Early developments in combination therapy

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Clin Exp Rheumatol 1999; 17 (Suppl. 18): S8-S12.

Key words: Rheumatoid arthritis, combination therapy.

ABSTRACT

The concept of combination therapy implies the concurrent use of two or more slow-acting antirheumatic drugs to treat rheumatoid arthritis. This review places such combination therapy into an historical context and evaluates studies carried out before 1990.

There were no published studies before 1980 of combination therapy, and between 1980 and 1990 there were 11 published studies. Three were conventional randomised controlled trials, three were non-randomised studies of parallel group design, four were observational open studies, and one was a retrospective review. Altogether 486 patients were studied with the numbers of cases in each study varying between 12 and 101. The main combinations used were penicillamine + hydroxychloroquine or chloroquine, gold + hydroxychloroquine, and sulphasalzine + penicillamine. Six studies concluded that combination therapy helped patients, three suggested possible benefits, and two gave essentially negative findings. These two negative studies were randomised controlled trials. Most studies indicated an increase in adverse events with combination therapy. The average erythrocyte sedimentation rate on combination therapy fell by 21.4%. A majority of patients remained on the therapy for 6 -12 months.

The balance of evidence in 1990 suggested that combination therapy had a modest advantage. However, the trials were too small to detect its true value, and the combinations used were not ideal. In particular, combining gold or penicillamine with other drugs appeared to give too much toxicity. The future development of the field would depend on identifying more effective combinations of drugs and undertaking larger and better-designed trials.

Background

Combination therapy, in the sense of giving patients several different drugs concurrently, is universally employed in the treatment of rheumatoid arthritis (RA). Severe RA is invariably treated by combining an analgesic, a non-steroidal anti-inflammatory drug, a slow-acting anti-rheumatic drug (SAARD) and, in many cases, systemic steroids. There is near-universal agreement that RA patients benefit from this sort of polypharmacy. However, the concept of combination therapy usually means the use of two or more SAARDs at the same time together with other antirheumatic drugs.

The purpose of this review is to place combination therapy with SAARDs into an historical context. In particular, we will attempt to resolve the intriguing question as to why the clinical trials that evaluated combination therapy with SAARDs in the 1980s were generally interpreted negatively, whereas the trials of such combination therapy in the 1990s have been generally interpreted positively.

This divergence is well illustrated by comparing the conclusion reached in a review of clinical trials of combination studies published in 1994 with the conclusion reached in an audit of clinical practice published in 1998. When Felson and his colleagues (1) published a meta-analysis of clinical trials in 1994, they concluded that combination therapy with two SAARDs did not offer a substantial improvement in effficacy and also had higher toxicity than single-drug therapy. They believed that the balance of evidence was such that combination therapy regimens should not be recommended for widespread use. By comparison, Maetzel *et al.* (2) audited the use of SAARDs in 1998 in a survey of all 263 members of the Canadian Rheumatology Association and 320 members of the American College of Rheumatology (ACR) (10% random sample weighted by region) known to practice adult rheumatology. Altogether 231 (87.8%) Canadian and 230 (71.9%) US rheumatologists responded, and 214 responses in each survey were analysable. In cases of aggressive RA, most of those surveyed said that they would use combination (38.3%) or triple (23.8%) therapy involv-

ing MTX plus sulphasalazine and/or hydroxychloroquine.
Evaluating the reasons for this relatively sudden change in the perception of combination therapy with SAARDs requires a working understanding of the historical development of combination therapy with SAARDs.

Methods
The MedLine was searched from 1966 through 1995 for associations of the terms Rheumatoid Arthritis, Combination, Clinical Trial, and each individual SAARD. This revealed 327 potential papers on the subject, and from these papers 11 main clinical trials were identified together with four key meta-analyses, reviews, and editorials which have been used as the basis of our review.

Studies conducted before 1980
There are no studies of SAARD combinations published prior to 1980. The main emphasis in combination therapy during this decade was on the combined use of two non-steroidal antiinflammatory drugs. An example of this type of study is the report by Willkens and Segre (3) of 36 RA patients, which evaluated the effectiveness and safety of combined therapy with naproxen and aspirin. This was an 8-week double-blind crossover trial in which naproxen and placebo were administered on a background of constant-dose aspirin. Interestingly, combination therapy was shown to be more effective than aspirin alone, and the tolerance of the two regimens was comparable.

Open studies reported after 1980 by McCarty and colleagues
The first report of combination therapy with SAARDs was from McCarty and Carerra (4). Seventeen patients (15 women, 2 men) with progressive, erosive seropositive RA refractory to conventional therapy were studied. They were treated with the combination of cyclophosphamide, azathioprine, and hydroxychloroquine in an open observational study for an average of 27 months (range 5 - 60 months). Fourteen patients achieved disease suppression within 3 - 16 months; 5 patients achieved complete remission, 2 had activity in a single joint only, and 7 had partial disease suppression. Only 3 cases showed no response. Nine of 10 patients were able to decrease their prednisone dosage or to stop steroid therapy altogether. The authors concluded that combination therapy with small doses of 3 drugs, each with proven anti-rheumatic activity when used separately in larger doses, had the propensity to achieve long-term disease control in intractable RA. They also noted, however, that this was an experimental regimen and that controlled trials were needed to prove efficacy.
McCarty subsequently suggested in a review (5) that not only is drug therapy for RA entirely empiric, but that single agents often fail to adequately control synovial inflammation. He suggested that the use of combination therapy with relatively small doses of several agents (shown in controlled trials to be effective when used alone) could produce therapeutic control of a sustained and marked nature. He also felt that, although the associated adverse effects were frequent, they were probably no greater than those associated with the use of an effective dose of a single agent. He commented that the use of potent drugs in combination might be advantageous, as seen in the treatment of malignancy or tuberculosis.
A further report by Csuka, Carrera and McCarty (6) described the clinical course of combination therapy with cyclophosphamide, azathioprine, and hydroxychloroquine in patients with refractory RA. Thirty-one patients were followed for an average of 43 months (range 12 - 102 months), among whom 16 achieved complete remission, 7 near remission, and 7 partial disease suppression; only one had no improvement. Three patients developed significant adverse reactions and subsequently discontinued therapy; of these, two were cases of pulmonary infection and one of thrombocytopenia. Of 4 patients developing malignancy during combination therapy (comprising colon cancer, lung cancer and erythroleukaemia), 3 died.
The final report from McCarty and colleagues in 1995 (7) described the long-term morbidity and mortality in patients with seropositive RA. One hundred sixty-nine patients were treated with a combination of pulsed oral methotrexate, azathioprine, and an antimalarial drug, and were followed for a mean of 7 years (range 1 - 18 years). The numbers of patients in remission (Lansbury articular index zero) and near remission (articular index < 6) were determined. On combination therapy the rate of remission was 45% and that of near remission was 69%. Prednisone use was reduced from 34% to 19% of the patients. The most striking side effects were herpes zoster (17 patients) and second attacks of varicella (2 patients). Survival was no different from that of the general population.

Other open studies between 1980 and 1990
Bitter (8) described his experience in giving a variety of SAARD combinations to 71 RA patients over 18 months. The study designs were complex but basically involved the addition of penicillamine, levamisole, or chlorambucil to established gold therapy in 42 patients, or penicillamine in a further 29 patients who had shown a partial response. The results suggested a small advantage with combination therapy, although there were insufficient case numbers to show a significant difference. Bitter considered gold and pencillamine to be the most promising combination.
Dawes and his colleagues (9) reported 25 RA patients with a partial response to gold or penicillamine monotherapy after 10 - 24 months of standard treatment. Sulphasalazine was added to the current therapy and combination therapy was maintained for 6 months in 22 of the 25 cases. Of these cases, there were significant improvements in 7 out of 8 clinical and laboratory indices of disease activity.
Farr and her colleagues (10) reported an open study of combination therapy with sulphasalazine (1.5 - 3.0 gm daily) and penicillamine (250 - 750 mg daily) in 31 RA patients with only a partial response to sulphasalazine monotherapy. Penicillamine was started 8 - 60 months after commencing sulphasalazine and patients were followed up for 1 - 3 years of combination therapy. Of the cases 68% demonstrated a favourable clinical response. Adverse reactions in the first year

of combination therapy led to the withdrawal of penicillamine in 9 (29%) patients and of sulphasalazine in 2 (6%).
In 1990 Schwarzer and colleagues (11) reported an open pilot study of 16 patients with refractory RA. A combination of hydroxychloroquine, prednisolone, and alternating months of treatment with sulphasalazine or weekly oral pulsed methotrexate was used. There were significant improvements in clinical and laboratory disease activity measurements after 3 months. Six and 12 months after the commencement of treatment, however, improvement was not maintained. A total of 8 patients had their therapy terminated, 4 due to lack of efficacy and 4 due to side effects.
Another open study, reported in 1990 by Lee and Solomon (12), retrospectively evaluated the combination of penicillamine and methotrexate in 16 patients with seropositive RA who were treated for 5-86 months. Three patients were lost to follow-up and one patient died of an unknown cause at another institution. Among the 12 remaining patients, the combination was well tolerated and there were no withdrawals due to side effects. All 12 patients demonstrated improved function and reduced clinical and laboratory measures of disease activity. Eight of the 12 patients achieved remission (ACR criteria) which was sustained for periods of 3-72 months.

Key randomised trials between 1980 and 1990

The first randomised, double-blind trial of combination therapy was reported by Bunch and his colleagues (13) in 1984. Patients with progressive RA were treated with penicillamine and hydroxychloroquine either alone or in combination for 2 years. The greatest improvement was seen in the group given penicillamine alone, but there was a linear fall-off in efficacy. The group receiving penicillamine alone fared better than the group on combination therapy. Prolonged benefit was seen in a subset of patients receiving hydroxychloroquine. Toxicity was not uncommon, but generally was not severe.
The second randomised trial was reported by Gibson and colleagues (14). It studied 72 patients with relatively early but progressive RA who were treated with chloroquine, penicillamine, or a combination of both drugs over one year. There were significant clinical improvements with each regimen which were indistinguishable between treatments. Toxicity appeared to be increased with combined treatment. Chloroquine produced significantly fewer side effects but had less impact on ESR and C-reactive protein levels than the other treatments. Radiological deterioration was most frequent amongst those given chloroquine alone. These study results were interpreted as showing that penicillamine and chloroquine combination treatment did not offer a major advantage.
Scott and his colleagues (15) reported the results of a 12-month prospective randomised controlled trial which compared combination therapy with gold and hydroxychloroquine to monotherapy with gold and placebo. A total of 101 patients were studied, of whom 52 received combination therapy and 49 monotherapy. Fifty-nine patients completed 12 months of therapy (27 taking gold/hydroxychloroquine and 32 taking gold/placebo) and they were compared using 13 variables (5 clinical, 7 laboratory, and 1 radiological measure). All of the variables favoured gold/hydroxychloroquine, with an overall advantage of 20-25% for the combination. However, these differences were statistically significant (at the 1% level) only for C-reactive protein. Combination therapy resulted in more adverse reactions, leading to a greater number of withdrawals (18 cases with combination compared with 10 receiving gold/placebo). An overall disease activity index was better at 12 months (at the 5% level) and indicated a more rapid response with gold/hydroxychloroquine. Despite their showing a significant advantage with a combination of two slow-acting drugs, these results were not regarded as a major clinical advance.

Other prospective studies with control groups between 1980-1990

Two studies were reported using the Leeds model system developed by Bird and his colleagues (16), one published in abstract form only and the other a full paper. In both studies, patients were assessed at regular intervals using clinical and biochemical tests designed to detect specific anti-rheumatic activity. In the first, Martin and collaborators (17) compared penicillamine monotherapy with penicillamine and hydroxychloroquine combination therapy over 6 months. Combination therapy was reported to be more effective, although this result is difficult to assess in the absence of a full paper.
In the second study using the same trial design, Taggart *et al*. (18) carried out a 6-month open trial in 30 patients with active RA to study sulphasalazine alone or in combination with penicillamine. Significant improvements were seen in the clinical and laboratory variables with both regimens, consistent with second-line activity. Combination therapy resulted in both greater and more numerous improvements (9 responders with combination therapy and 6 with sulphasalazine monotherapy). However, there were double the number of study withdrawals with combination therapy, suggesting that the greater efficacy of combination therapy versus monotherapy had been at the expense of greater toxicity.

Comparative analysis of studies reported from 1980 to 1990

Tables I and II summarise the main results from the 11 studies performed between 1980 and 1990, of which 3 were conventional randomised controlled trials. The main combinations used were pencillamine + hydroxychloroquine or chloroquine, gold + hydroxychloroquine and sulphasalazine + penicillamine. A total of 486 patients were studied, with the numbers of cases varying between 16 and 101. Six studies concluded that combination therapy helped patients more than monotherapy, 3 suggested possible benefits, and 2 gave essentially negative findings. However, these two studies were randomised controlled trials. Most studies indicated an increase in adverse events with combination therapy. The average ESR on combination therapy fell by 21.4%. A majority of patients remained on therapy for 6-12 months.

Overviews of trials reported before or during 1990

During the period 1987 to 1992, there

Table I. Summary of the studies of combination therapy conducted between 1980 and 1990.

Study	Year	Cases	Groups	Months	Design	Randomised controlled trial	Drugs	Benefit from combination therapy
Martin *et al*.	1982	45	3	6	Parallel groups	No	D-Pen, HCQ	Yes
McCarty *et al*.	1982	17	1	27	Observational	No	CYC, AZA, HCQ	Yes
Csuka *et al*.	1986	31	1	43	Observational	No	CYC, AZA, HCQ	Yes
Bitter *et al*.	1984	71	4	18	Parallel groups	No	Au, Lev, CHL, D-Pen	Yes
Bunch *et al*.	1984	56	3	12	Parallel groups	Yes	D-Pen, HCQ	No
Taggart *et al*.	1987	30	2	6	Parallel groups	No	SSZ, D-Pen	Yes
Farr *et al*.	1988	31	1	36	Observational	No	SSZ, D-Pen	Yes
Gibson *et al*.	1988	72	3	12	Parallel group	Yes	CQ, D-Pen	No
Scott *et al*.	1989	101	2	12	Parallel group	Yes	HCQ, gold	Possible
Schwarzer *et al*.	1990	16	2	12	Observational	No	HCQ, PRD, SSZ, MTX	Possible
Lee & Solomon	1990	16	1	5-86	Retrospective	No	D-Pen, MTX	Possible

Au: Auranofin; AZA: Azathioprine; CHL: Chlorambucil; CQ: Chloroquine; CYC: Cyclophosphamide; D-Pen: D-Penicillamine; HCQ: Hydroxychloroquine; Lev: Levamisole; MTX: Methotrexate; PRD: Prednisolone; SSZ: Sulphasalazine.

were several editorials and reviews of combination therapy with SAARDs, including contributions from Huskisson (19), Klippel (20), Jaffe (21), and Boers and Ramsden (22). These reached broadly similar conclusions along the lines that combination therapy may be effective in severe RA, but that the evidence for its efficacy is incomplete, some combinations increase toxicity, and further work is needed before it can be recommended for widespread use.

Klippel commented that the entire role of aggressive management, particularly with combination chemotherapy, at any stage of RA is in desperate need of answers. Combination chemotherapy is widely used in clinical practice, often as a last resort in treatment-resistant patients who have failed conventional therapies. A more fundamental role of combination chemotherapy, based on the observed successes in these "difficult-to-treat" patients, has been advocated. Well designed, randomised controlled trials are urgently needed to resolve these questions before combination chemotherapy gains an even stronger foothold.

When Boers and Ramsden formally reviewed the clinical trials conducted up to 1991, they found a total of 341 papers dealing with various aspects of combination therapy. These included 7 prospective trials specifically addressing the issue, of which only 3 were of sufficient quality to yield strong or moderately strong evidence, because of deficiencies in methods and reporting. There was no conclusive demonstration of benefit with a drug combination. Two trials suggested a benefit, and one of these trials also suggested increased toxicity. One suggested only increased toxicity. The remaining four trials yielded only weak evidence to support both increased efficacy and toxicity.

Subsequent developments

The balance of evidence in 1990 suggested that combination therapy may have a modest advantage. However, these trials had been too small to detect possible advantages to combinations, and the available drugs were not ideal.

Table II. Changes in ESR and retention on therapy in randomised trials of combination therapy.

Study	Drugs	Duration	Cases	Mean fall in ESR	Remaining on therapy
Bunch *et al.*	Penicillamine	12 months	21	25	86%
	Hydroxychoroquine		18	12	61%
	Penicillamine/Hydroxychloroquine combination		17	6	53%
Gibson *et al.*	Penicillamine	12 months	26	27	85%
	Chloroquine		20	31	90%
	Penicillamine/Chloroquine combination		26	19	65%
Scott *et al.*	Gold	12 months	49	27	65%
	Gold/Hydroxychloroquine combination		52	32	52%
Scott & Huskisson	Penicillamine or Sulphasalazine monotherapy	6 months	10	NA	40%
	Penicillamine/Sulphasalazine combination		20	10	70%
Taggart *et al.*	Sulphasalazine	6 months	15	40	80%
	Sulphasalazine/Penicillamine combination		15	24	53%

In particular, combining gold or penicillamine with other drugs appeared to result in too much toxicity. The future development of the field would depend on identifying more effective combinations of drugs and undertaking larger and better-designed trials.

The search for a less toxic and therefore more effective combination can be traced to two studies reported at the beginning of the 1990s, both involving methotrexate. The first of these was by Willkens and his colleagues from 1992 (23), who treated 212 active RA patients over a period of 24 weeks with azathioprine, or methotrexate, or a combination of both. Combination therapy was not statistically superior to methotrexate therapy alone. However, both combination therapy and methotrexate alone were superior to azathioprine alone when patients were analysed on an "intention-to-treat" basis, in which withdrawals were considered therapy failures. When only patients who continued taking the therapy were analysed, the mean improvement was greater for the combination. Adverse effects were not a major problem.

The second study, a large trial led by Williams (24), compared 335 patients with active RA who were treated with auranofin, methotrexate, and the combination of both in a prospective, controlled, double-blind, multicentre trial over 48 weeks. There were no statistically significant differences among the treatment groups for a wide range of clinical or laboratory variables measured. Adverse drug reactions were slightly more common in the monotherapy group, leading to more withdrawals, but the differences were not statistically significant. Withdrawals due to lack of response were more common for single-drug therapy, with the difference between auranofin and the combination reaching statistical significance.

These trials differed in two ways from previous studies. First, both included methotrexate as the base combination therapy, and toxicity was similar in the patients treated with combination versus monotherapy. Second, both studies involved far larger numbers of patients. The scene was therefore set for trials that were more positively received and which used methotrexate as a base therapy.

Subsequent trials therefore built on the base of these early studies to suggest that combination therapy is more effective than sequential monotherapy and, provided the optimal drugs are used at realistic doses, not more toxic than monotherapy. Nevertheless, it is worthwhile to point out that the magnitude of the effect with current combination therapy is modest. There is evidence of advantage to combinations, but the goal of remission remains difficult to achieve. Further research will be required to attain the optimal management of rheumatoid arthritis.

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