
Benefit/risk of combination therapies

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ABSTRACT

It is now accepted that rheumatoid arthritis is not a benign disease, and has considerable morbidity and increased mortality rates. Monotherapy with disease modifying anti-rheumatic drugs (DMARDs) is often ineffective, and rarely leads to sustained clinical remission. Many clinical trials suggest the effectiveness of using combination therapies, and also the benefit of aggressive management early in the course of the disease. However, recent publications studying a variety of combination therapies in rheumatoid arthritis have shown diverse results. Drug combinations at an early stage of rheumatoid arthritis which slow radiographic progression appear to be the most convincing. These data suggest that practitioners should begin with intensive therapy in early disease, and not reserve combination therapy for those who fail monotherapy. The therapeutic strategy should be positioned according to the severity of the disease: in RA with markers indicating severity, combination should be initiated at the start of therapy while it should be instituted in a rapid step-up fashion in mild RA if insufficient efficacy is seen for monotherapy. In general, combinations appear safe and well-tolerated, but continued caution with appropriate monitoring of long-term results and possible toxicities is required.

Introduction

Recognition of a need for aggressive therapy, introduction of new disease-modifying antirheumatic drugs (DMARDs), and recent data supporting the use of combination therapy have markedly changed rheumatoid arthritis (RA) treatment over the last 20 years. In 1989, Healy and Wilske proposed a new therapeutic approach to combination therapy called the "step-down bridge" (1). The concept was to introduce medications at the onset of therapy, and then to withdraw them sequen-

tially, in contrast to the traditional pyramid approach in which drugs were added sequentially. Thus, based on their own experience, the authors suggested the initiation of early treatment and the use of a combination of DMARDs.

What is the rationale for combination therapy?

The understanding that patients must be treated earlier (2-8) has led to great interest in combination treatments. Monotherapy with DMARDs is often ineffective and combining DMARDs might lead to additive effects (9, 10). The major concept is to enhance efficacy with an expected synergistic action, and possibly to reduce doses and avoid or reduce toxicities. DMARDs generally act via different mechanisms, suggesting that combination DMARD therapy might have extra beneficial effects. In addition, over the last decade a better understanding has been gained of the immunopathogenesis of RA and of the mechanisms of DMARD action. Combining two or more DMARDs has been now widely used and accepted (9, 10) without increasing drug side effects.

Nonetheless, despite significant advances in understanding RA and the introduction of more sophisticated therapies, the optimal approach remains undefined. In patients with early aggressive disease, it is unclear whether we should begin with intensive therapy – mostly methotrexate plus another agent – or reserve combination therapy for those who fail methotrexate monotherapy. In other words which regimen – step-up or step-down – should be used? The response is not unequivocal. Although many patients are adequately treated by methotrexate alone, this drug rarely leads to true remission, and for the most severe patients precious time can be lost. One approach would be to treat patients who have severe disease with combination therapy at the first

visit, but the majority with mild disease could have a single DMARD such as methotrexate, and be seen 8-12 weeks later to determine whether a further combination seems to be indicated.

Many other questions remain to be answered: Which drug(s) to use? How many drugs and which ones to combine? Which patients will be candidates? When to start them?

Over the past 4 years, several studies of combination therapy have been published, which are briefly summarized in Table I. Three main strategies are recognized (9,10): Step-up, in which patients with active disease despite prior drug therapy receive an additional drug; Step-down, in which a combination is initiated in the patient, with sequential removal of individual drugs over 3-12 months; and a "parallel" strategy, with neither the addition nor the subtraction of drugs.

Methotrexate plus sulfasalazine plus hydroxychloroquine

One of the first trials of combination therapy was reported by O'Dell *et al.*, who established the effectiveness of the triple combination of methotrexate + sulfasalazine + hydroxychloroquine over both methotrexate alone and the double combination of sulfasalazine + hydroxychloroquine (11). Later, the same authors confirmed their results, documenting the superior efficacy of the triple therapy versus the double therapies of methotrexate + sulfasalazine or methotrexate + hydroxychloroquine (12).

In the FINRACO (FINnish Rheumatoid Arthritis Combination therapy) trial, the triple combination of methotrexate, sulfasalazine, and hydroxychloroquine and prednisolone (5-10 mg/day) induced more remissions than did therapy using a single-drug strategy of sulfasalazine or methotrexate, with or without prednisolone, in DMARD-naïve patients with early arthritis (13). A delay to the introduction of therapy of less than 4 months was predictive of remission in the single drug-treated patients, while no variable was found to be predictive in the combination-treated patients. These data emphasize the value of introducing combination

DMARDs as an initial therapy, particularly when a delay in the initiation of therapy was seen (14). More recently, a 5-year follow-up study of patients showed an improvement in terms of work productivity in patients with combination therapy – with no work disability in those who had remission compared to substantial work disability in patients who had ACR 20 or 50 responses (15).

In the COBRA (Combinatietherapie Bij Reumatoïde Artritis) study, the combination of methotrexate (stopped after week 40) and sulfasalazine, as well as prednisolone (initially 60 mg/day, resulted in significantly better clinical outcomes in patients with early RA, compared to sulfasalazine alone (10). The corticosteroids were tapered in 6-weekly steps to prednisolone 7.5 mg/day and discontinued after week 28) (16). The combined therapeutic regimen slowed radiologic progression significantly more than sulfasalazine alone at weeks 28, 56, and 80. Moreover, the 5-year follow-up COBRA study showed a sustained reduction in the rate of radiological progression (17).

In contrast, in two studies – one by Haagsma *et al.* (18) and one by Dougados and associates (19) – no differences were seen in clinical or radiological effects between sulfasalazine and the combination of sulfasalazine and methotrexate in patients with RA. These results were confirmed in a 5-year follow-up study (20). Therefore, it appears possible that differences in effectiveness between combination therapy and sulfasalazine in the study by Boers and colleagues may have been due to the additional effect of prednisolone.

Methotrexate plus leflunomide

Open studies suggested an improved clinical response with combination therapy using methotrexate plus leflunomide (21). A 24-week randomized, double-blind, placebo-controlled study was conducted in patients who had persistently active RA despite six months of methotrexate therapy, by comparing leflunomide plus methotrexate to placebo plus methotrexate (22). This

step-up trial showed a clinical benefit with the combination therapy, but with slightly greater liver toxicity resulting in elevated levels of liver aminotransferase enzymes. Thus, this combination appears to be of benefit with appropriate liver enzyme and hematologic monitoring.

Methotrexate plus cyclosporin

Tugwell *et al.* performed a 6-month randomized, double-blind trial, comparing combination methotrexate plus cyclosporin to methotrexate plus placebo in 148 patients with active RA despite partial responses to prior methotrexate treatment (23). After 6 months, patients who received combination therapy showed greater clinical improvement than patients who were receiving methotrexate only. The frequency and causes of adverse events were similar to those of methotrexate and cyclosporin as monotherapies. More recently, a randomised single-blind controlled study (24) compared the same therapies with a parallel design in early RA, and did not find clinical advantage to the combination. However, the combination was found to reduce the damage score progression when considering the values greater than the smallest detectable difference. Gerards *et al.* compared the same combination with cyclosporin monotherapy in a 48-week randomised, double-blind controlled study also in early RA (25). A trend to the superiority of combination therapy was found in clinical measurements, but differences were not statistically significant. Nevertheless, the capacity of cyclosporin to slow radiological progression was confirmed. Regarding safety, these last two trials and two others (26,27) suggested an increased number of adverse events in the combination group, including hypertension and a rise in serum creatinine. In two studies comparing methotrexate plus cyclosporin with sulfasalazine alone, the combination appeared to be more efficient as rescue therapy (28), but when used as first-line therapy the aggressive regimen was not better than monotherapy, although it led to more rapid disease suppression (27). Differences in apparent effectiveness

Table I. Combination therapy trials published since 2000.

Author-Year	Study design	Early/late RA	No. pts.	Combinations	Therapy strategy	Follow-up	Clinical efficacy	Radiological efficacy	Toxicity
Proudman 2000 (20)	Randomised controlled	E	82	MTX+CsA+intraarticular corticoids vs SSZ	Parallel	48 weeks	No difference	No difference	No difference
Lipsky 2000 (23)	Randomised double-blind controlled	L	428	INF+MTX vs MTX	Step-up	54 weeks	Combination SB	Reduction of score progression	Autoantibodies levels significantly higher, asymptomatic
Kremer 2002 (15)	Randomised double-blind controlled	L	263	MTX + LEF vs MTX	Step-up	24 weeks	Combination SB	Not done	ALT levels significantly greater
O'Dell 2002 (5)	Randomised double-blind controlled	L	171	MTX+HCQ vs MTX+SSZ vs MTX+SSZ+HCQ	Parallel	2 years	Triple therapy (SB then MTX+SSZ) Trend better than MTX+HCQ	Not done	No difference
Landewé 2002 (13)	Open-label extension	E	144	MTX+SSZ+Pred vs SSZ	Step down	5 years	Initial DAS28 between-group difference tends to disappear	Sustained reduction of progression	Not done
Ferraccioli 2002 (21)	Open controlled	E	126	MTX+CsA vs SSZ MTX+CsA+SSZ vs SSZ	Step-up	3 years	2 Combinations SB SSZ alone	Not done	Adverse events significantly higher in combination with CsA
Maillefert 2003 (12)	Open-label extension	E	146	MTX+SSZ vs MTX vs SSZ	Parallel	5 years	No difference	No difference	Not done
Marchesoni 2003 (17)	Randomised single-blind controlled	E	61	MTX+CsA vs MTX	Parallel	12 months	No difference	Damage score progression >SDD significantly lower	Adverse events significantly higher
Gerards 2003 (18)	Randomised double-blind controlled	E	120	MTX+CsA vs CsA	Parallel	48 weeks	Trend better for combination	Reduction of score progression	Trend to increasing hypertension or serum creatinine
Weinblatt 2003 (27)	Randomised double-blind controlled	L	271	ADA+MTX vs MTX	Step-up	24 weeks	Combination SB	Not done	No difference
Klareskog 2004 (26)	Randomised double-blind controlled	L	686	ETA+ MTX vs MTX or ETA	Parallel	24 wks for clinical 52 wks for radiological response	Combination SB	Negative progression rate	No difference
Genovese 2004 (33)	Randomised double-blind controlled	L	244	ETA+ANA+MTX vs ETA+MTX	Step-up	24 weeks	Combinations SB MTX alone No difference between triple and double combination	Not done	Higher incidence of serious adverse effect with triple combination

ADA: Adalimumab ; ANA: Anakinra; CsA: Cyclosporin A; ETA: Etanercept; HCQ: Hydroxychloroquine; INF: Infliximab; LEF: Leflunomide; MTX: Methotrexate; Pred: Prednisolone; SSZ: Sulfasalazine; RA: Rheumatoid arthritis; SB: Significantly better; SDD: Smallest detectable difference.

between these trials may be explained primarily by differences in study design. The findings would suggest that a step-up strategy with the addition of cyclosporin in non-responders would be more appropriate than a step-down strategy, mainly because with an anchor drug like methotrexate (10,29), many patients can be effectively controlled, covering the apparent benefit of cyclosporin.

Methotrexate plus tacrolimus

A multi-center open-label study conducted at 13 United States sites enrolled 80 patients who had active RA despite methotrexate treatment (30). They received 3 mg tacrolimus as a single oral dose once per day for 6 months while continuing to receive methotrexate. The ACR20 clinical response rate at the end of treatment was 52.5% (95% confidence interval 41.6–63.4%). However 7 patients (12.5%) withdrew from the study because of adverse events, including one serious case (pancreatitis), possibly or probably related to treatment with tacrolimus.

TNF α blocking drug plus DMARDs

A multicenter, placebo-controlled trial – the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) – showed that infliximab in combination with methotrexate provided clinical and radiological benefit in patients with active RA who had only partial responses to methotrexate therapy (31, 32). No significant differences were seen in the number of adverse events in the infliximab plus methotrexate versus methotrexate only groups, but higher levels of autoantibodies were observed in the infliximab groups. It should be recognized that the design of this trial, as in many "step-up" trials, excluded patients who had responded effectively to methotrexate.

The clinical benefit of the combination of etanercept and methotrexate compared with methotrexate alone in patients with persistent active RA was demonstrated in a 24-week, step-up, double-blind trial (33). Mild injection-site reactions were reported to occur

more often in the combination group. These results were confirmed by the TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcome) study (34). This parallel trial with three arms compared the efficacy and safety of the same combination with the two monotherapies in 686 patients with active RA. The combination treatment was shown to be more effective than either monotherapy to control disease activity. The combination also led to a negative progression rate of the total Sharp score, suggesting the induction of the repair of structural damage (35). The number of patients reporting infections or adverse events was similar in each group, except that the number of injection-site reactions which was higher in the patients treated with etanercept.

The Anti-TNF Research Study Program of the Monoclonal Antibody Adalimumab (D2E7) in Rheumatoid Arthritis (ARMADA) trial was conducted with a step-up design in 336 patients with active RA, again after partial responses to methotrexate therapy (36). The addition of adalimumab was well tolerated and led to rapid clinical improvement, although again patients who had good responses to methotrexate had been excluded.

In early studies, such as the ATTRACT and ARMADA trials (32,36) which selected for patients who were only partial responders to methotrexate, the superiority of combination methotrexate with TNF blocker agents was documented in patients who demonstrated only partial responsiveness to prior monotherapy. However, recent trials like TEMPO (34), in which three arms were compared, suggest that combination therapy is more effective than methotrexate monotherapy in patients who had never been treated with this drug.

No controlled trial is available comparing the efficacy and safety of leflunomide alone with a combination of leflunomide plus a TNF blocking agent. However, two open studies provide information concerning leflunomide and infliximab. In an open-label study, 20 patients with active RA received leflunomide initially for 32 weeks followed

by the addition of infliximab (37). The results revealed a high frequency of adverse events leading to premature withdrawal in 55% of the patients. An open, retrospective study was conducted on the safety and efficacy of leflunomide in combination with infliximab in 88 patients (38). In general, leflunomide was used initially and infliximab was added to better control disease activity. Improvement was seen in efficacy measures and the safety profile appeared acceptable.

The interleukin 1 receptor antagonist (IL-1Ra), anakinra has demonstrated modest clinical efficacy in RA as monotherapy or combination therapy with methotrexate, including slowing radiographic progression (39,40). Animal data supported the hypothesis that IL-1Ra administered in combination with PEGylated soluble tumor necrosis factor receptor type I (PEG sTNFRI) might provide substantially more clinical benefit to RA patients than either agent alone, at the blood levels that are currently achievable in patients (41). To test this hypothesis, 244 patients with active RA despite methotrexate therapy were treated with addition of etanercept (soluble TNF α receptor) alone or combined with anakinra for 6 months in a double-blind study (42). The triple combination therapy offered no added benefit over the combination of etanercept + methotrexate, and appeared to increase the risks of serious infection and neutropenia.

Conclusions

Most available data support the use of combination DMARDs in early RA (43) and the early use of disease modifying drugs has become widespread. Combinations of traditional agents such as methotrexate with sulfasalazine or with cyclosporin appear to be not so positive in studies conducted in patients in an early stage of the disease. However, data concerning cyclosporin suggest a positive outcome in terms of the reduction of structural progression. Some possible explanations are differences in patient populations, methotrexate dose, dose strategy and, most of all, study design. Nonetheless, the safety profiles of most combinations are

good or satisfactory.

Studies using methotrexate in combination with leflunomide, and those including cyclosporin should be specifically monitored. Liver toxicity for leflunomide and nephrologic toxicity for cyclosporin should be further detailed. It appears that a combination of anti-TNF and methotrexate is superior to either therapy alone (44). The only study evaluating a biotherapy combination (i.e. anakinra and etanercept) based on animal data showed no added benefit but greater toxicity (42). This result suggests a need to maintain cautious monitoring of the potential side effects, particularly with any new drug combination.

The appropriate strategy for combining drugs remains under discussion. The step-down strategy seems to be the most appropriate for patients with severe disease. By contrast the step-up strategy, with the addition of DMARDs in non-responders, would appear to be more appropriate for most patients with mild disease activity, as many can be effectively controlled with an anchor drug like methotrexate (44). However, it is now recognized that radiological progression can be slowed by suppressing the inflammation response during the first year (20). In this respect, the most convincing combinations include those using prednisolone or TNF α blocker agents, showing the ability to slow radiographic progression (9, 32, 34). Thus, the early and aggressive use of combined treatment in severe forms of RA is supported by these findings. The next generation of studies should target people with early RA in order to analyze whether there is a critical "window of opportunity" during which these combined therapies might offer the greatest benefits (45,46). Also, in further studies, it would be of considerable interest to compare step-up and step-down strategies.

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