Combination DMARD therapy with hydroxychloroquine, sulfasalazine, and methotrexate

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ABSTRACT

Triple combination therapy with hydroxychloroquine, sulfasalazine, and methotrexate (MTX) has been shown in double-blind, placebo-controlled studies to be significantly superior to MTX alone (Paulus 50% responses of 77% versus 33%). In long-term follow-up studies, this therapy has now been shown to be well-tolerated with continued efficacy in the majority of patients.

Introduction

Combinations of disease-modifying antirheumatic drugs (DMARDs) are used by 99% of the rheumatologists in the United States to treat an estimated 24% of all RA patients with rheumatoid arthritis (RA) (1). These figures have increased significantly in the last few years. This near-universal acceptance of combination DMARD therapy is a new phenomenon. The increased use of combinations has evolved for three main reasons: first, rheumatologists have been increasingly unwilling to accept incomplete improvement of their patients when remissions seem possible; second, the recognition that most DMARDs lose whatever efficacy they do have over time; and finally, the recent accumulation of data that combinations can be given safely and with greater efficacy than mono-DMARD therapy (2-4).

A combination that has been shown to be the most effective in published clinical trials is the combination of methotrexate (MTX), sulfasalazine (SSZ), and hydroxychloroquine (HCQ), the so-called triple therapy (2, 5-7). The data to support the use of this combination will be reviewed in this report.

Triple DMARD therapy:Trial design

The initial protocol designed by the Rheumatoid Arthritis Investigational Network (RAIN) sought to treat patients with RA aggressively early in the course of their disease with a triple combination of DMARDs (2). This study was designed around several basic beliefs:

1. Clinicians should have a clear goal in mind when treating RA. We chose remission as the goal of treatment.
2. MTX was the best single DMARD available and, for the foreseeable future, would be the standard against which other therapies would be measured.
3. Because MTX was the best single DMARD available, it should be included in most combinations.
4. The dose of medications should be flexible, with increases permitted within certain limits to try to achieve the treatment goal, thereby assuring that doses used in the monotherapy arm and those in the combination arms would be the same unless patients met the treatment goal (in this case, remission).
5. The success of a treatment should be clinically apparent not only to the statistician but also to the clinician and, most importantly, to the patient. Therefore, we chose a 50% improvement of composite criteria rather than the more commonly used 20%.
6. Previous blinded studies have been too short; therefore, we continued our study for 2 years.
7. Finally, we required that patients not only show 50% improvement by 9 months but also maintain this degree of improvement for the duration of the 2-year blinded portion of the study. For practical reasons we did not want to continue patients in a blinded trial after the 9-month time point if they had not achieved a clinically significant degree of improvement. At the same time, we did not want to declare the treatment a success unless the improvement was maintained for at least 2 years. Most previous blinded trials had lasted between 3 and 12 months; even our 2-year trial, which

is one of the longest blinded trials ever performed in RA, represents a very short time in a lifelong disease.

Instead of studying patients with early disease as we had originally intended, our final design enrolled only those patients who had failed on at least one DMARD. This modification was made at the request of the Food and Drug Administration, which expressed concern for the toxicity of the drugs, and because such a study population would include patients who would be more likely to have ongoing disease. FDA approval was necessary as the medications and matching placebos were provided by pharmaceutical companies.

The dose of SSZ was kept low in our study because of concerns at that time about the possible toxicity of the combination of MTX and SSZ, and to avoid extensive premature withdrawals secondary to gastrointestinal toxicity.

Triple DMARD therapy: Characteristics of the study population

All patients met the American College of Rheumatology's (ACR) criteria for RA (8) and had failed on at least one DMARD prior to starting in this study. The clinical characteristics of the patients, by treatment group, are shown in Table I. Importantly, no significant differences were seen in any of the pretreatment characteristics of these patients.

This cohort had 3 notable features. The average disease duration was more than 9 years in the MTX and Triple groups, approximately 85% of the patients were rheumatoid-factor positive, and approximately 50% were taking low-dose prednisone (mean dosage 6 mg). A design flaw in this study allowed patients who had previously failed MTX to enroll. A larger number of such patients (who would naturally be expected to do poorly on MTX) or the random assignment of a disproportionate number of them to the MTX-alone group, might have caused a serious problem. Fortunately, only 10 such patients were enrolled and they were randomly assigned evenly among the 3 groups. Exclusion of these patients did not change the results of the study. We were fortunate that this oversight in our study design did not preclude our capacity to reach a meaningful conclusion concerning the differential efficacy of our treatment arms.

Table I. Baseline characteristics of the patients with rheumatoid arthritis, according to study group (plus-minus values are means ± SD).

Characteristic	Methotrexate (n = 36)	Sulfasalazine plus hydroxychloroquine (n = 35)	All 3 drugs (n = 31)
Age (yrs.)			
Mean	50	49	50
Range	21 - 69	36 - 63	27 - 67
Sex (F/M)	25/11	26/9	20/11
Duration of disease (yrs.)	10 ± 8	6 ± 6	10 ± 10
Rheumatoid factor present (%)	89	85	84
Current prednisone therapy (%)	53	46	52
Prednisone dosage (mg/day)	6 ± 3	5 ± 3	6 ± 3
DMARDs* previously used (no. of drugs)	1.6 ± 0.8	1.6 ± 0.8	1.5 ± 0.8
Prior methotrexate therapy (no.)	3	4	4
Erythrocyte sedimentation rate (mm/hr)	39 ± 29	45 ± 27	36 ± 26
Duration of morning stiffness (min.)	190 ± 109	156 ± 96	135 ± 98
Scores on assessment scales†			
Tender joints	31 ± 18	32 ± 14	29 ± 13
Swollen joints	31 ± 19	31 ± 20	27 ± 12
All joints	63 ± 33	62 ± 31	56 ± 19
Patient's global status and pain	6 ± 2	6 ± 2	6 ± 2
Physician's global assessment	6 ± 2	6 ± 2	6 ± 1
Hemoglobin (gm/dl)	13 ± 2	13 ± 2	13 ± 2
Platelets (x $10^{-3}/mm^3$)	376 ± 118	357 ± 100	340 ± 123
Serum aspartate aminotransferase (IU/l)	22 ± 10	19 ± 6	20 ± 10
Serum creatinine (mg/dl)§	10.84 ± 0.21	0.79 ± 0.16	0.89 ± 0.20

*DMARDs: Disease-modifying antirheumatic drugs.
†As described in the Methods section.
§To convert values to micromoles per liter, multiply by 88.4.

Tolerability

Rheumatologists are by nature conservative and take seriously Hippocrates' edict, "First, do no harm." Therefore, the initial question we sought to address was whether this aggressive approach would be well tolerated. Many were concerned about the possible additive or even synergistic toxicity of MTX and SSZ. Our results, with more toxicity withdrawals in the MTX-alone arm, were at first surprising. We believe, however, that the enhanced efficacy of triple therapy is the major reason for this; patients who are doing well are less likely to complain of minor toxicities and are therefore more likely to continue with the protocol. A similar observation was made by Boers *et al.* in a recent combination vs. monotherapy study in which patients in the combination arm also had enhanced efficacy and decreased withdrawals due to side effects (4).

Triple therapy: Enhanced efficacy

Figure 1 illustrates the major findings of the blinded portion of our study; therapy with all 3 active drugs provided a substantially greater benefit than treatment with what most would agree is the standard of treatment for RA, MTX alone (P = 0.003). All patients who failed because of efficacy, toxicity, or protocol violations were considered as failures for the

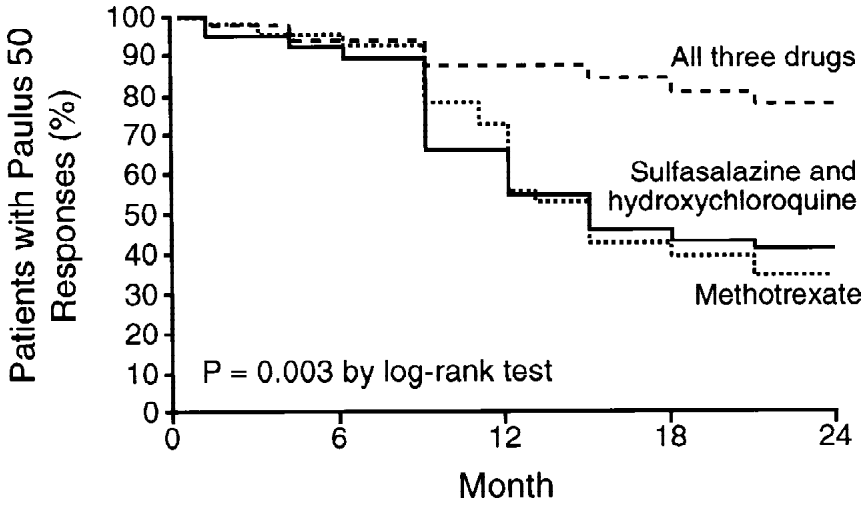

Fig. 1. Time until failure (toxicity or efficacy) of treatment. P = 0.003 by the log-rank test.

purposes of this Kaplan-Meier plot. Additionally, patients treated with the combination of SSZ and HCQ had efficacy similar to those treated with MTX alone. Some have criticized our results on the basis of the response of our MTX-alone group, arguing that our patients did not do as well as other MTX-treated patients. However, we have been unable to find any published series of MTX-treated patients who have done better than ours when the 50% improvement criteria are used. In the published reports that we are aware of, the percentages of patients who have achieved 50% improvement have been 35% by Weinblatt at four years (9) and 39% by Rau at one year (10).

Since the design of our study called for escalation of the dose of MTX, if tolerated, to aim for remission, and since few of our patients achieved remission, the dose of MTX for patients in the MTX-alone group (16.6 mg/week) and those in the triple arm (16.4 mg/week) were similar, thus allowing for the direct comparison of these treatments.

Triple therapy: Efficacy failures

Patients who were not randomized to the triple-therapy arm of the initial blinded trial and who failed to meet the 50% improvement criteria were offered an opportunity to receive triple therapy in an open observational trial (5). Table II shows the results when patients who took 17.5 mg/week of MTX (median dosage) in the blinded trial were then treated with the addition of SSZ (1 gram/day) and HCQ (400 mg/day) in the open trial.

Since MTX is the most commonly used DMARD in the US and the majority of patients treated with it will have a partial response, rheumatologists' offices are loaded with patients such as these, i.e., with partial but sub-optimal responses to MTX. Our results indicate that this group can be expected to experience substantial improvement when SSZ and HCQ are added to 17.5 mg/week of MTX.

When patients who had been treated with the combination of SSZ and HCQ in the original study failed because of efficacy, MTX was added and increased in a stepwise fashion to 17.5 mg/week. These patients had a similar degree of improvement (data not shown) to those shown in Table II.

Triple therapy: Long-term follow-up

We have now monitored 60 patients treated with triple therapy for a mean of 3.3 years (6). Thirty-one of these patients had been randomly assigned to triple therapy in the initial trial, while the other 29 had been treated with triple therapy after suboptimal responses in the initial protocol. Table III presents these data.

We now have 275 patient years of experience with this combination; 200 in the patient group described above and an estimated 75 in our current follow-up triple II study. Toxicity has forced withdrawal in 6 of the original 60 patients (10%). These toxicities included 3 withdrawals in the initial blinded study; one each for nausea, weight gain, and cervical cancer. The woman with cervical cancer was withdrawn 2 months into the study after she had visited her gynecologist for the first time in 20 years at the urging of our study coordinator. During the open portion of the study, 3 additional patients were withdrawn; one for liver enzyme elevations, one for possible ocular toxicity, and one for gastrointestinal intolerance. The patient who developed elevated liver enzymes had this occur at 51 months, simultaneously with psoriatic skin lesions (rheumatoid factor and shared-epitope [DRB1 0401] positive).

Forty-four patients (73%) have maintained 50% improvement while on triple therapy and 10 patients (17%) have failed to maintain this degree of improvement or have required changes in therapy. The other 10%, as mentioned above, had side effects. Eight patients (13%;

Table II. Results of triple therapy for patients with suboptimal response to MTX.

Variable	Initial	Follow-up	P
Erythrocyte sedimentation rate (mm/hr)	30.3	19.0	0.06
Morning stiffness (min.)	104.0	28.0	0.03
Swollen joint score	29.7	11.7	0.001
Tender joint score	30.1	10.4	0.001
Patient global status	4.1	2.6	0.03
Physician global status	5.1	3.1	0.009

Table III. Triple therapy: Results at 3.3 years (60 patients and 200 patient years of follow-up).

50% Improvement*	44 pts.	73%
Withdrawal: Side effects	6 pts.	10%
Withdrawal: Efficacy	10 pts.	17%

*Remission = 8 patients (13%)

Table IV. HLA-DRB1 typing: Selecting patients' combination therapy.

	MTX Rx		MTX + SSZ + HCQ Rx	
	SE +	SE -	SE +	SE -
Successful completers	7	5	17	7
Efficacy failures	15	1	1	1
% successful	32	83	94	88
	P = 0.03		P = 0.5	
	SE +: MTX versus Triple		P ≤ 0.001	
	SE -: MTX versus Triple		P = 0.69	

SE: Shared epitope.

examined at only one point) fulfilled modified ACR remission criteria (11). We have been unsuccessful in most of our attempts to withdraw any of the 3 DMARDs in this group of patients. Therefore, most of our patients are continuing to take all three DMARDs.

Predicting responses to therapy

One of the biggest challenges that faces most rheumatologists when treating RA patients is selecting the best DMARD or combination of DMARDs for each patient and doing so in a timely fashion. In most instances, unfortunately, while we are searching for the best drug our patient's arthritis is continuing to destroy bone and cartilage. Therefore, we are sorely in need of predictive markers early in the patient's disease process for which DMARDs are most likely to induce responses in individual patients. For our patients treated with triple therapy, we asked whether HLA-DRB1 typing might predict response to therapy [Table IV (7)].

Patients were classified as "shared epitope" positive or negative and then divided by treatment group. MTX-treated patients who were shared epitope-negative were much more likely to achieve a 50% response than those who were shared epitope-positive (83% versus 32%, P = 0.03). Shared-epitope positivity is known to be a poor prognostic factor in RA patients, and although it has not previously been reported, it was not a big surprise that shared epitope-positive MTX-treated patients did less well than like-treated shared epitope-negative patients. Further studies on the effects of the shared epitope dose confirmed this observation; patients who had a double dose of the shared epitope had the least chance of achieving a 50% response (P = 0.05).

Since there were very few efficacy failures in patients treated with triple therapy in our study, it was also not surprising that shared-epitope status did not predict response (88% versus 94% for negative versus positive, respectively, P = 0.53). Patients treated with SSZ-HCQ had similar response rates regardless of their shared-epitope status (38% if shared epitope-negative versus 43% if positive, P = 0.52).

Based on these data, one might speculate that all patients would benefit (at least in terms of the frequency of achieving a 50% improvement) if they received triple therapy. However, a closer inspection of these data in the shared epitope-negative patient group reveals that this subset of patients responded equally well to MTX alone as to triple therapy (83% versus 88%, respectively, P = 0.69). This observation suggests for the first time a clinically important differential response to therapy based on shared-epitope status.

These findings require confirmation by other investigators in other patient cohorts. If confirmed, early HLA-DRB1 typing might be indicated to facilitate more intelligent selections of DMARDs. The earliest possible selection of the most effective DMARD or DMARD combinations would be expected to lead to significant benefits for our patients.

Triple therapy versus MTX-cyclosporine A: Efficacy comparisons

The first double-blind, controlled trial to demonstrate a significant advantage of combination therapy over therapy with MTX alone was the MTX and cyclosporine A (CSA) trial published in 1995 (3). In this trial, patients were on baseline MTX, but had a less-than-optimal response to dosages as high as tolerated (up to 15 mg/week; mean dose of MTX 10.2 mg). These patients were then randomly assigned to receive CSA or placebo in addition to continuing the MTX that they were already receiving. The combination group had statistically significant improvement compared with the placebo group. Joint counts improved in the CSA group, but serum creatinine rose modestly as well (P = 0.02).

The triple-therapy data that are most similar are from our follow-up of patients treated with MTX alone in our original study (5). These patients, who were already taking 17.5 mg/week, had a 70% chance of improving by 50%, which compares favorably with those in the MTX-CSA study, who had a 48% chance of improving by 20%.

As is always the case, comparisons of results between studies is difficult; in this case the MTX-CSA patients were in a blinded study, while those treated with triple therapy after MTX had failed were in an open study, and patients in open studies can be expected to have better outcomes in general than those in blinded studies. However, the dosage of MTX in the CSA-treated patients was significantly lower than that in the MTX failures enrolled in the triple study (10.2 mg per week versus 16.4 mg/week), which might suggest a greater effect of the combination of SSZ and HCQ when added to MTX since it was added to a greater baseline dose of MTX. Additionally, our study used modified Paulus criteria (12) to measure improvement, while the MTX-CSA study used ACR criteria (13). The ACR criteria are more stringent for several reasons, but our requirement of 50% improvement rather than 20% in the MTX-CSA study more than made up for this difference.

Perhaps the biggest advantage of MTX-SSZ-HCQ over MTX-CSA, other than cost, is related to concern about the long-term toxicity of the MTX-CSA combination. Triple therapy has been shown to be well tolerated at 3 years, as previously discussed (6), while data on the long-term follow-up of CSA-treated pa-

tients reveals a dropout rate of 25% every 6 months, usually secondary to elevated creatinine or hypertension (14). The long-term renal toxicity of CSA is a concern, particularly in patients who receive concomitant MTX, a drug that depends on renal clearance.

Triple therapy: Questions

Many questions remain about the use of triple therapy to treat RA.

1. Should triple therapy be begun initially or only in a sequential fashion after patients have had a sub-optimal response to MTX alone?

The patients in our protocol had a mean disease duration of 9 years and had previously "failed" at least one DMARD; therefore, these patients do not directly address this question. The only study to do so comes from Finland, by Möttönen and colleagues (15). This study reported that the chance of achieving the goal of remission at 2 years is increased significantly if patients begin on MTX-SSZ-HCQ at the outset of therapy as opposed to taking SSZ alone (Odds ratio 2.7; 95% confidence intervals 1.3 - 5.4).

We strongly believe that the goal of treatment for RA should be remission, and to this end advocate the use of triple therapy early in the course of RA in patients who have only a partial response to MTX. If other studies corroborate our findings of the capacity of HLA-DRB1 typing to predict response to MTX, as well as the findings of Möttönen *et al.*, the initial use of triple therapy would be indicated, particularly in shared epitope-positive patients. Perhaps shared epitope-negative patients could be treated in a less aggressive manner.

2. Is it necessary to add both SSZ and HCQ to MTX to achieve the significantly enhanced response over MTX alone, or is one of them sufficient? If so, which one?

Our initial study clearly demonstrated that in the patient population we treated, therapy with MTX-SSZ-HCQ was superior to therapy with MTX alone or to therapy with SSZ-HCQ. We are currently addressing this important question with a follow-up study (Triple II) in which triple therapy is compared with MTX-SSZ and with MTX-HCQ. Of note, the combination of SSZ and HCQ was as potent as MTX alone at two years in our initial study, and attempts to stop either of these drugs in patients who are doing well on triple therapy have led to flares of disease. Early results from the Triple II study strongly suggest an advantage for the triple combination over the two double combinations.

3. When, if ever, can the therapy be tapered? And if it is tapered, which drug or drugs should be tapered first?

Even with triple therapy, most patients do not achieve remissions; remissions were seen in only 13% at 3 years. Therefore, if remission is the goal of therapy, few will be candidates for tapering. As previously noted, when we have attempted to taper any of the 3 drugs, patients have experienced flares.

4. Could higher doses of SSZ and/or MTX be used to further improve efficacy without significantly increasing toxicity?

This is an important question because the doses of MTX currently in use are significantly higher than those used in our study, which was begun in 1989. Low-dose SSZ (1gm/day) was used in our initial study. At that time, 17.5 mg/week of MTX was on the "high" side of what rheumatologists were using. In pursuit of remissions, or at least more complete responses, we frequently push MTX to 22.5 mg/week and SSZ to 2 gm/day. In patients on triple therapy, we have not seen any significant toxicity with this approach, although we continue to monitor these patients closely. In our current blinded study of triple therapy versus the double combinations, we are using 2 gm per day of SSZ. Except for a few patients who have some minor gastrointestinal side effects, we have not encountered problems.

5. What happens when folic acid is added to this regimen?

Folic acid use in patients on MTX is now widespread, as it does not interfere with efficacy but does appear to decrease toxicity in doses up to 27.5 mg/week (16, 17). Similar data on the effect of folic acid on the efficacy of SSZ do not exist, and little is known about this interaction. In the early part of our triple study, folic acid was not used, but since we allowed clinicians to use it at their discretion, it was frequently prescribed by the end of the study when its ability to alleviate toxicity without interfering with efficacy was apparent. We do not know whether this intervention had an effect on efficacy or side effects in the patients on triple therapy.

The future of combination DMARD therapy

The possible combinations and permutations of DMARDs that could be used to treat RA are extensive, particularly if one includes corticosteroids, steroids, biologicals, and drugs such as minocycline or doxycycline in these calculations. These choices are further complicated if certain combinations have differential effects in patients relative to the stage or duration of their disease, a likely possibility. Therefore, many more questions than answers exist for combination therapy.

I believe that for the foreseeable future, MTX will continue to hold its position as the primary anchor of combination therapy, and that both low-dose corticosteroids and metalloproteinase inhibitors will likely be important adjuncts.

Clearly, the goal of remission for a substantial portion of our patients remains elusive. However, with the recent success of combinations (2-6), biologicals (18-22), and metalloproteinase inhibitors (23-25), the pace of progress is accelerating, as we currently have many potent therapeutic agents. The challenge for the future will be to design and conduct innovative clinical research protocols that will uncover the answers we need to allow us to use these agents at the correct time relative to the stage or duration of disease and in the best possible sequences and combinations.

References

1. O'DELL J: Combination DMARD therapy for rheumatoid arthritis: Apparent universal acceptance. *Arthritis Rheum* 1997; 40 (Suppl.): S50.
2. O'DELL J, HAIRE C, ERIKSON N *et al*.: Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996; 334: 1287-91.
3. TUGWELL P, PINCUS T, YOCUM D *et al*.:

Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. *N Engl J Med* 1995; 333: 137-41.

4. BOERS M, VERHOEVEN AC, MARKUSSE HM *et al*.: Randomized comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997; 350: 309-18.
5. O'DELL JR, HAIRE C, ERIKSON N *et al*.: Efficacy of triple DMARD therapy in patients with RA with suboptimal response to methotrexate. *J Rheumatol* 1996; 23 (Suppl. 44): 72-4.
6. O'DELL J, HAIRE C, DRYMALSKI W *et al*.: Methotrexate (M)-Sulfasalazine (S)-Hydroxychloroquine (H) combination therapy in rheumatoid arthritis (RA): Continued efficacy with minimal toxicity at 3 years. *Arthritis Rheum* 1996; 39 (Suppl.): S123.
7. O'DELL JR, NEPOM BS, HAIRE C *et al*.: HLA-DRB1 typing in rheumatoid arthritis: Predicting response to specific treatments. *Ann Rheum Dis* 1998; 57: 209-13.
8. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
9. WEINBLATT ME: Methotrexate (MTX) in rheumatoid arthritis (RA): A 5-year multicenter prospective trial. *Arthritis Rheum* 1993;36: S79.
10. RAU R, HERBORN G, MENNINGER H, BLECHSCHMIDT J: Comparison of intramuscular methotrexate and gold sodium thiomalate in the treatment of early erosive rheumatoid arthritis: 12 month data of a double-blind parallel study of 174 patients. *Br J Rheumatol* 1997; 36: 345-52.
11. PINALS RS, MASI AT, LARSEN RA, and the Subcommittee for Criteria of Remission in Rheumatoid Arthritis of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee: Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum* 1981; 24: 1308-15.
12. PAULUS HE, EGGER MJ, WARD JR, WILLIAMS HJ, and the Cooperative Systematic Studies of the Rheumatic Diseases Group: Analysis of improvement in individual rheumatoid arthritis patients treated with disease-modifying antirheumatic drugs, based on the findings in patients treated with placebo. *Arthritis Rheum* 1990; 33: 477-84.
13. FELSON DT, ANDERSON JJ, BOERS M *et al*.: The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum* 1993; 36: 729-40.
14. YOCUM DE, STEIN M, PINCUS T: Long term safety of cyclosporin/SandimmuneTM (CsA/SIM) alone and in combination with methotrexate (MTX) in the treatment of active rheumatoid arthritis (RA): Analysis of open label extension studies. *Arthritis Rheum* 1998; 41 (Suppl.): S364.
15. MÖTTÖNEN T, HANNONEN P, LEIRISALO-REPO M, *et al*.: Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis. *Lancet* 1999; 353: 1568-73.
16. MORGAN SL, BAGGOTT JE, VAUGHN WH *et al*.: Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis. *Ann Intern Med* 1994; 121: 833-41.
17. MORGAN SL, BAGGOTT JE, VAUGHN WH, *et al*.: Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis. A double-blind, placebo-controlled trial. *Ann Intern Med* 1994; 121: 833-41.
18. MORELAND LW, BAUMGARTNER SW, SCHIFF MH *et al*.: Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *N Engl J Med* 1997; 337: 141-7.
19. ELLIOTT MJ, MAINI RN, FELDMAN M *et al*.: Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. *Lancet* 1994; 344: 1105-10.
20. MAINI RN, BREEDVELD FC, KALDEN JR, *et al*.: Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998; 41: 1552-63.
21. MORELAND LW, SCHIFF MH, BAUMGARTNER SW *et al*.: Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med* 1999; 130: 478-86.
22. BRESNIHAN B, ALVARO-GRACIA JM, COBBY M *et al*.: Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum* 1998; 41: 2196-204.
23. KLOPPENBURG M, BREEDVELD FC, TERWIEL JP, MALLEE C, DIJKMANS BAC: Minocycline in active rheumatoid arthritis. A double-blind, placebo-controlled trial. *Arthritis Rheum* 1994; 37: 629-36.
24. TILLEY BC, ALARCON GS, HEYSE SP *et al.*, for the MIRA Trial Group: Minocycline in rheumatoid arthritis. A 48-week, double-blind, placebo-controlled trial. *Ann Intern Med* 1995; 122: 81-9.
25. O'DELL JR, HAIRE CE, PALMER W *et al*.: Treatment of early rheumatoid arthritis with minocycline or placebo. *Arthritis Rheum* 1997; 40: 842-8.