patients with RA. A total of 190 patients with a mean disease duration of more than 10 years

were randomized for treatment with oral type II collagen or placebo and were followed up for 6 months. Seventy-five percent of these patients received nonsteroidal anti-inflammatory drugs, and 85% were treated with DMARDs. Except for concomitant use of cyclosporin A or cyclophosphamide, treatment with all DMARDs was allowed either alone or in combination. More than one fourth of all patients withdrew, mostly because of lack of efficacy. No significant difference in clinical efficacy between patients treated with placebo and patients treated with bovine type II collagen was seen, even when only patients who completed the study were analyzed.

Addition of synacthen or placebo to existing rheumatoid arthritis therapy
Taylor *et al*. [34] evaluated the efficacy of synacthen (tetracosactrin), a synthetic polypeptide consisting of the first 24 amino acids of natural corticotropin, added to existing antirheumatic therapy. Thirty-six patients with a mean disease duration of about 8 year received either subcutaneous synacthen depot or placebo within 24 hours of admission and after 48 hours. Concomitant intra-articular or intramuscular injections of corticosteroids were allowed in both groups. Compared with baseline, significant clinical improvement was seen in both the group of patients receiving synacthen and the group receiving placebo. The only difference between groups that could be demonstrated was that more patients in the synacthen group reached the American College of Rheumatology criteria for 50% improvement directly after discharge. There was a trend toward more use of concomitant intra-articular or intramuscular corticosteroids in the group receiving synacthen in the 3 months after discharge, indicating a possible rebound worsening of disease activity in this group, which might be caused by extra suppression of corticotrophin releasing hormone secretion. Although some additional benefit of synacthen depot was seen after discharge, this effect did not continue, and there was a suggestion of a rebound worsening of disease activity.

CONCLUSIONS

The past decade has witnessed a shift in the way rheumatologists treat their patients. Irvine *et al*. [35] reported that in the 1990s patients are referred to rheumatologists earlier and are prescribed DMARDs sooner in the course of disease then in the 1980s. However, because long-term results of treatment with single disease modifying drugs are still disappointing, even when started early in the course of disease, combining several DMARDs has become more popular [36]. The main goal in the management of rheumatoid arthritis is to achieve complete remission and prevent progressive joint damage [37-42]. To achieve this goal, many rheumatologists today advocate a more aggressive approach, using combinations of DMARDs. Large, well performed clinical trials of combination therapy are scarce, however, especially in patients with early RA, providing a shaky foundation for combination therapy [43].

In the past, O'Dell *et al*. [44] demonstrated the superiority of the combination of methotrexate, sulfasalazine, and hydroxychloroquine in patients with chronic RA, and

Tugwell *et al*. [45] demonstrated the superiority of the addition of cyclosporin A to methotrexate. During the last two years, most studies evaluating established DMARDs have been observational. Randomized trials particularly focussed on new drug combinations, such as anti-TNFα, synacthen and oral type II collagen, added to the existing RA therapy. These studies concentrate on patients who previously failed to respond to treatment with single DMARDs, thereby selecting a group of nonresponders and noncompliers. The results of these studies still provide useful information about the possible synergistic action of various drugs and can give hope to patients who also have failed to respond to new drugs. With new knowledge available that early suppression of disease activity is important, studies of the possible benefit of initial combination therapy in all patients with early RA would be even more interesting.

In 1997, Boers *et al*. [46] demonstrated the superiority of the combination of methotrexate, sulfasalazine, and step-down prednisolone to monotherapy with sulfasalazine in patients with early rheumatoid arthritis. Although clinical efficacy equalized after cessation of both prednisolone and methotrexate, sustained reduction of radiographic joint damage was seen even 4 years after the initial and single step-down approach [47]. During the past 2 years, the efficacy of the O'Dell combination together with low-dose prednisolone has been evaluated in patients with early RA in two open randomized clinical trials. Both Möttönen *et al*. [21·] and Çalgüneri *et al*. [22] demonstrated the superiority of this combination to treatment with the single components. Çalgüneri *et al*. [22] also showed the combination of methotrexate plus sulfasalazine and of methotrexate plus hydroxychloroquine to be better than monotherapy with the same agents; however, Dougados *et al*. [19] and Haagsma *et al*. [20] could not demonstrate the difference in efficacy between treatment with the combination of methotrexate plus sulfasalazine and monotherapy with these drugs to be significant.

It has become clear that early and sustained suppression of disease activity to prevent joint damage and functional decline should be the goal in the management of RA, but data on how to achieve this goal are still unsatisfactory. What should our new strategy be? Many trials concentrate on the composition of the combination tested rather than evaluating a strategy. When do we start combination therapy? Should it be given initially to all patients with RA, using a step-down or parallel approach, or only to a subset of patients not responding to treatment with single agents, thus using a step-up or add-on approach? And where does combination therapy stand in comparison with the introduction of new drugs like the TNF-α blocking agents? There is an obvious need for large, randomized, blinded studies comparing different treatment strategies to answer these questions.

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