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Starting a Disease Modifying Antirheumatic Drug or a Biologic Agent in Rheumatoid Arthritis: Standards of Practice for RA Treatment

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ABSTRACT. Our aim was to investigate the practices and standards by which disease modifying antirheumatic drugs (DMARD) and biologics are and have been prescribed. We reviewed the literature and examined data from patients with rheumatoid arthritis (RA) participating in a national cohort: the National Data Bank for Rheumatic Diseases (NDB). Four pathways for DMARD prescription were identified: (1) A time-based pyramidal approach (the RA pyramid); (2) a severity-based pyramid in which the most effective treatment is given to those with more active disease; (3) a cost-based pathway in which the primary goal is cost containment — this pathway intertwines with the severity-based pathway; and (4) a patient preference pathway where treatment is geared to patient needs and wishes regardless of severity. Data show that the time-based and severity-based pathways are not generally used in contemporary expert practice, and that patients with all degrees of severity and disease duration are receiving DMARD and biologic treatment. With the abandonment of the pyramid and the development of effective therapy, rheumatic disease care has swung away from the imperative of time and severity-based treatment to the imperative of care based on patient preference. It is the standard of practice to treat patients with mild and early disease with aggressive therapy, with the goal of limiting subsequent damage and retarding progression, and with the realistic purpose of relieving symptoms. The standard may at times be in conflict with the goals of insurers, but there is no legitimate medical reason for such limitations. (J Rheumatol 2001; 28:1704–11)

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RHEUMATOID ARTHRITIS TREATMENT PYRAMID OUTCOME
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With the first use of intramuscular gold therapy (IM gold)[1–3] it was recognized that patients who responded to this therapy often had a major response, much more of a response than could be expected from the nonsteroidal anti-inflammatory (NSAID) of the day, aspirin. Gold had another effect — it was toxic[4,5]. A third of patients starting gold had an adverse drug reaction (ADR) that required discontinuation, and there were even deaths[4-6]. The name given to this type of drug was DMARD, or disease modifying antirheumatic drug. Controversies arose as to whether such drugs were actually disease modifying[7], and other terms were suggested, such as slow acting antirheumatic drugs (SAARD)[8,9] or slow acting antiarthritis drugs and DC-ART — disease controlling antirheumatic therapy[10,11]. But the pattern seemed clear: the drugs could have major effectiveness but also had major toxicities. So to each of the subsequent "more effective" drugs that was released was attached the appellation of DMARD, carrying both a promise of special effectiveness but also of toxicity.

By the middle to late 1980s it became clear that this way of thinking was not correct, for some drugs had little toxicity and some had little effectiveness[12], and creeping into this therapeutic conundrum was the new idea that the "toxicity" of ineffectively treated RA was great, thus requiring more intensive therapy even at the cost of some toxicity[13-40].

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THE LIFE AND DEATH OF THE PYRAMID

The principle of *primum non nocere* and with it the famous "pyramid" of rheumatoid arthritis (RA) treatment held sway over RA treatment beginning in the 1950s[41]. The pyramid and other approaches toward treatment recommendation are shown in Table 1. In another article in this volume, Moreland, Russell, and Paulus describe what the pyramid entailed. Briefly, the pyramid approach was based on a first "layer" of therapies that all patients required, such as education, rest, joint protection, and physical therapy. Subsequent layers were utilized when needed. The second level added salicylates, the third NSAID and acetaminophen, the fourth hydroxychloroquine and gold. Following at higher levels were penicillamine, steroids, surgery, and cytotoxic therapy[41]. Although the pyramid was modified subsequently by others, this structure and the position of the drugs was continued through all modifications. Although there were special beliefs regarding various physical therapies and teachings — all of which were harmless enough though perhaps of limited usefulness — the force of the pyramid concept lay in the command to delay and use only with much caution all DMARD class drugs: first, use everything else. Within the spell of this concept, NSAID were a first-line therapy, and it was said and widely believed that most patients did well on a regimen of NSAID.

The consequence of this plan was that starting a DMARD was determined by how long the patient had had RA and by a failure to respond to non-DMARD therapy, though what was meant by response was never really defined. The late duration of DMARD onset was documented elegantly by Spector, *et al*[42]. They showed that the duration from symptom onset to DMARD therapy was a median of 85 months for persons in the UK referred between 1967 and 1971, but had fallen to 5 months between 1982 and 1988. In addition, 20% of patients had never received a DMARD during the earlier period. A recent report from Irvine, *et al* provides similar evidence[43]. In the decade of the 1980s a gradual change to earlier therapy became the trend. The tide was changing as data driven reports documented that RA patients had high rates of work disability, income deprivation, and mortality, and had, however one measured it, generally poor outcomes. Some patients did respond well to minimal therapy, but for most RA patients the outcome was bad[13-40].

With this recognition came the call to dismantle the pyramid[44-46]. While there was vigorous debate about this at the time[47-49], the pyramid by now is seen as an otiose idea with few remaining adherents. The pyramid was toppled for a number of reasons. First, it became clear that such a treatment model had not worked. Perhaps more than anyone else, Pincus, using actual clinical data, demonstrated the failure of the pyramid based approach and the general bad outcome of RA[36,38-40,50-59]. But there were many others involved in this effort, an effort that had certain characteristics: the research was data based and came from longitudinal observational studies[22,34,38,52,60-73]. What randomized controlled trials (RCT) had suggested might be effective treatment was thrown aside by data — "the army of unalterable law" of George Meredith.

Second, it was beginning to be understood that even if a treatment was of less than optimum effectiveness, it was better to administer that treatment early in the course when

Table 1. The basis of treatment in rheumatoid arthritis from 1950 to the present.

DMARD Category	Characteristic	Name	Era	
I	Time-based	Pyramid	1950–1985–90	1. Use DMARD late
II	Severity-based	Pyramid 2	1980s–present	1. Early DMARD treatment for those with poor prognoses 2. Aggressive treatment for those with poor prognoses 3. Aggressive treatment for those with severe disease
IIIa	Cost-based		1950–present	1. Restriction of therapies based on patients' ability to pay 2. Restriction of therapies based on rules of medical insurance payers
IIIb	Cost-based: managed care		1990–present	1. Copayments 2. Requirement that less expensive DMARD be used first 3. Restriction of DMARD use according to severity criteria 4. Response criteria for continuation of DMARD/biologic therapy
IV	Patient preference		2000+	1. Patient preference for improvement

it might be possible to delay functional and work disability rather than later in the course of disease when such events had already occurred and were irreversible[74-84]. But the most important reason to abandon the pyramid-based approach was the development of new and more effective therapies. Treatment now made more of a difference. As methotrexate became a routine part of the treatment armamentarium and was seen to be effective[67,86-100], rheumatologists began to initiate this treatment earlier and earlier. In 1998, Wolfe, *et al* showed that 64% of 750 RA patients in an inception cohort in 1996 were receiving DMARD therapy within 5 months of disease onset. The pyramid was dead.

THE PYRAMID IS DEAD. LONG LIVE THE PYRAMID

With the abandonment of the time-based pyramid, another type of pyramid arose, one based on severity (Table 1). The concept was simple. You would treat those patients who had more severe disease or who had a poor prognosis with DMARD, and you could treat such patients early in the course of disease. For patients with less severe disease, treatment was started with milder (less effective, less toxic?) drugs. So what was a poor prognosis and what was severe disease? Various definitions arose. Most were based on disease activity measures: many swollen and tender joints, persistent pain, functional loss, and elevated acute phase reactants (erythrocyte sedimentation rate or C-reactive protein). The American College of Rheumatology (ACR) added fatigue and morning stiffness to this definition[101]. The problem with this definition was 2-fold: where to draw the line (for one does not have either severe or non-severe disease) and how should the different therapies be distributed. Who would get the cyclosporine and methotrexate and who the minocycline or hydroxychloroquine? In addition, how would severity be assessed and documented? How would one address the older patient, one with comorbidities, one with great suffering though with less disease activity, one with only two bad but important joints, one who wants to do better?

The problems with patients with recent onset RA were also difficult. In this instance the prognosis was not always known. Was the illness to be remittent RA? Would it quiet down with time? Could future progression and damage be prevented with aggressive therapy early on, and in patients with apparently mild disease? Although the use of radiographs to identify persons who had early erosions was advocated, patients with recent onset RA did not yet have erosions. Emery and others suggested the use of magnetic resonance imaging (MRI), ultrasound, and HLA typing[102-107]. But MRI are not generally available and the (prospective) predictive value of MRI and HLA typing has not been determined.

Recent RCT of recent onset RA that compared patients receiving early DMARD therapy versus later therapy have provided evidence for the effectiveness of aggressive treatment versus non-aggressive treatment of RA, and it is also clear that more effective therapy is better than weaker therapy[43,75,76,107-112].

Nor does the severity pyramid face up to the issue of combination therapy. The data regarding combination therapy suggest an incremental benefit to some combination treatments, but longterm observational data are not yet in, and the full extent of the incremental benefit, if any, has not yet been determined[76,107,111,113-122].

As noted above, the real problem with a severity-based pyramid is there is no scientific or moral basis for restricting treatment to those with more severe disease. Every person's pain is important. The patient with "average" or even "mild" RA should get treatment as good as the patient with severe disease. Moreover, there is a substantial body of evidence that patients with milder disease respond better than those with severe disease[99,100,123].

Rheumatologists (arthritis experts) by now pay little attention to severity measures as the prime guide for starting therapy. Wolfe, *et al* studied DMARD usage in the practices of 303 US rheumatologists participating in the National Data Bank for Rheumatic Diseases (NDB)[124]. Patients were interviewed by questionnaire between August 1998 and April 1999. Of 3604 patients with RA, 94.1% had received a DMARD and 76.7% were receiving one now. Thus, almost all RA patients in rheumatology practice receive DMARD therapy. Although it might be thought that patients in rheumatology practices have more severe disease, the range of severities in the NDB was widely distributed[124,125], indicating the general prescription of DMARD rather than the segregation of such therapy to the more severely ill. In the community, where general physicians treat RA, a similar trend toward increased DMARD usage was seen[126].

These data suggest that standard practice has shifted to the general prescription of DMARD regardless of severity. Although severity must play some role, a severity-based pyramid does not reflect the standard of practice among rheumatologists. Instead, almost all RA patients receive such treatment.

COST-BASED TREATMENT OF RA

Cost-based treatment means that treatment is not determined on the grounds of efficacy or effectiveness primarily, but instead on economic grounds (Table 1). In the United States treatment is not automatic as it is in some countries, but is determined by age (Medicare), poverty (Medicaid), individual insurance plans including health maintenance organizations (HMO), and financial resources by the uninsured or the completely insured. Uninsured persons have great difficulty in affording contemporary arthritis treatment and the elderly often have similar problems, as Medicare does not now pay for self-administered medications. Except for the wealthy elderly, it is very difficult for older patients to afford

modern therapies such as leflunomide and etanercept. But an arcane twist of the Medicare law allows the elderly to receive infliximab because it is not self-administered. The effect of such a law is to drive therapy earlier and more frequently to infliximab. The completely uninsured have little ability to receive the newer NSAID and DMARD therapies except for the charitable dispensation of treatment by some of the pharmaceutical companies. The availability of drugs for patients with private insurance (e.g., Blue Cross/Blue Shield) depends on the patient's particular policy contract, over which they often have little control. Some policies do not pay for drugs, some have a copayment plan in which the patient pays ~20%, and some have plans that require out of pocket payments of a certain amount before insurance will pay.

The average age of onset of RA is around 50 years. That means that for about half of their remaining lifetime patients will be covered under Medicare in the US, but for the other half they will be below the qualifying age. For younger patients the major force in drug availability comes from managed care or HMO. Managed care has an interest in keeping treatment costs as low as possible, consistent with their obligation to provide appropriate care for patients in their organizations. One way is to require that less expensive drugs be used before more expensive ones; a second is to require copayments for some therapies; a third is to restrict use of drugs to patients meeting certain severity criteria to qualify for DMARD/biologic therapy; and finally, to require that a certain level of response be met for more expensive drugs to be continued.

Managed care and some private insurance plans, then, reintroduce the severity-based pyramid but add to it a cost component. It is based on cost benefit analysis, to be sure, but the benefit (and the potential benefit should a DMARD/biologic be prescribed) is more defined by the payer than the patient. The issue can clearly be seen this way. If anti-tumor necrosis factor agents are as good as RCT indicate, then why should every patient not receive such treatment if it were not for the cost?

PATIENT PREFERENCE IN STARTING DMARD/BIOLOGIC THERAPY (Table 1)

For a century, RA patients have been "living with" their arthritis, that is, accommodating to it and to the available treatments. An RA patient in flare, with multiple painful, swollen joints is very pleased when the rheumatologist improves the illness significantly: an ACR 50% response is nothing to be sneered at[127,128]; and patients are often satisfied with less: make the knee stop swelling, diminish the shoulder pain, fix it enough so that I can continue to work. Data from actual patient reports, however, show that RA patients still have substantial pain and dysfunction regardless of therapy. Figure 1 shows the distribution of pain scores among RA patients from the practices of US rheumatologists in the National Data Bank for Rheumatic Diseases. Figure 2 shows the distribution of scores among those starting a DMARD/biologic. Patients may be grateful for the skill of their doctors, but it is unlikely that they are satisfied with the scores in the figures.

Here are three scenarios in which patient preference might play a role: (1) Rheumatologist to a patient who doesn't meet ACR criteria for active disease[101]: "You are

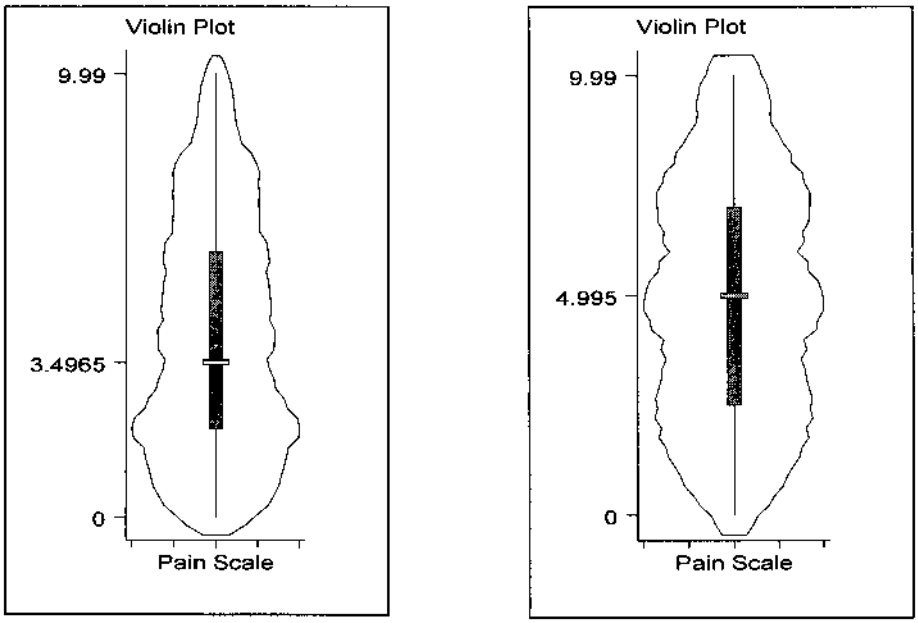

Figure 1. A. Visual analog scale (VAS) pain scores from 7165 patients with RA from practices of US rheumatologists. The median pain score is 3.6 (0–10 scale). B. VAS pain score for 4320 US patients with RA beginning DMARD. The median score is higher at 5.0.

doing pretty well with your arthritis. You are managing with your pain; you are able to work; you have only 2 swollen joints and 5 tender joints; your sedimentation rate is 20. But with time your deformities are likely to increase and you may find it more difficult to work or care for yourself in your old age. Would you like to receive a treatment that is far more effective than you have had previously?" (2) The rheumatologist presents the same question to a patient with only progressive wrist involvement, or to a patient with severe narrowing in one hip but only slight narrowing in the other. (3) Rheumatologist to a patient with very early RA: "We have new agents that might prevent your illness from progressing." In each of these situations it is hard to imagine patients rejecting effective therapy when there is a low probability of adverse reactions.

PUTTING IT ALL TOGETHER

The time-based pyramid lost favor and disappeared because it clearly did not work and because newer, more effective therapies became available. The severity-based pyramid had its forbears in the worries about toxicity: why expose patients to potentially toxic therapies, particularly those that didn't work too well, if their disease was mild (in the eye of the physician). Current evidence, however, indicates that rheumatologists ignore published criteria regarding severity and treat mild and severe disease, and early as well as late disease. There appears to be a determination, at least among many rheumatologists, to try to forestall disease and prevent disability in all patients. Thus physician and committee developed criteria for initiation of DMARD and biologic therapy are honored mostly in the breach. This extends to RA generally regardless of its duration.

The standards for treatment have changed as well as the drugs used. As reported by Wolfe[129], half the patients with recent onset RA who were receiving DMARD were taking methotrexate at an average disease duration of 5 months. This trend toward methotrexate therapy has been seen generally. Such changes suggest a trend toward respecting the problems and conditions of the patient, and of moving toward a patient preference in RA treatment.

The costs of antirheumatic therapy, particularly the newer DMARD and biologics, are not inconsequential for the patient, the insurer, or society. In preparing this review our purpose was not to denigrate such issues, but to clearly separate them from the identification of changing trends and standards of practice in the treatment of rheumatoid arthritis.

SUMMARY

In summary, with the abandonment of the pyramid and the development of effective therapy, rheumatic disease care has swung away from the imperative of time and severity-based treatment to the imperative of care based on patient preference. It is the standard of practice to treat patients with mild and early disease with aggressive therapy with the goal of limiting subsequent damage and retarding progression, and with the realistic purpose of relieving symptoms. The standard may at times be in conflict with the goals of insurers. Isaiah Berlin reminds us that "...the ends of men are many, and not all of them are in principle compatible with each other, [thus] the possibility of conflict — and of tragedy — can never be wholly eliminated from human life, either personal or social." There may be financial and societal reasons to deny or limit patients' care, but there is no legitimate medical reason for such limitations.

REFERENCES

1. Cecil RL, Kammerer WH, DePrume FJ. Gold salts in the treatment of rheumatoid arthritis: a study of 245 cases. Ann Intern Med 1942;16:811-27.
2. Hartfall SJ, Leeds MD. Gold treatment of arthritis. A review of 900 cases. Lancet 1937;October:838-42.
3. Forestier J. Treatment of rheumatoid arthritis with gold salts injections. Lancet 1932;441-4.
4. McCarty DJ, Brill JM, Harrop D. Aplastic anemia secondary to gold-salt therapy. JAMA 1962;179:655-7.
5. Anderson NL, Palmer WL. The danger of gold salt therapy. JAMA 1940;115:1627-30.
6. Kean WF, Anastassiades TP. Long term chrysotherapy: incidence of toxicity and efficacy during sequential time periods. Arthritis Rheum 1979;22:495-501.
7. Iannuzzi L, Dawson N, Zein N, Kushner I. Does drug therapy slow radiographic deterioration in rheumatoid arthritis? N Engl J Med 1983;309:1023-8.
8. Wolfe F, Michaud K. The comparative effectiveness of second-line antirheumatic (SAARD) therapy in rheumatoid arthritis [abstract]. Arthritis Rheum 1993;36 Suppl:S215.
9. Capell HA, Brzeski M. Slow drugs: slow progress? Use of slow acting antirheumatic drugs (SAARDs) in rheumatoid arthritis. Ann Rheum Dis 1992;51:424-9.
10. Edmonds J. Proposed new classification of antirheumatic therapies. Analysis of the DC-ART category [introduction]. J Rheumatol 1994;21 Suppl 41:2.
11. Edmonds J. DC-ART: The concept. J Rheumatol 1994;21:3-5.
12. Fries JF, Williams CA, Ramey DR, Bloch DA. The relative toxicity of alternative therapies for rheumatoid arthritis: implications for the therapeutic progression. Semin Arthritis Rheum 1993;23:68-73.
13. Pincus T, Callahan LF. The 'side effects' of rheumatoid arthritis: joint destruction, disability and early mortality. Br J Rheumatol 1993;32 Suppl 1:28-37.
14. Markenson JA. Worldwide trends in the socioeconomic impact and long-term prognosis of rheumatoid arthritis. Semin Arthritis Rheum 1991;21 Suppl 1:4-12.
15. Yelin E, Henke C, Epstein WV. The work dynamics of the person with rheumatoid arthritis. Arthritis Rheum 1987;30:507-12.
16. Meenan RF, Yelin EH, Nevitt M, Epstein WV. The impact of chronic disease: a sociomedical profile of rheumatoid arthritis. Arthritis Rheum 1981;24:544-9.
17. Yelin E, Meenan RF, Nevitt M, Epstein WV. Work disability in rheumatoid arthritis: effects of disease, social, and work factors. Ann Intern Med 1980;93:551-6.
18. Wolfe F, Kleinheksel SM, Spitz PW, et al. A multicenter study of hospitalization in rheumatoid arthritis: effect of health care system, severity, and regional difference. J Rheumatol 1986;13:277-84.
19. Wolfe F, Kleinheksel SM, Spitz PW, et al. A multicenter study of hospitalization in rheumatoid arthritis.Frequency, medical-surgical admissions, and charges. Arthritis Rheum 1986;29:614-9.

20. McDuffie FC. Morbidity impact of rheumatoid arthritis on society. Am J Med 1985;78:1-5.
21. Liang MH, Larson M, Thompson M, et al. Costs and outcomes in rheumatoid arthritis and osteoarthritis. Arthritis Rheum 1984;27:522-9.
22. Ehrlich GE. Social, economic, psychologic, and sexual outcomes in rheumatoid arthritis. Am J Med 1983;75:27-34.
23. Kramer JS, Yelin EH, Epstein WV. Social and economic impacts of four musculoskeletal conditions. Arthritis Rheum 1983;26:901-7.
24. Wolfe F, Mitchell DM, Sibley JT, et al. The mortality of rheumatoid arthritis. Arthritis Rheum 1994;37:481-94.
25. Mitchell DM, Spitz PW, Young DY, Bloch DA, McShane DJ, Fries JF. Survival, prognosis and causes of death in rheumatoid arthritis. Arthritis Rheum 1986;29:706-14.
26. Vandenbroucke JP, Hazevoet HM, Cats A. Survival and cause of death in rheumatoid arthritis: a 25-year prospective followup. J Rheumatol 1984;11:158-61.
27. Allebeck P. Increased mortality in rheumatoid arthritis. Scand J Rheumatol 1982;11:81-6.
28. Wolfe F, Hawley DJ, Cathey MA. The assessment and prediction of functional disability in RA. J Rheumatol 1991;18:1298-306.
29. Wolfe F. 50 years of antirheumatic therapy: the prognosis of rheumatoid arthritis. J Rheumatol 1990;17 Suppl 22:24-32.
30. Lubeck DP, Yelin EH. A question of value: measuring the impact of chronic disease. Milbank Q 1988;66:444-64.
31. Thompson PW. Functional outcome in rheumatoid arthritis. Br J Rheumatol 1988;27 Suppl 1:37-43.
32. Wolfe F, Kleinheksel SM, Cathey MA, Hawley DJ, Spitz PW, Fries JF. The clinical value of the Stanford Health Assessment Questionnaire Functional Disability Index in patients with rheumatoid arthritis. J Rheumatol 1988;15:1480-8.
33. Rasker JJ, Cosh JA. The natural history of rheumatoid arthritis over 20 years. Clinical symptoms, radiological signs, treatment, mortality and prognostic significance of early features. Clin Rheumatol 1987;6:5-11.
34. Scott DL, Symmons DPM, Coulton BL, Popert AJ. Long-term outcome of treating rheumatoid arthritis: results after 20 years. Lancet 1987;1:1108-11.
35. Rasker JJ, Cosh JA. The natural history of rheumatoid arthritis: a fifteen year follow-up study. The prognostic significance of features noted in the first year. Clin Rheumatol 1984;3:11-20.
36. Pincus T, Callahan LF. Remodeling the pyramid or remodeling the paradigms concerning rheumatoid arthritis — lessons from Hodgkin's disease and coronary artery disease. J Rheumatol 1990;17:1582-5.
37. Pincus T, Mitchell JM, Burkhauser RV. Substantial work disability and earnings losses in individuals less than age 65 with osteoarthritis: comparisons with rheumatoid arthritis. J Clin Epidemiol 1989;42:449-57.
38. Pincus T, Callahan LF. Reassessment of twelve traditional paradigms concerning the diagnosis, prevalence, morbidity and mortality of rheumatoid arthritis. Scand J Rheumatol 1989;Suppl 79:67-96.
39. Pincus T, Callahan LF. Formal education as a marker for increased mortality and morbidity in rheumatoid arthritis. J Chronic Dis 1985;38:973-84.
40. 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.
41. Kantor TG. Primary drug therapy for arthritis. Postgrad medical communications; January 1980.
42. Spector TD, Thompson PW, Evans SJW, Scott DL. Are slow-acting antirheumatic drugs being given earlier in rheumatoid arthritis. Br J Rheumatol 1988;37:498-9.
43. Irvine S, Munro R, Porter D. Early referral, diagnosis, and treatment of rheumatoid arthritis: evidence for changing medical practice. Ann Rheum Dis 1999;58:510-3.
44. Wilske KR, Healey LA. The need for aggressive therapy of rheumatoid arthritis. Rheum Dis Clin North Am 1993;19:153-61.
45. Wilske KR. Inverting the therapeutic pyramid — observations and recommendations on new directions in rheumatoid arthritis therapy based on the author's experience. Semin Arthritis Rheum 1993;23:11-8.
46. Wilske KR, Healey LA. Remodeling the pyramid — a concept whose time has come. J Rheumatol 1989;16:565-7.
47. Hess EV, Luggen ME. Remodeling the pyramid — a concept whose time has not yet come [editorial]. J Rheumatol 1989;16:1175-6.
48. Kantor TG. Order out of chaos — the primary mission of the pyramid [editorial]. J Rheumatol 1990;17:1580-1.
49. McCarty DJ. Suppress rheumatoid arthritis early and leave the pyramid to the Egyptians. J Rheumatol 1990;17:1115-8.
50. Pincus T, Callahan LF. The 'side effects' of rheumatoid arthritis: joint destruction, disability and early mortality. Br J Rheumatol 1993;32 Suppl 1:28-37.
51. Pincus T, Callahan LF. What is the natural history of rheumatoid arthritis? Rheum Dis Clin North Am 1993;19:123-51.
52. Pincus T. The paradox of effective therapies but poor long-term outcomes in rheumatoid arthritis. Semin Arthritis Rheum 1992;21:2-15.
53. Pincus T, Callahan LF. Early mortality in RA predicted by poor clinical status. Bull Rheum Dis 1992;41:1-4.
54. Pincus T, Wolfe F. Treatment of rheumatoid arthritis: challenges to traditional paradigms [editorial]. Ann Intern Med 1991;115:825-7.
55. 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.
56. Mitchell JM, Burkhauser RV, Pincus T. The importance of age, education, and comorbidity in the substantial earnings losses of individuals with symmetric polyarthritis. Arthritis Rheum 1988;31:348-57.
57. Pincus T. Rheumatoid arthritis: disappointing long-term outcomes despite successful short-term clinical trials. J Clin Epidemiol 1988;41:1037-41.
58. Pincus T. Is mortality increased in rheumatoid arthritis? J Musculoskel Med 1988;5:27-46.
59. Pincus T, Callahan LF. Taking mortality in rheumatoid arthritis seriously — predictive markers, socioeconomic status and comorbility [editorial]. J Rheumatol 1986;13:841-5.
60. Pincus T, Callahan LF. What is the natural history of rheumatoid arthritis? Rheum Dis Clin North Am 1993;19:123-51.
61. Wolfe F. Rheumatoid arthritis. In: Wolfe F, Bellamy N, editors. Prognosis in the rheumatic diseases. 3rd ed. Dordrecht: Kluwer Academic Publishers; 1991:37-82.
62. Wolfe F, Hawley DJ, Cathey MA. Clinical and health status measures over time — prognosis and outcome assessment in rheumatoid arthritis. J Rheumatol 1991;18:1290-7.
63. Bensen WG, Bensen W, Adachi JD, Tugwell PX. Remodelling the pyramid: The therapeutic target of rheumatoid arthritis. J Rheumatol 1990;17:987-9.
64. Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. Results of two metaanalyses. Arthritis Rheum 1990;33:1449-61.
65. Fries JF. Reevaluating the therapeutic approach to rheumatoid arthritis: the "sawtooth" strategy. J Rheumatol 1990;17 Suppl 22:12-5.
66. Reilly PA, Cosh JA, Maddison PJ, Rasker JJ, Silman AJ. Mortality and survival in rheumatoid arthritis: a 25 year prospective study of 100 patients. Ann Rheum Dis 1990;49:363-9.

67. Wolfe F, Hawley DJ, Cathey MA. Termination of slow acting antirheumatic therapy in rheumatoid arthritis: a 14-year prospective evaluation of 1017 consecutive starts. J Rheumatol 1990;17:994-1002.
68. Kushner I. Does aggressive therapy of rheumatoid arthritis affect outcome. J Rheumatol 1989;16:1-4.
69. Wolfe F, Hawley DJ, Cathey MA. The risk of functional disability and the rate of its development in patients with rheumatoid arthritis [abstract]. Arthritis Rheum 1989;32 Suppl:S88.
70. McConkey B. Outcome of long-term treatment of rheumatoid arthritis with second-line agents. Scand J Rheumatol 1987;64 Suppl:25-8.
71. Scott DL, Coulton BL, Popert AJ. Long term progression of joint damage in rheumatoid arthritis. Ann Rheum Dis 1986;45:373-8.
72. Scott DL, Grindulis KA, Struthers GR, Coulton BL, Popert AG, Bacon PA. Progression of radiographical changes in rheumatoid arthritis. Ann Rheum Dis 1984;43:8-17.
73. Spitz PW. The medical, personal, and social costs of rheumatoid arthritis. Nurs Clin North Am 1984;19:575-82.
74. Dougados M, Combe B, Cantagrel A, et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. Ann Rheum Dis 1999;58:220-5.
75. Odell JR, Paulsen G, Haire CE, et al. Treatment of early seropositive rheumatoid arthritis with minocycline — Four-year followup of a double-blind, placebo-controlled trial. Arthritis Rheum 1999;42:1691-5.
76. Boers M. Randomised comparison of combined step-down prednisolone, methotrexate, and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309-18.
77. Alarcon GS. Slow progression of joint damage in early rheumatoid arthritis treated with cyclosporin A or methotrexate [comment]. Arthritis Rheum 1997;40:791-2.
78. Odell JR, Haire CE, Palmer W, et al. Treatment of early rheumatoid arthritis with minocycline or placebo: Results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 1997;40:842-8.
79. Vangestel AM, Haagsma CJ, Furst DE, van Riel PLCM. Treatment of early rheumatoid arthritis patients with slow-acting anti-rheumatic drugs. Bailliere Clin Rheumatol 1997;11:65-82.
80. Dawes PT, Fowler PD. Treatment of early rheumatoid arthritis: A review of current and future concepts and therapy. Clin Exp Rheumatol 1995;13:381-94.
81. Emery P. Therapeutic approaches for early rheumatoid arthritis. How early? How aggressive? Br J Rheumatol 1995;34:87-90.
82. Emery P, Salmon M. Early rheumatoid arthritis: Time to aim for remission? Ann Rheum Dis 1995;54:944-7.
83. Donnelly S, Scott DL, Emery P. The long-term outcome and justification for early treatment. Baillieres Clin Rheumatol 1992;6:251-60.
84. Wilke WS, Clough JD. Therapy for rheumatoid arthritis: combinations of disease-modifying drugs and new paradigms of treatment. Semin Arthritis Rheum 1991;21:21-34.
85. Borg G, Allander E, Lund B, et al. Auranofin improves outcome in early rheumatoid arthritis. Results from a 2-year, double blind, placebo controlled study. J Rheumatol 1988;15:1747-54.
86. Hoffmeister RT. Methotrexate therapy in rheumatoid arthritis: 15 years experience. Am J Med 1983;75:69-73.
87. Kremer JM. Longterm methotrexate therapy in rheumatoid arthritis: a review. J Rheumatol 1985;12 Suppl 12:25-8.
88. Kremer JM, Lee JK. The safety and efficacy of the use of methotrexate in long-term therapy for rheumatoid arthritis. Arthritis Rheum 1986;29:822-31.
89. Kremer JM, Lee JK. A long-term prospective study of the use of methotrexate in rheumatoid arthritis. Update after a mean of fifty-three months. Arthritis Rheum 1988;31:577-84.
90. Rau R, Herborn G, Karger T, Werdier D. Retardation of radiologic progression in rheumatoid arthritis with methotrexate therapy — a controlled study. Arthritis Rheum 1991;34:1236-44.
91. Rau R, Herborn G, Karger T, Menninger H, Elhardt D, Schmitt J. A double blind randomized parallel trial of intramuscular methotrexate and gold sodium thiomalate in early erosive rheumatoid arthritis. J Rheumatol 1991;18:328-33.
92. Rau R, Wassenberg S. Paucity of radiographic progression in rheumatoid arthritis treated with MTX as the first disease modifying antirheumatic drug [letter]. J Rheumatol 1999;26:2280.
93. Weinblatt ME, Coblyn JS, Fox DA, et al. Efficacy of low-dose methotrexate in rheumatoid arthritis. N Engl J Med 1985;312:818-22.
94. Weinblatt ME, Trentham DE, Fraser PA, et al. Long-term prospective trial of low-dose methotrexate in rheumatoid arthritis [see comments]. Arthritis Rheum 1988;31:167-75.
95. Weinblatt ME, Weissman BN, Holdsworth DE, et al. Long-term prospective study of methotrexate in the treatment of rheumatoid arthritis. 84-month update. Arthritis Rheum 1992;35:129-37.
96. Wilkens RF, Watson MA, Paxson CS. Low dose pulse methotrexate therapy in rheumatoid arthritis. J Rheumatol 1980;7:501-5.
97. Willkens RF. Reappraisal of the use of methotrexate in rheumatic disease. Am J Med 1983;75:19-25.
98. Willkens RF. Resolve: methotrexate is the drug of choice after NSAIDs in rheumatoid arthritis. Semin Arthritis Rheum 1990;20:76-80.
99. Wolfe F, Cathey MA. Analysis of methotrexate treatment effect in a longitudinal observational study: utility of cluster analysis. J Rheumatol 1991;18:672-7.
100. Wolfe F, Hawley DJ, Pincus T. Methotrexate alters the course of rheumatoid arthritis (RA). Increased survival of methotrexate treated RA patients: a 25-years study of 1,842 patients [abstract]. Arthritis Rheum 1998;41 Suppl:S188.
101. Kwoh CK, Simms RW, Anderson LG, et al. Guidelines for the management of rheumatoid arthritis. Arthritis Rheum 1996;39:713-22.
102. Conaghan PG, McGonagle D, Wakefield R, Emery P. New approaches to imaging of early rheumatoid arthritis. Clin Exp Rheumatol 1999;17:S37-S42.
103. Devlin J, Lilley J, Gough A, et al. Clinical associations of dual-energy X-ray absorptiometry measurement of hand bone mass in rheumatoid arthritis. Br J Rheumatol 1996;35:1256-62.
104. Emery P, Faint J, Birley A, Gough A, Pilling D, Salmon M. Use of genetic typing versus other markers for predicting outcome in patients with inflammatory arthritis [reply]. Arthritis Rheum 1995;38:874.
105. Gough A, Faint J, Salmon M, et al. Genetic typing of patients with inflammatory arthritis at presentation can be used to predict outcome. Arthritis Rheum 1994;37:1166-70.
106. Emery P, Salmon M, Bradley H, et al. Genetically determined factors as predictors of radiological change in patients with early symmetrical arthritis. BMJ 1992;305:1387-9.
107. Wolfe F, Albert DA, Pincus T. A survey of United States rheumatologists concerning effectiveness of disease-modifying antirheumatic drugs and prednisone in the treatment of rheumatoid arthritis. Arthritis Care Res 1998;11:375-81.
108. Egsmose C, Lund B, Borg G, et al. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year followup of a prospective double blind placebo controlled study. J Rheumatol 1995;22:2208-13.
109. Verhoeven AC, Bibo JC, Boers M, Engel GL, van der Linden S. Cost-effectiveness and cost-utility of combination therapy in early rheumatoid arthritis: randomized comparison of combined step-down prednisolone, methotrexate and sulphasalazine with

sulphasalazine alone. COBRA Trial Group. Combinatietherapie Bij Reumatoide Artritis. Br J Rheumatol 1998;37:1102-9.
110. van de Putte LBA, Vangestel AM, van Riel PLCM. Early treatment of rheumatoid arthritis: rationale, evidence, and implications. Ann Rheum Dis 1998;57:511-2.
111. Boers M. Combination therapy in rheumatoid arthritis. Lancet 1999;354:952.
112. Mottonen TT, Hannonen PJ, Boers M. Combination DMARD therapy including corticosteroids in early rheumatoid arthritis. Clin Exp Rheumatol 1999;17:S59-S65.
113. 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:S78-S82.
114. Hurst NP. Combination therapy in rheumatoid arthritis. Rheumatology 1999;38:789.
115. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. Lancet 1999;353:1568-73.
116. Odell JR, Scott DL. Rheumatoid arthritis: new developments in the use of existing therapies. Rheumatology 1999;3824-6.
117. Pincus T, Odell JR, Kremer JM. Combination therapy with multiple disease-modifying antirheumatic drugs in rheumatoid arthritis: A preventive strategy. Ann Intern Med 1999;131:768-74.
118. Weinblatt ME, Kremer JM, Coblyn JS, et al. Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. Arthritis Rheum 1999;42:1322-8.
119. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309-18.
120. Pincus T, 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.
121. Odell JR, Haire C, Erikson N, et al. Efficacy of triple DMARD therapy in patients with RA with suboptimal response to methotrexate. J Rheumatol 1996;23:72-4.
122. McCarty DJ, Harman JG, Grassanovich JL, Qian CL, Klein JP. Combination drug therapy of seropositive rheumatoid arthritis. J Rheumatol 1995;22:1636-45.
123. Wolfe F, Hawley DJ. The longterm outcomes of rheumatoid arthritis: Work disability: A prospective 18 year study of 823 patients. J Rheumatol 1998;25:2108-17.
124. Wolfe F, Hawley DJ, Pincus T. Disease modifying antirheumatic drugs (DMARD) and DMARD combination use by 3604 patients of 303 US rheumatologists [abstract]. Arthritis Rheum 1999;42 Suppl:S379.
125. Wolfe F, Flowers N, Anderson J. The National Rheumatic Disease Data Bank: case mix and severity characteristics of patients in rheumatological practice [abstract]. Arthritis Rheum 1998;41 Suppl:S132.
126. Ward MM. Trends in the use of disease modifying antirheumatic medications in rheumatoid arthritis, 1980-1995: Results from the national ambulatory medical care surveys. J Rheumatol 1999;26:546-50.
127. Felson DT, Anderson JJ, 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.
128. Felson DT. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis [reply]. Arthritis Rheum 1996;39:536-7.
129. Wolfe F, Pincus T, Fries JF. Use of second line "disease modifying" anti-rheumatic drugs (DMARDs) within 5 months of disease onset by 64% of 750 rheumatoid arthritis patients under the care of 142 US rheumatologist: an inception cohort study [abstract]. Arthritis Rheum 1997;40 Suppl:S218.