Leaders

Combination DMARD therapy for rheumatoid arthritis: a step closer to the goal

"The physician without physiology and chemistry practices a sort of popgun pharmacy, hitting now the malady and again the patient, he himself not knowing which."
Sir William Osler

Without question the use of combinations of disease modifying antirheumatic drugs (DMARD) to treat rheumatoid arthritis is increasing. A recent survey found that 90% of rheumatologists in the United States use combinations to treat an estimated 17% of their patients with rheumatoid arthritis.[1] This compares to use by approximately 50% of rheumatologists in Canada and Australia one decade ago.[2] Similar figures are not available in Europe, where the use of combinations seems to be less common. The relative frequency of combination therapy used by rheumatologists in the United States suggests their aggressive pursuit of remissions, while the apparent reticence of European rheumatologists may reflects the lack of objective data to support the safety and efficacy of combination DMARD therapy. Rheumatologists in the United States appear to be more aggressive in general, as evidenced by the use of methotrexate as their drug of choice for treatment of rheumatoid arthritis,[1] while sulphasalazine appears to hold this position in Europe.

This trend toward the use of combinations of DMARD to treat patients with rheumatoid arthritis reflects a new standard of care. This new standard is not the use of the combinations themselves but rather the recent acknowledgement by rheumatologists that the goal of treatment for all patients with rheumatoid arthritis should be remission.[3] The ultimate goal, a cure for rheumatoid arthritis, remains elusive; therefore remission will have to suffice as a surrogate goal. Since complete remission is rare with even the best DMARD monotherapy,[4,5] expanded use of combinations is a natural and necessary result of trying to achieve remissions for our patients with rheumatoid arthritis.

The premise behind the use of combination therapy to treat rheumatoid arthritis is that two or more drugs used together will be more effective than these drugs used alone. Although the rationale is different, no one would question the efficacy of this strategy in oncology and infectious disease where it has been used successfully for years. When one chooses which DMARD to combine, selecting them in a rational way based on the pathogenesis of rheumatoid arthritis and the mechanisms of action of the drugs would be desirable, and this approach has been reviewed by Furst.[6] Unfortunately, Sir William Osler's observation remains appropriate today and reminds us that until we better understand the pathogenesis of rheumatoid arthritis and the relevant mechanisms of action of the drugs we are using, we will be left making imperfect choices based on inadequate data. To be clinically useful, enhanced efficacy must be accompanied by a level of toxicity of combinations that is acceptable—ideally in the range seen with monotherapy – and this should always be considered when combining DMARD. Kremer has stated that since methotrexate is the single most effective treatment for rheumatoid arthritis (based on long term continuation data), most combination DMARD protocols should include this drug[7] or be compared against this drug.

Rheumatologists have been combining NSAID, DMARD, and steroids in difficult to manage rheumatoid arthritis patients since the early 1950s. The use of combinations of DMARD has been a more recent development, and several excellent reviews of combination therapy have been published.[8–10] The first study on the use of combinations of DMARD appeared in 1963,[11] and reported on the successful use of the combination of chloroquine and gold. However, rheumatologists by nature are not very aggressive, and a statement in Hollander's *Textbook of rheumatic diseases* in 1966[12] advised against the use of combinations and seemed to curb enthusiasm for their use for more than a decade. McCarty then published dramatic response rates when a combination of cyclophosphamide, azathioprine, and hydroxychloroquine was used.[13] This report briefly increased enthusiasm for combinations until McCarty's group reported rather dramatic toxicities of this regimen, with a number of malignancies and at least three deaths.[14] Nonetheless, McCarty's response rate, with remissions in about 50% of patients, showed that there was substantial potential for improving efficacy with combination therapy.

Recently Wilske and Healey have advocated the "step-down bridge" approach: treating rheumatoid arthritis patients early in their disease with multiple DMARD, as well as prednisone and NSAID, and then decreasing the number of drugs sequentially when the disease is under control.[15] This approach has the theoretical advantage of controlling disease early, before irreversible damage occurs. Paulus has advocated the "serial" approach to combination therapy, where DMARD are added to partially successful DMARD already in use.[8] This more closely mimics what is done in practice. Recently, McCarty

reported impressive results with combination DMARD used in an uncontrolled fashion in his clinic.[16] Almost 50% of his patients were in near remission (articular index < 6), primarily using the combination of methotrexate, azathioprine, and hydroxychloroquine. While all of these approaches appear promising, they need further study in controlled trials.

The double blind controlled trial is the standard scientifically accepted way to show efficacy of interventions in disease processes. When the daunting obstacles of performing a successful clinical trial are considered, particularly with combination therapy, it is not surprising that data to support the use of combinations have been slow to accumulate. Confounding factors include funding for clinical research, patient recruitment, which drugs to use and in what combination, duration of the study, accepted endpoints to measure efficacy, dosage of the medications, numbers and kinds of control groups needed, and the numbers of patients in each study needed to show real efficacy differences.

Despite all these obstacles, several blinded trials have been published recently,[17-23] particularly over the last few years. A meta-analysis by Felson and colleagues recently examined the efficacy and toxicity of combination therapy.[24] They accepted only those trials that were blinded, and directly compared combination therapy with monotherapy. These investigators discovered only five trials that fulfilled their criteria.[17-21] With their meta-analysis, they found little to support the use of combination therapy at this time. However, only two of the five trials included methotrexate.[17 18] In one of the studies of methotrexate treatment, the methotrexate dose in the combination group was only one half of the dose in the methotrexate alone group,[17] making direct comparisons difficult. In the other methotrexate study,[18] the maximum dose of methotrexate was only 7.5 mg per week. Three of the studies included in the meta-analysis used oral gold or d-penicillamine, drugs that are currently seldom used by rheumatologists, at least in the United States.[18-20] One major problem with this meta-analysis was that it lumped all combinations together and therefore did not increase the chance of finding a benefit from one particular combination over monotherapy. Unfortunately, without meta-analysis the sample sizes of many of the individual studies would be too small to show a difference in efficacy unless these differences were dramatic.

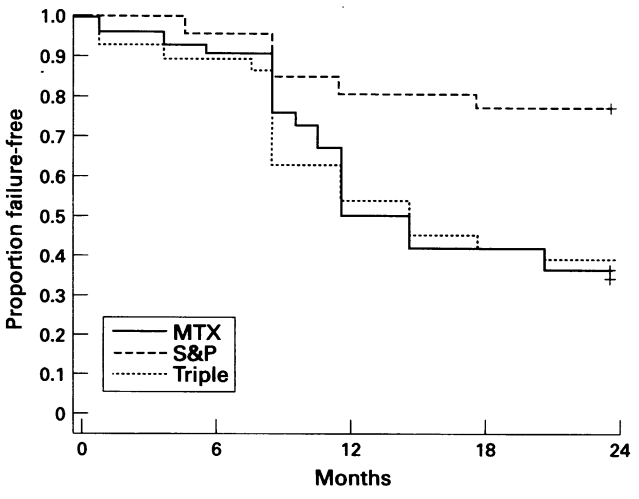
Recently, encouraging results have appeared about enhanced efficacy when cyclosporin is added to the treatment of patients who had had suboptimal responses to methotrexate.[22] This well designed protocol randomised patients on methotrexate with a favourable but suboptimal response to receive cyclosporin A or placebo in addition to their methotrexate. The investigators were able to show a statistically significant benefit of cyclosporin A and methotrexate over those receiving placebo and methotrexate. Small increases in the serum creatinine were reported for those patients receiving cyclosporin A. As the authors themselves stated, this was a six month study and long term data on toxicity and efficacy are needed.

We have recently published our results of a double blind controlled trial comparing the combination of methotrexate-sulphasalazine-hydroxychloroquine to methotrexate alone and to the combination of sulphasalazine-hydroxychloroquine.[23] Seventy seven per cent of patients treated with all three active drugs completed two years of the blinded study, having achieved 50% improvement criteria without significant toxicity. This improvement compared with 40% of the patients treated with sulphasalazine and hydroxychloroquine, and 33% of the patients in the methotrexate alone group (figure). The difference between the group treated with all three active drugs and the methotrexate alone group was statistically significant by the log rank test (P = 0.003).

Several points about the design of our study are worth emphasis. We included a combination of the three most widely used disease modifying drugs. We compared combination therapy directly to methotrexate which is felt by many rheumatologists to be the most effective DMARD. The goal of this study was to produce remissions; thus we increased the dose of methotrexate to achieve this (up to 17.5 mg per week). The dose of the other drugs was stable in the two groups which received them, so that direct efficacy comparisons between or among the treatment groups could be made. The two year duration is one of the longer controlled trials of combination or other therapy in rheumatoid arthritis. Finally, the main endpoint to define efficacy was chosen to be 50% improvement of composite criteria rather than the often used 20% improvement. The dose of sulphasalazine in our study was low (1 g per day); this dose was chosen because of concerns about possible overlapping toxicities with methotrexate. We found, as others have now shown,[25 26] that the combination of methotrexate and sulphasalazine was well tolerated. It is entirely possible that our efficacy would have improved further if we had used 2 g per day, and a protocol is in progress to study this.

The low percentage of patients in the methotrexate alone group who successfully completed the two years of the study is at first surprising. However, we have discovered no reports that suggest better results when 50% improvement criteria are used. Weinblatt has found in his cohort of patients[27 28] that 35% had achieved 50% improvement at three or four years.[28]

An open trial of patients who failed methotrexate alone or the sulphasalazine hydroxychloroquine arm of the original trial further supports the efficacy of triple therapy.[29] Since this was an open trial, the results are subject to all the bias inherent in such trials. Patients who had already been given methotrexate (17.5 mg per week) but failed to improve by 50%, improved significantly when treated with the triple protocol in the open trial. In many ways, these patients more closely mimic patients seen in clinical practice. This group of suboptimal methotrexate responders also appears similar to the group of patients reported by Tugwell *et al*[22] in the above mentioned methotrexate and cyclosporin A study. Direct comparisons between studies are always problematic, but efficacy and cost seem to favour the addition of sulphasalazine and plaquenil (rather than cyclosporin A) to methotrexate for patients with rheumatoid arthritis who are failing to respond optimally to methotrexate. The long term toxicity of both these



Time to protocol failure (intention to treat analysis).

approaches needs to be considered; triple therapy has been reported to be well tolerated at three to five years, while similar data are not available for methotrexate and cyclosporin A.

The success of combination DMARD therapy in recent double blind controlled studies is encouraging.[22 23] As is frequently the case, however, the success of these approaches raises as many questions as it answers. Should all patients with rheumatoid arthritis receive combination DMARD therapy, or should it be reserved for only those with severe disease? Are there ways to predict who will respond best? When in the course of disease should combinations be used? Which combinations are best, or does this vary among patients? After an excellent response occurs, can some or all of these drugs be tapered or discontinued? Where do biological agents fit in, and should they be used in combinations? I do not have the answer to any of these questions. Until these answers are available, we will have to do as we have always done—make the best decisions we can based on the limited data available. As I stated earlier, our goal when treating patients with rheumatoid arthritis should be remission. As we try to achieve this goal, the data available now support the use of certain combinations of DMARD. Whether combinations should be used early in the disease process as suggested by Wilske and Healey[15] or added later is still open to question.

As we better understand the mechanisms of actions of drugs and the disease process itself, we will be able to intervene more intelligently at the right time with the right drugs or combinations of drugs to improve the long term outcome for our patients with rheumatoid arthritis.

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1 O'Dell JR, Case L. The treatment of rheumatoid arthritis in 1995: results of a survey [abstr]. *Arthritis Rheum* 1995;**38**:S366.
2 Bellamy N, Brooks PM. Current practice in antimalarial drug prescribing in rheumatoid arthritis. *J Rheumatol* 1986;**13**:551–5.
3 American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for the management of rheumatoid arthritis. *Arthritis Rheum* 1996;**39**:713–22.
4 Pinals RS, Masi AT, Larsen rheumatoid arthritis, and the subcommitte 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.
5 Alarcon GS, Blackburn WD, Calvo A, Castaneda O. Evaluation of the American Rheumatism Association preliminary criteria for remission in rheumatoid arthritis: a prospective study. *J Rheumatol* 1987;**14**:93–6.
6 Furst DE. Optimizing combination chemotherapy for rheumatoid arthritis. *Ann NY Acad Sci* 1993;**696**:285–91.
7 Kremer JM. The changing face of therapy for rheumatoid arthritis. *Rheum Dis Clin* 1995;**21**:845–52.
8 Paulus HE. The use of combinations of disease-modifying antirheumatic agents in rheumatoid arthritis. *Arthritis Rheum* 1990;**33**:113–120.
9 Boers M, Ramsden M. Long acting drug combinations in rheumatoid arthritis: a formal overview. *J Rheumatol* 1991;**18**:316–24.
10 Williams HJ. Overview of combinationa second-line or disease-modifying antirheumatic drug therapy in rheumatoid arthritis. *Br J Rheumatol* 1995; **34S**:96–9.
11 Sievers K, Hurri L. Combined therapy of rheumatoid arthritis with gold and chloroquine. *Acta Rheumatol Scand* 1963;**9**:48–55.
12 Hollanders JL, McCarty DJ, eds. In: *Arthritis and allied conditions*, 7th ed. Philadelphia: Lea and Febiger, 1966.
13 McCarty DJ, Carrera GF. Treatment of intractable rheumatoid arthritis with combined cyclophosphamide, azathioprine, and hydroxychloroquine. *JAMA* 1982;**248**:1718–23.
14 Csuka ME, Carrera GF, McCarty DJ. Treatment of intractable rheumatoid arthritis with combined cyclophosphamide, azathioprine, and hydroxychloroquine. A follow-up study. *JAMA* 1986;**255**:2315–9.
15 Wilske KR, Healey LA. Remodeling the pyramid—a concept whose time has come. *J Rheumatol* 1989;**16**:565–7.
16 McCarty DJ, Harman JG, Grassanovich JL, Qian C, Klein JP. Combination drug therapy of seropositive rheumatoid arthritis. *J Rheumatol* 1995; **22**:1636–45.
17 Willkens RF, Urowitz MB, Stablein DM, McKendry RJ, Berger RG, Box JH, *et al.* Comparison of azathioprine, methotrexate, and the combination of both in the treatment of rheumatoid arthritis: a controlled clinical trial. *Arthritis Rheum* 1992;**35**:849–56.
18 Williams HJ, Ward JR, Reading JC, Brooks RH, Clegg DO, Shosey JL, *et al.* Comparison of auranofin, methotrexate, and the combination of both in the treatment of rheumatoid arthritis: a controlled clinical trial. *Arthritis Rheum* 1992;**35**:259–69.
19 Gibson T, Emery P, Armstrong RD, Crisp AJ, Panayi GS. Combined dpenicillamine and chloroquine treatment of rheumatoid arthritis: a comparative study. *Br J Rheumatol* 1987;**26**:279–84.
20 Taggart AJ, Hill J, Astbury C, Dixon JS, Bird HA, Wright V. Sulphasalazine alone or in combination with d-penicillamine in rheumatoid arthritis. *Br J Rheumatol* 1987;**26**:32–6.
21 Scott DL, Dawes PT, Tunn E, Fowler PD, Shadforth MF, Fisher J, *et al.* Combination therapy with gold and hydroxychloroquine in rheumatoid arthritis: a prospective, randomized, placebo-controlled study. *Br J Rheumatol* 1989;**28**:128–33.
22 Tugwell P, Pincus T, Yocum D, Stein M, Gluck O, Kraag G, *et al.* Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. *N Engl J Med* 1995;**333**:137–41.
23 O'Dell JR, Haire CE, Erickson N, Drymalski W, Palmer W, Eckhoff PJ, *et al.* Treatment of rheumatoid arthritis with methotrexate, sulfasalazine, and hydroxychloroquine, or a combination of these medications. *N Engl J Med* 1996;**334**:1287–91.
24 Felson DT, Anderson JJ, Meenan RF. The efficacy and toxicity of combination therapy in rheumatoid arthritis. A meta-analysis. *Arthritis Rheum* 1994;**37**:1487–91.
25 Haagsma CJ, van Riel PL, de Rooji DJ, Vree TB, Russel FJ, Van't-Hof MA, *et al.* Combination of methotrexate and sulphasalazine vs methotrexate alone. A randomized open clinical trial in rheumatoid arthritis patients resistant to sulphasalazine therapy. *Br J Rheumatol* 1994;**33**:1049–55.
26 Shiroky JB. Combination of sulphasalazine and methotrexate in the management of rheumatoid arthritis—view based on personal clinical experience. *Br J Rheumatol* 1995;**34S**:109–12.
27 Weinblatt ME, Kaplan H, Germain BF, Block S, Solomen SO, Merriman RC, *et al.* Methotrexate in rheumatoid arthritis. A five-year prospective multicenter study. *Arthritis Rheum* 1994;**37**:1492–8.
28 Weinblatt ME. Methotrexate (MTX) in rheumatoid arthritis (RA): a 5-year multicenter prospective trial [abstr]. *Arthritis Rheum* 1993;**36**:S79.
29 O'Dell JR, Haire C, Erikson N, Drymalski W, Palmer W, Maloley P, *et al.* Efficacy of triple DMARD therapy in rheumatoid arthritis patients with suboptimal response to methotrexate. *J Rheumatol* 1996;**23S**:72–4.

The misconduct of redundant publication

Misconduct in medical research publication has been increasingly debated in the last two decades.[1–3] There are various levels and forms of misconduct ranging from unequivocal fraud (forgery, piracy, plagiarism), through manipulation of data ("trimming" and "cooking" of results[4]) and undeclared interest, to unintentional errors through bias and self delusion.[5] There are few defined boundaries and many grey zones. Conscious intent to deceive is often difficult to judge. Nevertheless all such misconduct reflects badly on the integrity of the perpetrators. It is counterproductive to the advancement of medical knowledge and is widely condemned.[1–5]

Duplicate and redundant publication are two examples within this spectrum of misconduct. "Duplicate" reports are rarely identical because of conscious manipulation by the authors, differences in journal style, or varying revisions during peer review and editing. Nevertheless they share the same hypothesis, dataset, information, discussion points, and conclusions. Such publication may not be rare, occurring in up to 13% of published papers in one United Kingdom journal.[6] Few would condone such duplicate publication except in certain circumstances,[7] most notably publication in two languages. In these situations the fact that the work has already been published should be clearly stated and referenced. More common than duplicate publication, however, is the reporting of overlapping and related facets of the same work under different titles, often with reordered or altered authorship, without disclosure.