Does partial control of inflammation prevent long-term joint damage? Clinical rationale for combination therapy with multiple disease-modifying antirheumatic drugs

T. Pincus, F.C. Breedveld, P. Emery

Theodore Pincus, M.D., Professor of Medicine, Division of Rheumatology and Immunology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA.
Prof. Ferdinand C. Breedveld, MD, Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands.
Prof. Paul Emery, BA, MA, MBBChir, MD, FRCP, Rheumatology & Rehabilitation Unit, University of Leeds, Leeds, UK.

Please address correspondence to:
Prof. Theodore Pincus, M.D., Division of Rheumatology and Immunology, Vanderbilt University School of Medicine, 203 Oxford House, Box 5, Nashville, TN 37232-4500, USA.

Clin Exp Rheumatol 1999; 17 (Suppl. 18): S2-S7.

Key words:
Rheumatoid arthritis, combination therapy, disease-modifying antirheumatic drug, outcome, damage.

Only a decade ago, combination disease-modifying antirheumatic drug (DMARD) therapy was regarded as an unusual approach to patients with rheumatoid arthritis (RA), reserved for only a few patients with the most severe disease (1-3). At this time, however, almost all rheumatologists use combination DMARD therapy in as many as 24% of patients (4, 5). This shift in the approach to people with RA may be explained in part by three developments over the last decade: accurate description of the natural history of RA; availability of improved DMARDs - most notably methotrexate; and perhaps, above all, recognition that partial control of inflammation likely does not prevent joint damage. These developments are discussed briefly below.

Accurate description of the "natural history" of RA

It is of course not possible to describe the natural history of RA, independent of therapies, for pragmatic and ethical reasons (6). However, early epidemiologic studies had indicated that many people who met criteria for RA had a self-limited process with spontaneous remission and no evidence of disease 3-5 years later (7). This course was thought to reflect the natural history of RA as seen in the clinic. However, most patients with RA seen in clinical settings have "persistent inflammatory symmetrical arthritis" (PISA) (8), or Type III rheumatoid arthritis (9), a progressive disease which has not responded adequately to traditional therapies (10).

It is recognized that patients monitored in rheumatology treatment centers in the 1970s and 1980s generally experienced poor long-term outcomes (11-14), including radiographic progression (15-22), joint deformity (23, 24), functional declines (13, 25-27), work disability (12, 13, 28), joint replacement surgery (29), high costs (30-33), extra-articular disease (34), and premature mortality (14, 24, 35-37). Furthermore, more than 70% of patients who develop radiographic erosions do so within the first two years of disease, a phenomenon first described in 1966 (18, 19, 38, 39). Although control of inflammation may preserve some function even after some damage occurs, medication generally cannot restore a severely damaged joint to a normal state. Therefore, many rheumatologists at this time advocate a "preventive" strategy of aggressive treatment prior to joint damage in RA (40-44).

Advances in DMARD therapy

DMARDs were once referred to as "remission-inducing," a term which should no longer be used, as sustained remission is seen in fewer than 2% of patients treated with traditional DMARD monotherapy (45). RA is a disorder of regulation, and as no (traditional or even new) drugs address the dysregulation, it may not be expected that any drug, even new biological agents, will lead to a clinical remission of established RA without requiring ongoing treatment. Nonetheless, continuous treatment with DMARDs does ameliorate the course of RA (46-49), including retardation of radiographic progression (50-53). Furthermore, contemporary DMARDs such as methotrexate, hydroxychloroquine, and sulfasalazine have a considerably greater efficacy/toxicity ratio than traditional agents such as gold salts, penicillamine, and azathioprine (54-56).

Over the last decade, new powerful DMARDs have become available, including cyclosporine A (57, 58), leflunomide (59, 60), etanercept (61), and infliximab (62), all of which have been studied as monotherapy and in combination with methotrexate. Methotrexate emerged as a major advance during the 1990s with long-term effectiveness (63-

65), and fewer long-term toxicities than other available DMARDs, and even than many non-steroidal anti-inflammatory drugs (56). While traditional DMARDs such as injectable gold salts, penicillamine, and azathioprine were discontinued within two years by 80% of patients (generally because of inefficacy, toxicity, or loss of efficacy) (54, 55, 66), methotrexate was continued for over 5 years by more than 50% of patients (54, 55). Nonetheless, sustained remission is unusual even with methotrexate, the most effective DMARD (4, 40-42, 67, 68). When response to one drug is inadequate in many diseases ranging from hypertension to cancer, multiple agents are used. Few patients with RA are in complete remission, and many, if not most, may be candidates for combination therapy (3, 10, 42).

Partial control of inflammation does not appear to prevent joint damage

Emphasis in RA clinical trials and clinical research has been directed to measures of inflammatory activity, such as joint tenderness, joint swelling, and the erythrocyte sedimentation rate (ESR), over weeks or months. Such measures of inflammation are included in the Core Data Set of measures for use in clinical trials endorsed by professional organizations (69-71). Control of inflammatory activity is regarded as an effective strategy to prevent long-term damage, although relatively few studies are available to assess how completely inflammation must be controlled to prevent long-term joint damage.

The possibility that partial control of inflammation may nonetheless be associated with long-term damage is suggested by reports which document that measures of inflammatory activity may be stable or even somewhat improved over periods of 5-10 years, while patients experience disease progression according to measures of damage (24, 72-74). Hawley and Wolfe (Fig. 1) reported improvement or unchanged joint tenderness scores, grip strength, global severity, morning stiffness, ESR, and hemoglobin, but significant progression of functional disability according to health assessment questionnaire (HAQ) scores (72). Fex *et al.* reported that values for morning stiffness, pain scores, general health, Ritchie Articular Index for tender joints, HAQ scores, ESR, and hemoglobin were similar to baseline after 5-6 years, while radiographic scores indicated significant progression (73). Mulherin *et al.* (Fig. 2) reported improvement in morning stiffness, pain scores, grip strength, Ritchie Articular Index, ESR and hemoglobin over 6 years, while radiographic scores indicated progression (74). Callahan *et al.* (Fig. 3) reported that joint tenderness, swelling, ESR, hemoglobin, morning stiffness, pain and modified HAQ (MHAQ) were unchanged or improved, while scores for joint deformity, radiographic damage, grip strength, and walking time indicated progression (24).

These data raise a concern that partial control of inflammation according to measures of inflammatory activity in a short-term clinical trial may not be translated into optimal or even clinically adequate long-term effectiveness to prevent joint damage, although further analyses are required to analyze this phenomenon.

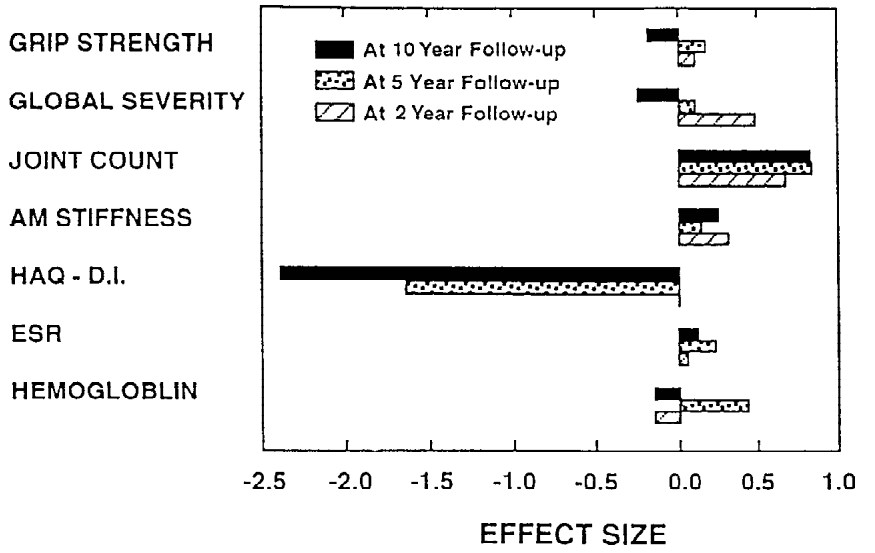

Fig. 1. Effect sizes for major clinical variables for patients with rheumatoid arthritis followed for 10 years are compared at 2, 5, and 10 years of treatment (Group II). Effect sizes are calculated at each time using values from the initial visit. Reproduced with permission from *Arthritis Care Res* 1992; 5: 130-6.

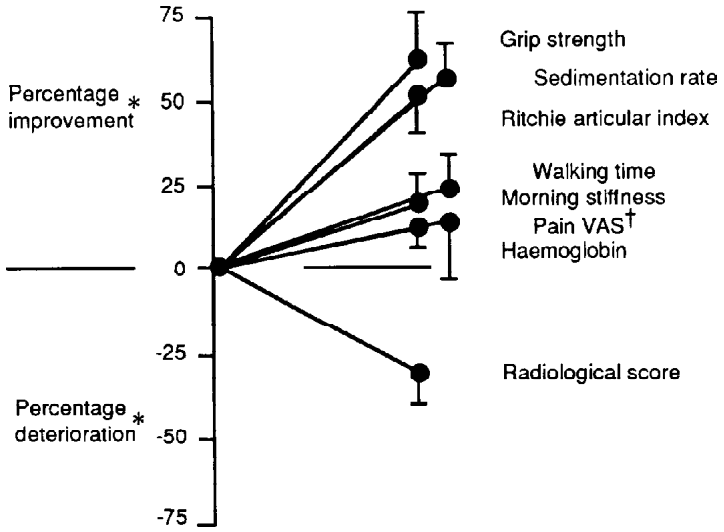

Fig. 2. Contrast between improvement in measures of disease activity and deterioration in the Larsen radiological score. S.E.M. bars are indicated. *Improvement is the mean actual change between enrollment and review expressed as a percentage of the value at enrollment; deterioration is the mean actual change expressed as a percentage of the total change possible. † VAS, 10 cm visual analog scale. Reproduced with permission from *Br J Rheumatol* 1996; 35; 1263-8.

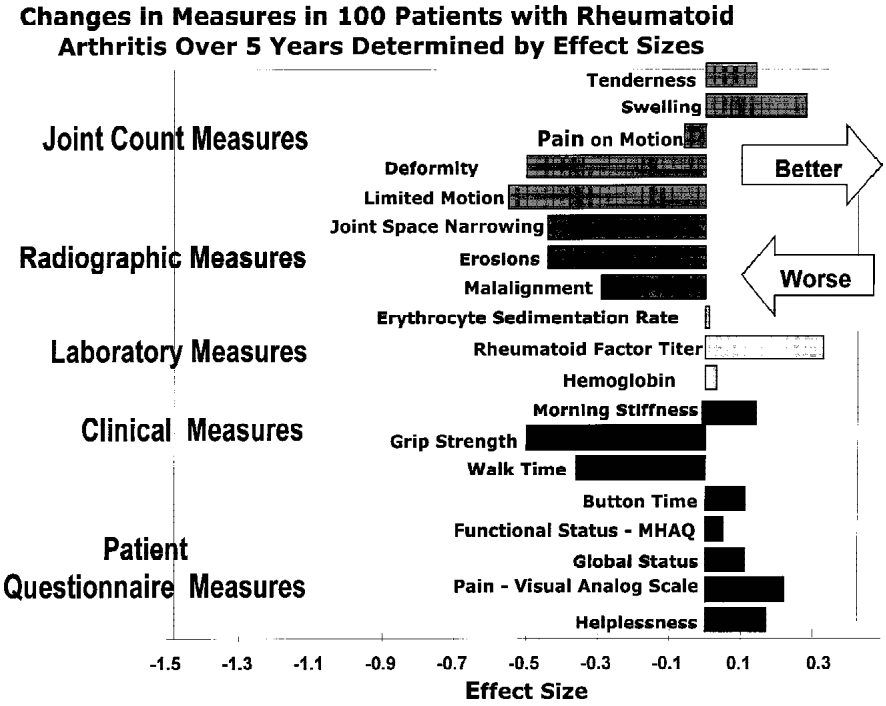

Fig. 3. Changes in measures in 100 patients with rheumatoid arthritis over 5 years, determined by effect size. MHAQ = Modified Health Assessment Questionnaire; ADL = activity of daily living. Reproduced with permission from *Arthritis Care Res 1997; 10: 381-94.*

Nonetheless, such standards for clinical response (75) as the American College of Rheumatology criteria for a 20% response (ACR 20), which provides greater statistically significant differences than a 50% or 70% response (76), may be reassessed over time as more powerful DMARDs are used earlier in disease and in combination (77).

Taken together, we believe the evidence presented above provides powerful arguments that combination DMARD therapy should be considered in most patients with RA, particularly in early disease prior to extensive joint damage, when drug therapy might prevent long term damage (10, 40-42, 44). We invite the reader to review evidence presented in the ensuing 20 contributions in decisions about whether to use combination DMARDs, including which combinations of which DMARDs in which patients would appear optimal.

Organization of the supplement

This overview of combination DMARD therapy in RA is divided into four sections: (i) Overview of combination DMARD therapy; (ii) Evidence from clinical trials of the superiority of DMARD combinations to monotherapy; (iii) Evidence from clinical studies of the superiority of DMARD combinations to monotherapy; and (iv) Experimental combination DMARD therapy.

Overview of combination DMARD therapy

The first section, "An overview of combination DMARD therapy", includes seven reports, beginning with this introductory report concerning the "Rationale for combination DMARD therapy" (78). The next paper is a report on "Early developments in combination therapy" by D.L. Scott, S. Farrow, and S.I. Yeo, which summarizes the early literature that indicated no added benefit versus monotherapy to combinations involving traditional DMARDs such as gold and penicillamine (79). This is followed by a brief but comprehensive summary of development of combination DMARD therapy, "Pyramids to myriads: The combination conundrum in rheumatoid arthritis" by D. O'Gradaigh and D.G.I. Scott (80). A contemporary review of the mechanisms of action of modern DMARDs by E. Choy and G. Panayi (81) is followed by description of the rationale for "Pharmacotherapeutic strategies for disease-modifying antirheumatic drug (DMARD) combinations to treat rheumatoid arthritis (RA)" by T. Münster and D.E. Furst (82). New observations concerning the imaging of rheumatoid joints prior to the development of erosions by P.G. Conaghan, D. McGonagle, R. Wakefield, and P. Emery are summarized in "New approaches to imaging of early rheumatoid arthritis" (83). The final introductory chapter, "Methotrexate and emerging therapies", by J.M. Kremer summarizes the basis for inclusion of methotrexate in most current DMARD combinations (84).

Evidence from clinical trials of the superiority of DMARD combinations to monotherapy

The second section, "Evidence from clinical trials of the superiority of DMARD combinations to monotherapy," includes summaries of seven major randomized controlled clinical trials which have appeared since 1995 to support the efficacy of combination DMARD therapy versus monotherapy. "Combination treatment of rheumatoid arthritis with cyclosporine and methotrexate," by C.M. Stein and T. Pincus, summarizes a randomized controlled clinical trial, as well as an extension study of this combination (85). A summary of triple therapy with hydroxychloroquine, sulfasalazine and methotrexate by J.R. O'Dell presents long-term results with this combination therapy (86). "Combination DMARD therapy including corticosteroids in early rheumatoid arthritis" by T.T. Möttönen, P.J. Hannonen, and M. Boers, summarizes two studies of aggressive therapy with corticosteroids and combination DMARDs performed in Finland and The Netherlands (87). Clinical trials of combination DMARDs which have appeared in 1998 and 1999 with newer DMARDs include "Methotrexate and leflunomide combination therapy for patients with active rheumatoid arthritis" by P.J. Mroczkowski, M.E. Weinblatt, and J.M. Kremer (88); "Etanercept and methotrexate combination therapy" by A.D. Bankhurst (89); and "Combination therapy of the chimeric monoclonal anti-tumor necrosis factor α antibody (infliximab) with methotrexate in patients with rheumatoid arthritis" by C. Antoni and J.R. Kalden (90).

Evidence from clinical studies of the superiority of DMARD combinations to monotherapy

The third section reviews "Evidence from clinical studies of the superiority of DMARD combinations to monotherapy." An analysis of the clinical use of combination DMARDs by rheumatologists and their patients is presented in "Use of combination therapy in the routine care of patients with rheumatoid arthritis: Physician and patient surveys" by D.J. Hawley, F. Wolfe, and T. Pincus (91). Reports of analyses of "Combination DMARD treatment with parenteral gold and methotrexate" by R. Rau (92); "Clinical experience with combination disease-modifying antirheumatic drug therapy with cyclosporine" by K. Johns and G. Littlejohn (93); and "Combination cyclosporine and (hydroxy)chloroquine in rheumatoid arthritis" by B.A.C. Dijkmans, R.B.M. Landewe, B.E.E.M. van den Borne, and F.C. Breedveld (94), present the experience of these clinical investigators with these combination DMARD regimens. A clinical approach presented by Wm. Bensen and W. Bensen describes efforts to "Aim for remission or 'personal best' using combination DMARD therapy with methotrexate and hydroxychloroquine" (95).

Experimental combination DMARD therapy

The fourth and final section, "Experimental combination DMARD therapy," presents innovative approaches in experimental animals. The paper "TNFα and IL-1β are separate targets in chronic arthritis" by W.B. van den Berg, L.A.B. Joosten, and F.A.J. van de Loo, reviews studies of these combinations in experimental mice (96). Studies of "Combination therapy with DMARDs and biological agents in collagen-induced arthritis" by R.O. Williams, A.-M. Malfait, D.M. Butler, M.J. Walmsley, M. Feldmann, and R.N. Maini, analyzes combination DMARDs as elucidating pathogenetic mechanisms in RA (97). The final chapter, by J.D. Isaacs, A.W. Morgan, and V. Strand, describes innovative "Combination biologic therapy" (98) .

We hope that the reader will find these 21 manuscripts challenging, innovative, and stimulating. This an exciting time in the development of new therapies for RA. We thank the individual authors for their excellent contributions, the editorial and production staff at *Clinical and Experimental Rheumatology* for their skilled and helpful assistance, and Centocor Inc., Hoechst Marion Roussel, Immunex Corporation, Novartis Pharma, Sanofi Synthelabo Canada Inc., and Wyeth-Ayerst Laboratories for generous financial support to make this supplement possible. We and the individual authors welcome comments and critiques from readers through the Journal and direct correspondence.

References

1. MCCARTY DJ, HARMAN JG, GRASSANOVICH JL, QIAN C, KLEIN JP: Combination drug therapy of seropositive rheumatoid arthritis. *J Rheumatol* 1995; 22: 1636-45.
2. BENSEN W, TUGWELL P, ROBERTS RM: Combination therapy of cyclosporine with methotrexate and gold in rheumatoid arthritis (2 pilot studies). *J Rheumatol* 1994; 21: 2034-8.
3. VERHOEVEN AC, BOERS M, TUGWELL P: Combination therapy in rheumatoid arthritis: Updated systematic review. *Br J Rheumatol* 1998; 37: 612-9.
4. O'DELL J: Combination DMARD therapy for rheumatoid arthritis: Apparent universal acceptance. *Arthritis Rheum* 1997; 40: S50 (Abstract).
5. WOLFE F, PINCUS T, FRIES JF, and the US Inception Cohort Group: Use of second line "disease modifying" anti-rheumatic drugs (DMARDs) within 5 months of disease onset by 64% of 750 rheumatoid arthritis patients under care of 142 US rheumatologists: An inception cohort study. *Arthritis Rheum* 1997; 40: S218.
6. STEIN CM, PINCUS T: Placebo-controlled studies in rheumatoid arthritis: Ethical issues. *Lancet* 1999; 353: 400-3.
7. O'SULLIVAN JB, CATHCART ES: The prevalence of rheumatoid arthritis: Follow-up evaluation of the effect of criteria on rates in Sudbury, Massachusetts. *Ann Intern Med* 1972; 76: 573-7.
8. EMERY P: Rheumatoid arthritis: Not yet curable with early intensive therapy. *Lancet* 1997; 350: 304-5.
9. PINCUS T, CALLAHAN LF: How many types of patients meet classification criteria for RA? *J Rheumatol* 1994; 21: 1385-9.
10. VAN DER HORST-BRUINSMA IE, SPEYER I, VISSER H, BREEDVELD FC, HAZES JMW: : Diagnosis and course of early onset arthritis: Results of a special early arthritis clinic compared to routine patient care. *Br J Rheumatol* 1998; 37: 1084-8.
11. YELIN E, MEENAN R, NEVITT M, EPSTEIN W: Work disability in rheumatoid arthritis: Effects of disease, social, and work factors. *Ann Intern Med* 1980; 93: 551-6.
12. PINCUS T, CALLAHAN LF, SALE WG, BROOKS AL, PAYNE LE, VAUGHN WK: Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. *Arthritis Rheum* 1984; 27: 864-72.
13. PINCUS T, WOLFE F, CALLAHAN LF: Updating a reassessment of traditional paradigms concerning rheumatoid arthritis. *In:* WOLFE F and PINCUS T (Eds.): *Rheumatoid Arthritis: Pathogenesis, Assessment, Outcome, and Treatment.* New York, Marcel Dekker, Inc., 1994: 1-74.
14. VON ZEBEN D, HAZES JMW, ZWINDERMAN AH, VANDEBROUCKE JP, BREEDVELD FC: The severity of rheumatoid arthritis: A 6-year followup study of younger women with symptoms of recent onset. *J Rheumatol* 1994: 21: 1620-5.
15. SHARP JT: Radiographic evaluation of the course of articular disease. *Clin Rheum Dis* 1983; 9: 541-57.
16. LARSEN A, DALE K, EEK M, PAHLE J: Radiographic evaluation of rheumatoid arthritis by standard reference films. *J Hand Surg [Am]* 1983; 8: 667-9.
17. SCOTT DL, BACON PA: Joint damage in rheumatoid arthritis: Radiological assessments and the effects of anti-rheumatic drugs. *Rheumatol Int* 1985; 5: 193-9.
18. FUCHS HA, KAYE JJ, CALLAHAN LF, NANCE EP, PINCUS T: Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. *J Rheumatol* 1989; 16: 585-91.
19. VAN DER HEIJDE DMFM, VAN LEEUWEN MA, VAN RIEL PLCM, *et al.*: Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. *Arthritis Rheum* 1992; 35: 26-34.
20. VAN LEEUWEN MA, VAN RIJSWIJK MH, VAN DER HEIJDE DMFM, *et al.*: The acute-phase response in relation to radiographic progression in early rheumatoid arthritis: A prospective study during the first three years of the disease. *Br J Rheumatol* 1993; 32: 9-13.
21. WOLFE F, SHARP JT: Radiographic outcome of recent-onset rheumatoid arthritis: A 19-year study of radiographic progression. *Arthritis Rheum* 1998; 41: 1571-82.
22. RAU R, HERBORN G: A modified version of Larsen's scoring method to assess radiologic changes in rheumatoid arthritis. *J Rheumatol* 1995; 22: 1976-82.
23. FUCHS HA, CALLAHAN LF, KAYE JJ, BROOKS RH, NANCE EP, PINCUS T: Radiographic and joint count findings of the hand in rheumatoid arthritis: Related and unrelated findings. *Arthritis Rheum* 1988; 31: 44-51.
24. CALLAHAN LF, PINCUS T, HUSTON JW III, BROOKS RH, NANCE EP JR, KAYE JJ: Measures of activity and damage in rheumatoid arthritis: Depiction of changes and prediction of mortality over five years. *Arthritis Care Res* 1997; 10: 381-94.
25. WOLFE F, CATHEY MA: The assessment and prediction of functional disability in rheumatoid arthritis. *J Rheumatol* 1991; 18: 1298-1306.
26. PINCUS T, CALLAHAN LF: Rheumatology Function Tests: Grip strength, walking time, button test and questionnaires document and predict longterm morbidity and mortality in

rheumatoid arthritis. *J Rheumatol* 1992; 19: 1051-7.

27. GARDINER PV, SYKES HR, HASSEY GA, WALKER DJ: An evaluation of the health assessment questionnaire in long-term longitudinal follow-up of disability in rheumatoid arthritis. *Br J Rheumatol* 1993; 32: 724-8.
28. CALLAHAN LF, BLOCH DA, PINCUS T: Identification of work disability in rheumatoid arthritis: Physical, radiographic and laboratory variables do not add explanatory power to demographic and functional variables. *J Clin Epidemiol* 1992; 45: 127-38.
29. WOLFE F, ZWILLICH SH: The long-term outcomes of rheumatoid arthritis: A 23-year prospective, longitudinal study of total joint replacement and its predictors in 1,600 patients with rheumatoid arthritis. *Arthritis Rheum* 1998; 41: 1072-82.
30. LUBECK DP, SPITZ PW, FRIES JF, WOLFE F, MITCHELL DM, ROTH SH: A multicenter study of annual health service utilization and costs in rheumatoid arthritis. *Arthritis Rheum* 1986; 29: 488-93.
31. GABRIEL SE, CROWSON CS, CAMPION ME, O'FALLON WM: Indirect and nonmedical costs among people with rheumatoid arthritis and osteoarthritis compared with nonarthritic controls. *J Rheumatol* 1997; 24: 43-8.
32. YELIN E, CALLAHAN LF: The economic cost and social and psychological impact of musculoskeletal conditions. *Arthritis Rheum* 1995; 38: 1351-62.
33. LUBECK DP: The economic impact of arthritis. *Arthritis Care Res* 1995; 8: 304-10.
34. GORDON DA, STEIN JL, BRODER I: The extra-articular features of rheumatoid arthritis: A systematic analysis of 127 cases. *Am J Med* 1973; 54: 445-52.
35. PINCUS T, CALLAHAN LF: Taking mortality in rheumatoid arthritis seriously - Predictive markers, socioeconomic status and comorbidity. *J Rheumatol* 1986; 13: 841-5.
36. PINCUS T, CALLAHAN LF, VAUGHN WK: Questionnaire, walking time and button test measures of functional capacity as predictive markers for mortality in rheumatoid arthritis. *J Rheumatol* 1987; 14: 240-51.
37. PINCUS T, BROOKS RH, CALLAHAN LF: Prediction of long-term mortality in patients with rheumatoid arthritis according to simple questionnaire and joint count measures. *Ann Intern Med* 1994; 120: 26-34.
38. THOULD AK, SIMON G: Assessment of radiological changes in the hands and feet in rheumatoid arthritis: Their correlation with prognosis. *Ann Rheum Dis* 1966; 25: 220-8.
39. BROOK A, CORBETT M: Radiographic changes in early rheumatoid disease. *Ann Rheum Dis* 1977; 36: 71-3.
40. EMERY P, SALMON M: Early rheumatoid arthritis: time to aim for remission? *Ann Rheum Dis* 1995; 54: 944-7.
41. WEINBLATT ME: Rheumatoid arthritis: Treat now, not later ! (editorial). *Ann Intern Med* 1996; 124: 773-4.
42. PINCUS T, STEIN CM, WOLFE F: "No evidence of disease" in rheumatoid arthritis using methotrexate in combination with other drugs: A contemporary goal for rheumatology care ? *Clin Exp Rheumatol* 1997; 15: 591-6.
43. BREEDVELD FC: New perspectives on treating rheumatoid arthritis. *N Engl J Med* 1995; 333: 183-4.
44. PINCUS T: Aggressive treatment of early rheumatoid arthritis to prevent joint damage. *Bull Rheum Dis* 1999; 47: 2-7.
45. WOLFE F, HAWLEY DJ: Remission in rheumatoid arthritis. *J Rheumatol* 1985; 12: 245-52.
46. LUUKKAINEN R, KAJANDER A, ISOMAKI H: Effect of gold on progression of erosions in rheumatoid arthritis: Better results with early treatment. *Scand J Rheumatol* 1977; 6:189-92.
47. VAN DER HEIJDE DMFM, VAN RIEL PLCM, NUVER-ZWART IH, GRIBNAU FWJ, VAN DE PUTTE LBA: Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet* 1989; I: 1036-8.
48. RAU R, SCHATTENKIRCHNER M, MÜLLER-FASSBENDER H, KAIK B, ZEIDLER H: A three year comparative multicenter study of auranofin (AF) and gold sodium thiomalate (GST) in the treatment of rheumatoid arthritis (RA). *Clin Rheumatol* 1987; 6 (Suppl. 2): 43-52.
49. VAN DER HEIDE A, JACOBS JW, BIJLSMA JW, *et al.*: The effectiveness of early treatment with "second-line" antirheumatic drugs: A randomized controlled trial. *Ann Intern Med* 1996; 124: 699-707.
50. FØRRE Ø: Radiologic evidence of disease modification in rheumatoid arthritis patients treated with cyclosporine: Results of a 48-week multi-center study comparing low-dose cyclosporine with placebo. *Arthritis Rheum* 1994; 37: 1506-12.
51. VAN RIEL PLCM, VAN DER HEIJDE DMFM, NUVER-ZWART IH, VAN DE PUTTE LBA: Radiographic progression in rheumatoid arthritis: Results of 3 comparative trials. *J Rheumatol* 1995; 22: 1797-9.
52. PASERO G, PRIOLO F, MARUBINI E, *et al.*: Slow progression of joint damage in early rheumatoid arthritis treated with cyclosporin A. *Arthritis Rheum* 1996; 39: 1006-15.
53. ABU-SHAKRA M, TOKER R, FLUSSER D, *et al.*: Clinical and radiographic outcomes of rheumatoid arthritis patients not treated with disease-modifying drugs. *Arthritis Rheum* 1998; 41: 1190-5.
54. WOLFE F, HAWLEY DJ, CATHEY MA: Termination of slow acting anti-rheumatic therapy in rheumatoid arthritis: A 14-year prospective evaluation of 1017 consecutive starts. *J Rheumatol* 1990; 17: 994-1002.
55. PINCUS T, MARCUM SB, CALLAHAN LF: Long-term drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second-line drugs and prednisone. *J Rheumatol* 1992; 19: 1885-94.
56. FRIES JF: Clinical implications of the relative therapeutic toxicity of medications used to treatment rheumatoid arthritis. *In:* WOLFE F and PINCUS T (Eds.): *Rheumatoid Arthritis: Pathogenesis, Assessment, Outcome, and Treatment.* New York: Marcel Dekker, Inc., 1994: 403-13.
57. 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.
58. STEIN CM, PINCUS T, YOCUM D, *et al.*: Combination treatment of severe rheumatoid arthritis with cyclosporine and methotrexate for forty-eight weeks: An open-label extension study. *Arthritis Rheum* 1997; 40: 1843-51.
59. MLADENOVIC V, DOMLJAN Z, ROZMAN B, *et al.*: Safety and effectiveness of leflunomide in the treatment of patients with active rheumatoid arthritis. Results of a randomized, placebo-controlled, phase II study. *Arthritis Rheum* 1995; 38: 1595-1603.
60. WEINBLATT ME, KREMER JM, COBLYN JS, *et al.*: Leflunomide plus methotrexate in refractory rheumatoid arthritis: a pilot study. *Arthritis Rheum* 1997; 40: S193 (Abstract).
61. WEINBLATT ME, KREMER JM, BANKHURST AD, *et al.*: A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999; 340: 253-9.
62. MAINI RN, BREEDVELD FC, KALDEN JR, *et al.*: Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998; 41: 1552-63.
63. HOFFMEISTER RT: Methotrexate therapy in rheumatoid arthritis: 15 years experience. *Am J Med* 1983; 75 (Suppl. 6A): 69-73.
64. KREMER JM: Safety, efficacy, and mortality in a long-term cohort of patients with rheumatoid arthritis taking methotrexate: Followup after a mean of 13.3 years. *Arthritis Rheum* 1997; 40: 984-5.
65. WEINBLATT ME, MAIER AL, FRASER PA, COBLYN JS: Longterm prospective study of methotrexate in rheumatoid arthritis: Conclusion after 132 months of therapy. *J Rheumatol* 1998; 25: 238-42.
66. THOMPSON PW, KIRWAN JR, BARNES CG: Practical results of treatment with disease-modifying antirheumatoid drugs. *Br J Rheumatol* 1985; 24: 167-75.
67. WEINBLATT ME: Efficacy of methotrexate in rheumatoid arthritis. *Br J Rheumatol* 1998; 34 (Suppl.): 43-8.
68. KREMER JM: Historical overview of the treatment of rheumatoid arthritis with an emphasis on methotrexate. *J Rheumatol* 1996; 23 (Suppl. 44): 34-7.
69. 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.
70. TUGWELL P, BOERS M: OMERACT Committee. Proceedings of the OMERACT Conferences on outcome measures in rheumatoid arthritis clinical trials, Maastrict, The Netherlands. *J Rheumatol* 1993; 20: 527-91.
71. VAN RIEL PLCM: Provisional guidelines for measuring disease activity in clinical trials on rheumatoid arthritis (Editorial). *Br J Rheumatol* 1994; 31: 793-4.
72. HAWLEY DJ, WOLFE F: Sensitivity to change of the Health Assessment Questionnaire (HAQ) and other clinical and health status measures in rheumatoid arthritis: Results of short term clinical trials and observational studies versus long term observational studies. *Arthritis Care Res* 1992; 5: 130-6.

73. FEX E, JONSSON K, JOHNSON U, EBERHARDT K: Development of radiographic damage during the first 5-6 yr of rheumatoid arthritis. A prospective follow-up study of a Swedish cohort. *Br J Rheumatol* 1996; 35: 1106-15.
74. MULHERIN D, FITZGERALD O, BRESNIHAN B: Clinical improvement and radiological deterioration in rheumatoid arthritis: Evidence that pathogenesis of synovial inflammation and articular erosion may differ. *Br J Rheumatol* 1996; 35: 1263-8.
75. FELSON DT, ANDERSON JJ, BOERS M, *et al.*: American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 727-35.
76. FELSON DT, ANDERSON JI, LANGE MLM, WELLS G, LAVALLEY MP: Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent ? *Arthritis Rheum* 1998; 41: 1564-70.
77. PINCUS T, STEIN CM: ACR20: Clinical or statistical significance? *Arthritis Rheum* 1999; 42: 1572-6.
78. PINCUS T, BREEDVELD FC, EMERY P: Does partial control of inflammation prevent long-term joint damage? Clinical rationale for combination therapy with multiple disease-modifying antirheumatic drugs. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S2-S7.
79. SCOTT DL, FARROW S, YEO SI: Early developments in combination therapy. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S8-S12.
80. O'GRADAIGH D, SCOTT DGI: Pyramids to myriads: The combination conundrum in rheumatoid arthritis. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S13-S19.
81. CHOY E, PANAYI G: Mechanisms of action of second-line agents and choice of drugs in combination therapy. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S20-S28.
82. MÜNSTER T, FURST DE: Pharmacotherapeutic strategies for disease-modifying antirheumatic drug (DMARD) combinations to treat rheumatoid arthritis. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S29-S36.
83. CONAGHAN PG, MCGONAGLE D, WAKEFIELD R, EMERY P: New approaches to imaging of early rheumatoid arthritis. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S37-S42.
84. KREMER JM: Methotrexate and emerging therapies. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S43-S46.
85. STEIN CM, PINCUS T: Combination treatment of rheumatoid arthritis with cyclosporine and methotrexate. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S47-S52.
86. O'DELL JR: Combination DMARD therapy with hydroxychloroquine, sulfasalzine and methotrexate. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S53-S58.
87. MÖTTÖNEN TT, HANNONEN PJ, BOERS M: Combination DMARD therapy including corticosteroids in early rheumatoid arthritis. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S59-S65.
88. MROCZKOWSKI PJ, WEINBLATT ME, KREMER JM: Methotrexate and leflunomide combination therapy for patients with active rheumatoid arthritis. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S66-S68.
89. BANKHURST AD: Etanercept and methotrexate combination therapy. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S69-S72.
90. ANTONI C, KALDEN JR: Combination therapy of the chimeric monoclonal anti-tumor necrosis factor α antibody (infliximab) with methotrexate in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S73-S77.
91. HAWLEY DJ, WOLFE F, PINCUS T: Use of combination therapy in the routine care of patients with rheumatoid arthritis: Physician and patient surveys. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S78-S82.
92. RAU R: Combination DMARD treatment with parenteral gold and methotrexate. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S83-S90.
93. JOHNS K, LITTLEJOHN G: Clinical experience with combination disease-modifying antirheumatic drug therapy with cyclosporine. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S91-S94.
94. DIJKMANS BAC, LANDEWÉ RBM, VAN DEN BORNE BEEM, BREEDVELD FC: Combination cyclosporine and (hydroxy)chloroquine in rheumatoid arthritis. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S103-S104.
95. BENSEN WM, BENSEN W: Aim for remission or "personal best" using combination DMARD therapy with methotrexate and hydroxychloroquine. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S95-S101.
96. VAN DEN BERG WB, JOOSTEN LAB, VAN DE LOO FAJ: TNFα and IL-1β are separate targets in chronic arthritis. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S105-S114.
97. WILLIAMS RO, MALFAIT A-M, BUTLER DM, WALMSLEY MJ, FELDMANN M, MAINI RN: Combination therapy with DMARDs and biological agents in collagen-induced arthritis. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S115-S120.
98. ISAACS JD, MORGAN AW, STRAND V: Combination biologic therapy. *Clin Exp Rheumatol* 1999: 17 (Suppl. 18): S121-S124.