Combination DMARD therapy including corticosteroids in early rheumatoid arthritis

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ABSTRACT

A number of reports indicating the growing acceptance of simultaneous therapy with multiple disease-modifying antirheumatic drugs (DMARDs), as well as the use of more aggressive treatment measures in the early phases of disease to combat rheumatoid arthritis (RA), have appeared during the last decade. However, only a few randomized controlled clinical trials have been conducted on the use of DMARD combinations in early RA. We review these trials in this article.

In two separate one-year studies combination therapy with sulphasalazine (SSZ) and methotrexate (MTX) seemed to offer no benefits compared to either drug used as monotherapy. On the other hand, the DMARD combinations so far proven to be superior to single DMARDs have initially also included a corticosteroid component.

In the COBRA study (Combinatietherapie Bij Reumatoide Artritis) the combination of SSZ (2 gm/day), MTX (7.5 mg/week for 40 weeks), and prednisolone (Prd) (initially 60 mg/day, tapered in 6 weekly steps to 7.5 mg/day and stopped after 28 weeks) compared to SSZ alone (2 gm/day) resulted in significantly better clinical outcomes at week 28. Although the difference in clinical response between the treatment arms was lost at week 58, the progression of joint damage remained statistically significantly slower at week 80 in the patients initially assigned to the combination therapy.

Furthermore, in the FIN-RACo trial (Finnish Rheumatoid Arthritis Combination Therapy Trial), therapy using a "tailored-steps" strategy with SSZ (1-2 gm/day), MTX (7.5-15 mg/week), hydroxychloroquine (300 mg/day), and Prd (up to 10 mg/day) yielded a significantly increased remission rate and less peripheral joint damage at two years than the single DMARD treatment strategy (initially SSZ 2 gm/day), with or without Prd. Adverse effects in both study arms were comparable.

Two additional preliminary reports (in abstract form) suggest that intensive local therapy in the form of intra-articular injections added to single or combination therapy improves both local and systemic disease control, with increased remissions and less damage.

Although still preliminary, these results should encourage the rheumatological community to treat selected RA patients with DMARD combinations from the very start.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease with a varying (1) and unpredictable (2) course. Indeed, the clinical presentation of RA may include a group of diseases with different natural courses and prognoses. Nevertheless, only over the last decade have rheumatologists become aware that the majority of patients in clinical settings develop a disease with serious consequences including progressive joint damage, a marked decline in functional status, increased comorbidity, and even premature death (3). Consequently, calls for more powerful therapies have increased (4, 5) and appear more justified (3).

The goal of treatment in RA should be disease remission (6-8). However, since the causes of RA are not established, the basis of drug treatment has remained empirical, and surrogate goals have included the control of inflammatory synovitis, improvement of functional impairment, and reduction of tissue damage.

Although treatment with disease-modifying antirheumatic drugs (DMARDs) in controlled clinical trials alters the short-term course of RA (9-13), insufficient evidence exists regarding their sustained benefits (14-16). The DMARDs as a group are chemically diverse, their modes of action are largely unknown, their pharmacokinetics are not fully understood and they are potentially toxic (15). Despite the limitations of DMARDs,

more intensive use of the traditional DMARDs has been advocated, because: (i) the "pyramidal" treatment strategy with DMARDs is not effective over long periods in the vast majority of patients in preventing the progression of RA; (ii) preliminary data indicate that DMARD therapy offers the potential for a better long-term outcome; and (iii) the long-term use of DMARDs appears safe (17). Therefore, new treatment strategies have been proposed with the use of more than one DMARD simultaneously in the hope of achieving an additive efficacy (4).

The theoretical rationale for the use of DMARD combinations is also well established (18). Since the inflammatory activity of RA, as well as the rate of development of joint damage, is often most rapid during the first two years of disease, the early phase appears the optimal time for aggressive interventions. Furthermore, one should initiate therapy to control inflammation before irreversible damage is seen (19). However, most studies of combination DMARD therapy so far have included primarily patients with advanced RA, i.e., those who have shown an inadequate response to traditional therapy. These selected patients have a decreased chance of future response, as well (20).

On the other hand, only limited information is available from randomized clinical trials of DMARD combination therapy which include early and DMARD-naive RA patients.

Combination therapy in RA has recently been reviewed (20). In this paper, we focus on the reports of treatment of patients with early RA with combinations of DMARDs (21-25). We used the database from our previous review, and extended the search to June 1999. In addition, we searched the abstracts from the ACR meetings of 1997 and 1998, and contacted the authors to obtain additional details (26, 27).

How early is early ?

Initiation of DMARD therapy early in the course of RA may be more beneficial than delayed introduction (28). One study indicated that a relatively short delay of 2 - 24 months between the start of symptoms and initiation of DMARD therapy had little impact on the func-

tional and radiological outcomes after six years (2). However, the studies of Egmose et al. (29) and Munro et al. (30) indicated that the early initiation of DMARDs resulted in statistically significantly better long-term functional capacity than a delayed start. It appears reasonable to suppose that the prompt initiation of DMARD combinations offers better prospects for the control of disease in most RA patients.

The goal of initiating treatment in early disease requires an effective health care system. Despite manageable cooperation in primary and specialist patient care in Finland, our own experience indicates that a patient with recent-onset arthritis can seldom be admitted to specialist care before 2 - 6 months have elapsed from the start of symptoms. In a U.S. study, it was found that only 20% of patients with symmetric polyarthritis and positive rheumatoid factor were diagnosed within 2 months, and in more than 40% of these patients, the diagnostic delay was more than 6 months (31). Thus, the five randomised combination therapy trials reviewed in this paper represent patients with RA who were seen as early as seems feasible in clinical practice (Table I).

Patient assessment during follow up

The rheumatology community has agreed upon a certain set of core measures to be used as clinical endpoints in controlled clinical trials (32). The same endpoints can be applied to clinical studies as well.

Since RA appears to comprise a group of diseases with various natural courses, it is likely that a particular therapy may benefit certain patients but not others. Thus, differences seen with various therapies in mean (median) changes in the agreed endpoints in the whole patient group cannot necessarily be applied to all the potential patients in a cohort. It would appear appropriate to analyze as endpoints the frequencies of patients who reach specific response or remission criteria (33).

The ultimate target of treatment in RA is the induction of remission (6, 7). Reported remission rates in six-month to two-year assessments in patients with recent-onset RA treated either by a sin-

gle DMARD or placebo have varied between 12% and 27% (16, 25, 34-38). No evidence exists that one particular traditional DMARD therapy can induce remission more frequently than others in early RA. On the other hand, a study by ten Wolde et al. showed that the discontinuation of long-term DMARD therapy in patients in remission is associated with a doubling of the flare rate compared with uninterrupted treatment (39). Since RA is a disease of dysregulation, and no therapy affects this dysregulation (but rather its consequences), continued long-term therapy appears to be necessary in most patients.

Evidence of the efficacy of early combination DMARD therapy

Information regarding the reviewed studies, including study group sizes, the individual drugs and drug combinations compared to one another, as well as the treatment strategies, endpoints applied, and study durations, are summarised in Table I.

Combination therapy with sulphasalazine (SSZ) and methotrexate (MTX) has been reported to be no more effective than the individual components given as monotherapy in two randomised, controlled, double-blind, one-year follow-up studies of early RA patients (21, 22). In addition, toxicity was comparable between the three treatment groups in the trial of Haagsma et al. (21), while nausea was significantly more prevalent in the patients allocated to the combination therapy than in those assigned to single drugs in the trial by Dougados et al. (22). The development of joint damage was also assessed in the multinational study, and progression was found to be comparable in each treatment arm (22).

Van den Borne et al. enrolled early RA patients with a sub-optimal response to chloroquine monotherapy into a randomised, placebo-controlled, double-blind, 24-week study to investigate the efficacy and tolerability of the addition of low-dose cyclosporine A (CSA) (1.25 mg/kg/day or 2.5 mg/kg/day) or identical placebo into the regimen. No significant benefits were found, but the addition of CSA (2.5 mg/kg/day) resulted in the significant loss of renal function (Table I) (23).

Table I. Randomised controlled trials of combination treatment strategy with early RA patients.

First author (ref.)	Number of patients, selection criteria	Symptom duration at baseline	No. of groups	Drugs compared	Corticosteroid use during trial	Combination treatment strategy	Evaluation at (time)	Clinical efficacy and (x-ray) [sig.]	Toxicity
Haagsma (21)	105, DMARD naive	Mean 3 mos. (≤ 1 yr.)	3	MTX + SSZ vs. MTX vs. SSZ	Not allowed	Parallel with dose adjustment	52 wks.	ACR20: 78% vs. 74% vs. 71% (NS)	Similar
Dougados (22)	209, DMARD naive	Mean 13 mos. (diag. RA < 1 yr.)	3	MTX + SSZ vs. MTX vs. SSZ	Not reported	Parallel with dose adjustment	52 wks.	ACR20: 65% vs. 59% vs. 59% (x-ray [NS])	Combination slightly more adverse events
van den Borne (23)	88, sub-optimal responders to CQ	Mean 4 mos. (< 3 yrs.)	3	CQ + Pl vs. CQ + CSA 1.25 mg/kg/day vs. CQ + CSA 2.5 mg/kg/day	Not reported	Parallel	24 wks.	ACR20: 28% vs. 34% vs. 50% (P=0.07)	CQ+CSA 2.5: Signif. renal function loss
Boers (24) COBRA trial	155, previous treatment with HCQ in 23% of patients	Median 4 mos. (≤ 2 yrs.)	2	SSZ + MTX + Prd vs. SSZ	Combi: Prd 60 mg/day tapered to 7.5 mg and stopped after 28 wks. Single: not allowed	Step-down	28 wks. / 56 wks.	ACR50: 49% vs. 27% (P=0.007) Rem*: 28% vs. 16% (P=0.14) (x-ray [P ≤ 0.0001]) ACR, Rem not sig.; Effic. withdr. 5% vs. 15% (x-ray [P=0.004])	Total withdr. (eff.+ tox.) 8% vs. 29% (P=0.0008)
Möttönen (25) FIN-RACo trial	199, DMARD naive	Mean 8 mos. (< 2 yrs.)	2	Combi.: Mainly SSZ + MTX + HCQ + Prd vs. single DMARD ± Prd	Combi: up to 10 mg/day Single: 0–10 mg/day	Tailored steps with flexible dose adjustment	2 yrs.	ACR50: 71% vs. 58% (P=0.058) Rem#: 37% vs. 18% (p=0.003) [x-ray [P=0.002]]	Similar
Proudman (26+pers. commun.)	82, DMARD naive fulfilling criteria for poor outcome	Median 8 mos. (< 1 yr.)	2	Combi: MTX + CSA + Cs injections in all inflamed joints vs. single SSZ + injections	Apart from i.a. injections in both groups, 1 x 120 mg methylpred. on failure to respond	Flexible selection of joints, fixed injection dose/joint	24 wks. / 48 wks.	ACR50: 40% vs. 24% (P=0.15) Efficacy withdr.: 2% vs. 24% (P=0.007) ACR50: 40% vs. 31% (NS) Rem*: 43% vs. 36%, persistent 12% vs. 10% (NS) (x-ray [P=0.28])	Similar; CSA limited serum creatinine increase

DMARD = Disease-modifying antirheumatic drug; MTX = Methotrexate; SSZ = Sulphasalazine; CQ = Chloroquine; HCQ = Hydroxychloroquine; CSA 1.25 mg/2.5 mg = Cyclosporine A 1.25 mg/2.5 mg/kg; Prd = Prednisolone/Prednisone; Cs = Corticosteroids; Pl = Placebo; Combi = Combination therapy group; Single = Single therapy group; RA = Rheumatoid arthritis; ACR20/50 = fulfilling American College of Rheumatology (ACR) 20%/50% response criteria; Rem = Remission rate; * = ACR criteria for probable or definite remissions; # = ACR criteria for definite remission (fatigue and duration excluded; but all others had to be fulfilled); i.a. = intra-articular; x-ray = Radiographic analysis; NS = not significant.

COBRA study

In the randomized double-blind COBRA (Combinatietherapie Bij Reumatoide Artritis) clinical trial, Boers *et al.* compared the combination of SSZ (2 gm/day), MTX (7.5 mg/week for 40 weeks), and prednisolone (Prd) (initially 60 mg/day, tapered in 6 weekly steps to 7.5 mg/day) with SSZ as monotherapy in 155 early RA patients (24). Prd was stopped after 28 weeks. A response to combination treatment was almost immediately seen in the clinical parameters. At week 28, patients allocated to the combination treatment were statistically significantly better in all the primary endpoints, including the tender joint count, overall assessment of an independent assessor, grip strength, erythrocyte sedimentation rate (ESR) and the McMaster Toronto arthritis questionnaire, than the patients treated with SSZ only. Furthermore, 72% and 49% of the patients respectively in the combination treatment arm met the 20% and 50% response criteria of the ACR, compared with 49% and 27%, respectively, in the SSZ-only treatment arm. The difference in clinical efficacy between the treatment groups decreased and was not statistically significant after the withdrawal of Prd.

During the 56-week study period, 24/76 patients (32%) in the combined treatment group and 19/79 (24%) patients in the SSZ-only group showed either probable or definite clinical remission (P = 0.38). Of these patients, only one in the combined treatment group and three in the SSZ- group had persisting remission at week 56. Nevertheless, the total radiographic damage score (Sharp, van der Heijde method) for the hands and feet increased significantly more in the SSZ group than in the combined treatment group at 28 weeks (median [range]) 1 [0 - 28] versus 4 [0 - 44]; P   0.0001), and at 56 weeks (2 [0-43] versus 6 [0-54]; P = 0.004). Moreover, the difference in the total damage score remained significant at week 80 (4 [0 - 80] vs 12 [0 - 72]; P = 0.01) (24).

Significantly fewer patients were withdrawn from the combined treatment than from the SSZ treatment, due to either inefficacy or toxicity. None of the adverse effects were classified as serious or irreversible. This study with its "step-down" combination treatment strategy indicated that a combination of a relatively high dose of corticosteroid therapy with SSZ and a relatively low dose of MTX rapidly improves clinical disease activity and physical function in most patients with early RA. Furthermore, the described combination treatment appears to retard peripheral joint destruction for at least up to 80 weeks. In multiple regression analyses, a better clinical effect at 28 weeks was seen in those patients with greater baseline physical function loss and a shorter disease duration; lower levels of radiological progression were seen in patients with lower baseline disease activity, lower radiological damage, no rheumatoid factor, and HLA-DR4 negativity.

The obvious problem with this treatment schedule is the rapid loss of the initially achieved advantage in terms of clinical improvement over that of the SSZ group, most likely due to the cessation of Prd. In view of the results of the Fin-RA Co study (below), it appears likely that continued Prd may have resulted in prolonged clinical benefits.

FIN-RACo Study

In the randomised FIN-RACo (Finnish Rheumatoid Arthritis Combination Therapy Trial) clinical study, 199 DMARD-naive early RA patients were randomly assigned to combination treatment (n = 97) or single DMARD treatment (n = 98) (4 patients refused to participate). The therapies were rated for their capacity to: (i) induce clinical remission and (ii) improve the clinical as well as (iii) radiologic outcomes (25). The enrolled patients had somewhat less severe RA than in the COBRA study, as evidenced by disease activity measures, physical function and radiologic damage at baseline. The protocol allowed flexible dose adjustments in both treatment arms to mimic clinical practice. In addition, local corticosteroid injections were permitted if clinically indicated.

Combination therapy was initiated with SSZ (1 gm/day), MTX (7.5 mg/week), hydroxychloroquine (HCQ) (300 mg/day), and Prd (5 mg/day). If the initial combination was tolerated, it was continued for 3 months. In patients who did not have sufficient clinical improvement at 3 months, the respective dosages of MTX and Prd were increased to 10 mg/week and 7.5 mg/day. The highest drug dosages at 9 months and thereafter for SSZ, MTX, HCQ, and Prd were 2 gm/day, 15 mg/week, 300 mg/day, and 10 mg/day, respectively. In contrast, if the patient met the criteria for remission (ref. 33; fatigue and duration criteria excluded), the drug doses were tapered, and Prd and MTX might even be discontinued at 9 and 18 months, respectively. Furthermore, if the patient relapsed, DMARD doses were increased with the aim of once again reaching remission. If it was necessary to discontinue one or more components of the combination drugs, a combination of 3 DMARDs was reinstated by replacing the lost drug(s) with other DMARDs.

The single-drug strategy was also targeted to achieve remission. Patients allocated to the single treatment arm were allowed to take oral Prd if clinically indicated, while the simultaneous use of two or more DMARDs was strictly prohibited. SSZ (2 - 3 gm/day) was initiated in all patients, but due to insufficient efficacy or adverse events it was replaced by MTX in 51 patients during the follow up. A total of 63 patients in the single DMARD group were also treated with oral Prd (the patients with the most severe disease).

At one year, remission was seen in 24 (25%) patients assigned to the combined therapy and in 11 (11%) patients assigned to the single-drug therapy (P = 0.011). At two years, the corresponding figures were 36 (37%) and 18 (18%), respectively (P = 0.003). Furthermore, 75% of the patients who were assigned initially to combination therapy and 60% of those assigned to the single therapy, and who completed the study protocol, met the ACR 50% improvement criteria at two years (P=0.028). At endpoint analysis this difference was not statistically significant (P = 0.058). The mean improvements in symptoms, clinical signs, and physical function were comparable in both treatment groups at the 2-year visit, and the number of patients with the most resistant disease (not meeting the ACR 20% response criteria) also was comparable in both treatment groups at the 2-year assessment (22% versus 16%).

The median (interquartile range) Larsen radiographic score (range 0-210) for the hands and feet increased from baseline to month 24 in both the combination group (from 2 [0-4] to 4 [0-14]) and in the single-treatment group (from 2 [0-8] to 12 [4-20]). The differences in the increased Larsen scores were statistically significant (P = 0.002). Similarly the change in the number of eroded joints was greater in the single-treatment group (from 1 [0-3] to 4 [2-7]) than in the combination group (from 0 [0-2] to 2 [0-5]) (P = 0.006).

The median dose of MTX in the 51 patients who received it as single therapy was higher than that in the patients who received MTX in a combined regimen. More patients in the single than in the combination therapy used oral Prd during the latest month of the study (50 versus 43) and intra-articular corticosteroid injections were given more frequently in the single-treatment group than in the combination group (median 10 versus 3). The tolerability of the drugs used in both treatment strategies was similar. About 70% of the patients in each group had at least one adverse event, and with the exception of abnormal liver function, which was observed more often in the single-treatment patients, the distribution of adverse events was comparable in both treatment groups (25).

The combination treatment strategy in this study was tailored according to the patient's clinical response. "Step-down" dosing of DMARDs was allowed, while "step-up" dosing was strongly recommended for patients who had an increase in clinical disease activity or loss of the remission achieved with therapy. The described "tailored-steps" treatment strategy with a combination of several DMARDs induced remissions more frequently than treatment with a single DMARD. To our knowledge, this is the first study in RA which showed that the initially induced differences in remission rates of treatment arms may be maintained for up to 2 years. Interestingly, disease duration or disease activity at baseline were not significant predictors of remission states at 2 years (25).

The Leeds group study

The Leeds group has presented two abstracts on intensive local corticosteroid therapy in early RA. In one, Proudman *et al.* compared the combination of MTX, CSA, and corticosteroid injections into all symptomatic joints with SSZ and joint injections only when clinically indicated (26). No differences in these groups were seen in a 48-week clinical trial involving 82 patients (26). The number of patients in persistent remission was low in both treatment groups. Although patients in the combination group showed a more rapid response at 24 weeks, the total numbers of ACR responders and remissions, and the total amount of radiographic progression, showed trends in favor of the combination group which were not statistically significant.

In the second report, the combination of MTX plus injections into all the symptomatic joints was compared with MTX alone over 3 months in 26 early RA patients (27). Improved local disease control was noted in the combination group, in whom erosion-like lesions on MRI and ultrasound were seen to progress less rapidly, and even to regress compared with the MTX group (27).

Data from these two studies suggest that neither local injections nor the combination of MTX and CSA can replace the remission-inducing effect of systemic corticosteroids. However, injections may have an important local impact. Only long-term radiographic observations will allow us to determine the significance of MRI and ultrasound findings.

The role of corticosteroids

The role of corticosteroids in the treatment of RA has recently been reviewed (40). Most of the available evidence is derived from clinical trials involving combination therapy (20). Two of these trials are not reported here because they included patients with RA of longer duration (41, 42). Another trial analyzed the role of low-dose prednisone added to conventional therapy (approximately 80% of the patients were treated with DMARDs) in early RA (43). In brief, the available evidence suggests that:

1. Both the magnitude and longevity of the corticosteroid effect on disease activity depend on the timing, daily dose, total dose, and dosing schedule. The optimum dosing schedule remains to be found, but the symptomatic effect may be just as great as it was in the 1950s, i.e., as large or larger than that of any other antirheumatic drug, including the new biologic agents such as anti-tumour necrosis factor (anti-TNF). The effects appear to be at least additive to those of the other antirheumatic drugs tested.

2. There is a beneficial effect on the progression of radiographic damage that is already apparent at low doses. It may be independent of the symptomatic effect, and appears to be at least additive to the effects of other disease-controlling drugs. These effects may continue well after treatment is stopped. Results from the Fin-RA Co study suggest that corticosteroids should be given right from the first day, rather than after an unsatisfactory response has been noted (25). On the other hand, the reports from Leeds (see above) suggest that local corticosteroids may contribute to local disease control, i.e., to the slowing of damage progression in injected joints.

3. Adverse effects with short-term use are limited, manageable, reversible, and, in one study, less frequent than in the non-steroid control group. Although the manageability of potential long-term side effects such as osteoporosis has been improved through new agents such as biphosphonates and better medical care, the rate of other side effects (e.g., metabolic, immunosuppressive, development of cataracts) is still very high.

Conclusions and prospects

Although the disease course in an individual RA patient is unpredictable at diagnosis, most patients develop function losses and radiographic damage during an early phase of the disease. Furthermore, present therapies, including available DMARDs as single agents, are usually insufficient to prevent this development over long periods, although they may retard progression somewhat. The use of DMARDs in combinations may result in the more effective slowing of disease progression than DMARD monotherapy, and combinations appear to be safe provided that they are monitored carefully.

Of the combinations investigated in ran-

domised clinical trials, therapy with SSZ and low-dose MTX in the short term seem to offer no benefits compared with these drugs used singly. Most effective drug combinations include a corticosteroid as an initial component. It is likely that the immediate and highly effective suppression of inflammation as propagated by corticosteroids is of central importance in the modern management of early RA, which is targeted towards the induction of remission and the prevention of disability and damage. Whether this effect is specific to corticosteroids or is generic to any agent with a similar impact remains to be shown.

We are fortunate that new DMARDs are becoming available to treat RA. Leflunomide is a drug with a strong but traditional DMARD/DCART (disease controlling antirheumatic agent) profile resembling MTX and SSZ. Biological agents that block the action of TNF appear to have a clinical efficacy impact that is similar to high dose corticosteroids. Both agents may also have effects that slow or prevent structural damage. However, current clinical experience with these agents in early RA is limited. Despite present enthusiasm, we must approach these drugs with at least as much caution as we approach our traditional drugs, including corticosteroids. While we are increasingly able to manage the hazards associated with prolonged corticosteroid and traditional DMARD treatment, we are ignorant of the long-term hazards associated with the use of these new DMARDs.

Combination treatment with HCQ, SSZ, MTX, and Prd using a "tailored-steps" strategy as an initial therapy appears to increase the efficacy of treatment in the majority of patients compared with a single-drug strategy with or without Prd, at least for two years. This result confirms the earlier reported finding of the success of this triple therapy in patients with advanced RA (44). However, the therapy proved inefficacious in 20% of the patients.

The selection of appropriate patients for aggressive therapy remains an important problem. One argument is that patients with a good prognosis should not be subjected to the potential toxicity associated with aggressive therapy. However,

several studies have suggested our limited ability to identify patients with a poor prognosis, and these difficulties may worsen as we move toward the earlier initiation of disease-controlling therapy.

In a cohort of RA patients monitored prospectively from the start, and actively treated with DMARDs according to the "saw-tooth" therapy, only initial high disease activity and seropositivity at one year were significant predictors of a severe disease outcome (2). In contrast to earlier reports (45), the distribution of genetic factors (DR4, "shared epitope") did not differ in this cohort, which included patients with both a "benign" and a "malignant" outcome. Furthermore, in the FIN-RACo study (25), the allocation to the combination treatment regimen was the only variable of significance in predicting remission, while rheumatoid factor positivity, the swollen or tender joint count, and the disease duration at onset were not of prognostic significance.

Our as yet unpublished preliminary results from the FIN-RACo trial (25) unexpectedly suggest that the presence of DR4 is a significant predictor of remission in patients assigned to combined therapy, but not in those allocated to treatment with a single DMARD. In the COBRA trial, several well-known prognostic factors were available, although they did not modify the treatment effect. Whether these results are confirmed and whether the principle of genetic testing will in the future be more widely utilised in the selection of patients for specific therapies remain challenging prospects for clinical investigation.

The counter-argument is that a "good prognosis" does not exist in RA, only slow versus rapid progression. In addition, for the majority of patients with early RA who meet our current trial eligibility criteria, even aggressive therapies have had only limited success, and better treatment strategies are needed. Possibly our current aggressive therapies are more successful in patients with milder disease and should be applied in these patients, i.e., without selection. Rapid remission in these cases would imply only limited exposure to toxic drugs, and easy maintenance on single drugs.

In conclusion, the early phase of illness appears to us to be the most appropriate time to initiate aggressive DMARD therapy, including combination DMARDs. Current evidence shows this to be beneficial in patients with severe clinical disease activity, i.e., those with many swollen and tender joints, a high ESR and C-reactive protein level, and decreased function at presentation. Further studies should help us to delineate the role of such therapies in patients with milder disease.

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