Methotrexate as the "anchor drug" for the treatment of early rheumatoid arthritis

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ABSTRACT

The two major advances over the 1990s in the treatment of rheumatoid arthritis (RA) were a shift in strategy from a "pyramid", in which disease modifying anti-rheumatic drugs (DMARDs) were deferred for several years, to the early aggressive use of DMARDs and wide - spread acceptance of methotrexate as the DMARD with the most long-term effectiveness and safety. Methotrexate courses are continued far longer than those of any other DMARD, an excel - lent indicator of greater effectiveness and safety. In one recent series, methotrexate was the first DMARD used in more than 80% of patients with RA. Studies which document the supe - riority of combinations of methotrexate with biological agents to methotrexate monotherapy select for only a minority of contemporary patients with RA who have severe disease activity and incom - plete responses to methotrexate. In one locale, only 5% of patients met criteria for the Anti-Tumor Necrosis Factor Trial in RA with Concomitant Therapy (ATTRACT) trial and only 30% met the criteria for the Early Rheumatoid Arthritis (ERA) trial. In studies com - paring methotrexate directly with bio - logical agents, the biological agents have greater efficacy in patients with very severe disease, but the best results are seen in patients who take a combi - nation of methotrexate and biologic agents. These data establish that methotrexate is the anchor drug and probably should be the first DMARD used in the majority of patients with RA at this time.

Introduction

The history of the treatment of rheumatoid arthritis (RA) in the 20th century presents a steady evolution of new agents and new approaches. At the beginning of the century, the only available drug therapy was aspirin (1). During the 1930s gold salts were introduced by Forrestier and colleagues (2) and became the mainstay of therapy through the 1980s. Penicillamine was introduced in the 1970s (3), and antimalarials gained widespread usage in the 1980s (4, 5). Sulfasalazine was actually developed in 1948, but did not reach widespread use until the 1980s (6).

Each of these advances provided meaningful benefit to many patients in coping more effectively with their RA. However, despite the fact that rheumatologists spoke of secondary agents for the treatment of RA as "remission inducing agents" (7), most patients experienced progressive disease, and RA was not adequately controlled in most patients (8-11). By contrast, at this time control of RA appears to be a reasonable goal in most patients (12-14), comparable to the control of other chronic dysregulatory diseases such as hypertension and diabetes (15), albeit requiring ongoing therapy, as the etiology and treatment of the dysregulation remain unknown.

Two major advances may account for the improved status of patients with RA over the last decade. The first involved a major shift in the strategies for patient care. Earlier approaches had emphasized deferring treatment with disease modifying anti-rheumatic drugs (DMARDs) until disease had been present for a few years (16), explained in part by reports of population-based and clinical studies in the 1960s and 1970s that most people who met the criteria for RA appeared to have a good prognosis (17, 18). In addition, available DMARDs such as injectable gold salts and penicillamine had substantial toxicities and were thought of as best avoided, wherever possible.

During the 1980s it became apparent that most clinical patients with RA who were seen in rheumatology treatment settings had a progressive disease, in contrast to individuals seen in the early

population and clinical studies. Important differences were recognized between symptoms due to inflammation, such as swollen joints or an elevated erythrocyte sedimentation rate (ESR), which were reversible, and symptoms due to joint damage which were cumulative and irreversible (19). Severe long-term outcomes such as work disability, joint replacement surgery, and premature death were common in many patients (20, 21). Clinical trials appropriately include only short-term reversible measures, and suggested that good control of inflammation was seen over relatively short periods (22). However, long-term remission was unusual (11), and evidence of cumulative joint damage and poor long-term outcomes emerged from longitudinal studies over 10 to 20 years (8-11). A new approach to RA was proposed in the late 1980s involving "remodeling the pyramid" (23-25) and thinking of RA as a "medical emergency" (26, 27), which requires early, aggressive intervention with a goal of remission, not mere improvement (12-14).

The second major advance in the treatment of RA over the last two decades was a DMARD which was far more potent and safe than previously available DMARDs – weekly low dose methotrexate. Methotrexate had been used in the 1960s in the treatment of inflammatory arthritides, but fell into disuse except in a few sites through the 1970s and early 1980s, because it was felt to be too aggressive and toxic for the treatment of RA. A few pioneering rheumatologists such as Hoffmeister (28, 29) and Scherbel (30, 31) treated patients who had RA with methotrexate during the 1960s and 1970s. This practice led to clinical studies by Willkens (32), Weinstein (33), and others, and ultimately to a large multi-center clinical trial organized by Weinblatt (34), which clearly documented the efficacy and safety of methotrexate for the treatment of RA.

Methotrexate is often included on lists of DMARDs as though it were one of a group of secondary agents for the treatment of RA. However, methotrexate differs substantially from all available DMARDs, showing greater efficacy and a high level of safety. New DMARDs such as cyclosporine (35, 36) and leflunomide (37, 38), as well as the biologic agents – etanercept (39, 40), infliximab (41), anakinra (42, 43) and adalimumab (44, 45) – represent major advances, providing mechanism-driven, targeted therapies for patients with RA. It is recognized that 20-30% of patients remain poorly controlled with methotrexate and require further therapy. Some patients have shown spectacular responses to anti-TNF agents. Nonetheless, methotrexate continues to be the "anchor drug" for most patients with RA. It is generally the first drug used in the treatment of RA among the community of rheumatologists in Nashville, Tennessee (46), although this is not the case in other contemporary rheumatology care settings, as discussed below.

In this review, we summarize briefly the rationale for considering methotrexate as the anchor drug for RA, which is based on five phenomena: 1. the excellent long-term effectiveness of methotrexate in most patients; 2. the long-term safety of methotrexate in most patients; 3. the increasing use of methotrexate and its acceptance as the most effective DMARD by the rheumatology community; 4. recognition that studies which document the superiority of biological agents or combinations of drugs with methotrexate compared to methotrexate monotherapy select for a minority of contemporary patients with RA, who have severe disease activity and incomplete responses to methotrexate; and 5. evidence from early RA clinical trials that methotrexate is almost as effective as biological agents in patients with very severe RA.

Long-term effectiveness of methotrexate in most patients

Clinical observational studies and randomized controlled trials which established the efficacy of methotrexate in RA (29, 32-34, 47-50) were followed by careful long-term clinical observational studies by Weinblatt and colleagues (51, 52), Kremer and colleagues (53, 54), Sany and colleagues (55, 56) and others. These reports clearly established that methotrexate was effective over long periods, with considerably lower toxicity than previously available DMARDs.

Several long-term analyses of data from routine clinical care indicated that courses of methotrexate were continued substantially longer than courses of other DMARDs, one of the best measures of the long-term effectiveness of a DMARD. In 617 patients who had 1,017 DMARD courses (57) and in 532 patients in 7 US private practices (58), more than 50% of courses of methotrexate were continued over 5 years or more, in contrast to fewer than 20% of courses of injectable gold salts, penicillamine, hydroxychloroquine, and azathioprine. In 460 patients from 7 private practices in Melbourne, Australia, 75.4% of patients were still taking methotrexate after 6 years (59), and 53% of patients were continuing at 12 years (60).

Reports of improved mortality rates (61, 62) in patients with RA at this time compared to previous periods can be attributed in large part to methotrexate. Choi *et al.* recently reported that both methotrexate and sulfasalazine were more cost-effective than the newly available treatment options of leflunomide and etanercept to achieve ACR 20 responses and a weighted average of proportions achieving ACR 70, ACR 50 and ACR 20 over a 6-month period (63).

Long-term safety of methotrexate

Methotrexate has been one of most carefully studied DMARDs for adverse events associated with therapy. The experience at the Hospital for Special Surgery (64) indicated that only 94 (3.4%) liver function tests out of a total of 2,791 performed in 182 RA patients were abnormal. One hundred fifty-two patients (83.5%) with 2007 evaluations had no abnormal results, compared with 30 patients (16.5%) who had at least one abnormal liver function result in 784 tests. Twenty-two of the 30 patients with at least one abnormality (73.3%) continued treatment despite an abnormality, without further evaluation or change in therapy, and subsequent

liver function assessments were within normal limits. The most common reason for discontinuation was inadequate response, and not side effects. These data were interpreted to suggest that guidelines developed by the ACR to monitor methotrexate-taking patients every 6 weeks may be in need of revision, a suggestion supported in a survey of U.S. rheumatologists (65).

A review of 362 RA patients enrolled in an outpatient clinic at the Rheumatology Department of Vienna General Hospital indicated that liver enzyme abnormalities in patients taking methotrexate virtually always occurred within the first 4 months of therapy (66). These elevations did not lead to changes in therapy, and liver biopsy was not performed in any patients. The vast majority of laboratory abnormalities were fully reversible and no costly complications were seen. The data led to a suggestion that monitoring should be more frequent (every 2-4 weeks) in the first 4 months and then performed every 4-6 months, which was validated in another cohort of RA patients from another hospital in Vienna. It was calculated that a mean of 48-78% of costs could be saved if the proposal for less frequent monitoring was implemented (67).

Methotrexate has a well-defined toxicity profile and physicians monitor patients for gastrointestinal, hepatic, and pulmonary toxicity, bone marrow suppression and stomatitis. As methotrexate prescribing patterns have changed from initially being reserved for patients who had "climbed the RA treatment pyramid" to earlier in the disease course, the toxicity profile has improved. Patients are relatively healthier early in their disease and appear to be less vulnerable to adverse events (12). In multiple cohorts, methotrexate appears to have very few clinically significant side effects, possibly due in part to the routine use of folic acid supplementation (68).

Increasing use of methotrexate and its acceptance as the most effective DMARD by rheumatologists

When methotrexate was initially used by a large number of rheumatologists in the late 1980s, as noted above, it was generally begun after the patient had tried (and failed) several DMARDs, including injectable gold salts, penicillamine, hydroxychloroquine, and (in Europe) sulfasalazine. For example, the report of 532 patients from 7 private US practices published in 1992 (58) indicated that methotrexate was the first DMARD used in 11.5% of patients, compared to 38.9% starting with parenteral gold, 24.4% with hydroxychloroquine, 10.3% with penicillamine, 16.9% with azathioprine, and 1% with auranofin. Among 1,427 patients in Edmonton, Canada seen between 1985 and 1994, parenteral gold was the most frequently prescribed initial DMARD from 1985 to 1987, sulfasalazine from 1988 to 1990, and hydroxychloroquine after 1991, while methotrexate was the initial DMARD in fewer than 5% of patients until 1994 (69). An analysis of 428 patients with RA of less than one year's duration in Greece treated between 1987-1995 indicated that the first DMARD was methotrexate in 27% of patients, hydroxychloroquine in 20%, penicillamine in 19%, cyclosporin in 8%, intra-muscular gold in 7%, and other DMARDs in 21% of patients (70).

The early reluctance to use methotrexate as the initial DMARD may be based on at least three explanations: a) rheumatologists had experience with more traditional DMARDs; b) a perception that the most potent drugs have the highest level of toxicities; c) concern about possible adverse events involving hematologic and hepatic toxicities, as well as a possible predisposition to later malignancies. However, experience of more than 15 years has reinforced recognition of the long-term effectiveness, as well as safety, of low-dose weekly methotrexate, particularly the recognition that high dose methotrexate and low-dose weekly methotrexate have very different toxicity profiles. Methotrexate has been used increasingly by rheumatologists as the initial DMARD in many settings, and attitudes about methotrexate have changed considerably.

Documentation of changes in clinical practice may be seen in a number of reports. In a study of DMARD use in 671 patients between 1975 and 1988, intra-muscular gold was taken by 100% of patients in 1975 versus fewer than 2% in 1988, while methotrexate use had changed from 0% up until 1980 to 44% in 1988, although methotrexate was rarely the first DMARD when these analyses were compiled in 1988 (57). In Tromso, Norway methotrexate was used in 7% of patients between 1979 and 1987 compared to 40% of patients in 1988 through 1996 (71). Among the 593 patients monitored in Vienna, Austria, methotrexate was prescribed in fewer than 10% of patients prior to 1988 versus 38% of patients in 1998, and was the initial DMARD in 30% of patients in 1998 (67). In Finland, sulfasalazine was the most prescribed DMARD from 1995 through 2000, but was overtaken by methotrexate in 2001 (72).

The changing patterns of increased use of methotrexate in RA are reflected in surveys of rheumatologists. A 1992 survey in the United Kingdom indicated that sulfasalazine was the most favored DMARD, as fewer than 10% of rheumatologists chose methotrexate as an initial DMARD (73). By contrast, a 2002 survey of 331 rheumatologists in the United Kingdom indicated that the first choice DMARD of 46.5% of rheumatologists was methotrexate compared to 43.5% who chose sulfasalazine (74).

Acceptance of methotrexate has been earlier and greater in North America than in Europe. A survey in the fall of 1996 indicated that methotrexate was regarded as the first choice by 78.5% of 214 United States rheumatologists and by 68.7% of Canadian rheumatologists (75). A survey of US rheumatologists in 1995 and 1999 indicated that 82% used a combination of methotrexate + hydroxychloroquine in 1995 compared to 96% in 1999, and 16% used combination DMARDs, which generally included methotrexate, in more than 30% of patients in 1995 versus 46% in 1999 (76).

Reports of recent early RA databases in the United States indicate the more widespread use of methotrexate. In the

Western Consortium of Practicing Rheumatologists established between 1993 and 1996 (77), methotrexate was used by 35.7% of patients at baseline and by 57.4% after two years. In the early rheumatoid arthritis treatment evaluation registry (ERATER) (46), methotrexate was the first DMARD used by 84.2% of patients, and was used in 89% of patients seen in Nashville, Tennessee (none of whom were patients of any of the authors). Nonetheless, patients in this database from other sites showed different trends, including a group of patients from Burlington, Massachusetts, in whom 37% were treated with methotrexate and 40% with hydroxychloroquine as the first DMARD, and a group in Brooklyn, New York, in whom 38% were treated initially with methotrexate and 24% with hydroxychloroquine (78). In Europe, a slower acceptance of methotrexate can be seen in the Italian early arthritis database, in which methotrexate was used in 19% of patients with early rheumatoid arthritis of less than 4 months' duration compared to 42% in those with arthritis of 4 months to 2 years duration (79). Methotrexate was used by only 4.6% of patients in the Norfolk arthritis register (NOAR) in the United Kingdom compared to sulfasalazine in 57% (80).

One important further consideration is that weekly methotrexate therapy with doses of 10 mg per week or less may have limited effectiveness, with substantially lower retention rates than that seen for doses of 12.5 mg per week or more (81). Therefore, methotrexate doses of 15-25 mg should be given if tolerated. In many instances, parenteral administration of methotrexate results in both greater tolerability and greater efficacy. The most recent trials comparing the efficacy of methotrexate with that of biologicals employed high dose methotrexate therapy with rapid acceleration of the dose.

Taken together, although there remain disparities between beliefs and practice (82), these reports indicate a trend towards more widespread use of methotrexate by many rheumatologists in patients with early RA. The data suggest that many rheumatologists now regard methotrexate as the primary "anchor drug" for treatment of RA.

Studies documenting superiority of biological agents or drug combinations compared to MTX monotherapy select for only a minority of RA patients

Over the last decade, a number of randomized controlled clinical trials have been published indicating greater efficacy for combinations of DMARDs or biological agents with methotrexate compared to methotrexate only, including cyclosporine (83), leflunomide (84), etanercept (39), infliximab (85), adalimumab (45), and anakinra (43). However, these studies may have included only a small fraction of patients with RA at the study sites, based on two important selection criteria which are sometimes neglected in the interpretation of the data.

The first type of selection involves the "step up" or "add on" design of most studies, in which patients are eligible only if they respond incompletely to methotrexate (86). It would be expected that patients who respond incompletely to any drug, whether an antihypertensive agent or even a nonsteroidal anti-inflammatory drug, will respond with greater efficacy to the addition of a second drug versus the addition of a placebo. This is not to criticize the add-on clinical trial, which was developed at a time when the available DMARDs were not nearly as potent as the DMARDs available now, and the consensus was that combination therapy offered no advantages over DMARD monotherapy (87,88). Efforts to document the potential efficacy of new DMARDs appeared to have been overwhelmed by the substantially greater efficacy of methotrexate than other available DMARDs. Therefore, it appeared appropriate to have patients obtain maximum efficacy from methotrexate, and then analyze whether an additional agent could provide incremental efficacy. However, this procedure selected for patients who were poor responders to methotrexate, who appear to represent a relative minority of patients.

The "step up" or "add on" design is also the most appropriate approach in testing a new agent in RA, when its efficacy and toxicity are unknown, as it is ethical to offer the optimal available therapy initially. Furthermore, the selection of partial responders is sensible in order to exclude totally refractory patients. However, there have been few analyses concerning how many patients seen in standard clinical care for RA who were treated with methotrexate and other DMARDs may have been ineligible for inclusion in these clinical trials, because of a favorable clinical status.

The second type of selection involves inclusion criteria for contemporary RA clinical trials, designed for patients with the most severe RA. Most recent RA clinical trials continue to list inclusion criteria which were developed several decades ago, such as 6 tender joints, 6 swollen joints, an ESR $\geq$ 28 mm/hour, and morning stiffness of $\geq$ 45 minutes (89), although the clinical status of patients with RA appears to have improved substantially over this period (90,91). Two cohorts of patients seen in Nashville, Tennessee were reviewed using a standard protocol for the evaluation of RA (SPERA) and were analyzed to determine the proportion of patients who met 3 or 4 of these criteria (89). Cohort E (early) included 232 patients with less than 3 years of symptoms seen by 5 full-time private practice rheumatologists. Cohort L (late) included all 138 consecutive patients with RA (other than 14 who did not have a joint count recorded or who had taken infliximab or etanercept), who had been under the care of one rheumatologist (TP) at a weekly academic rheumatology clinic for a mean of 4.6 years (range 0 – 19 years).

Overall, 15.3% of Cohort L and 34.1% of Cohort E patients had 6 or more swollen and tender joints, as well as an ESR of 28 or more, or morning stiffness of 45 minutes or more (89). Only 4.1% of Cohort L and no patients in Cohort E met ARA criteria for remission. In analyses of specific clinical trials (92), among all 232 patients in Cohort E, 37 (16%) met inclusion criteria for the ERA clinical trial of methotrexate versus etanercept (40,

93). Among the 138 patients in cohort L who had a joint count recorded and were not taking etanercept or infliximab, only 7 (5%) met the primary inclusion criteria for the Anti-Tumor Necrosis Factor Trial in RA with Concomitant Therapy (ATTRACT) study (85, 94).

It is recognized that the sponsors of these clinical trials deliberately sought patients with more severe disease, as should be the case with early clinical trials of new therapies. However, it is also recognized that most patients in the clinical cohorts from standard rheumatology care were ineligible for most contemporary clinical trials, including the ERA trial and ATTRACT study. The majority of patients seen in the standard clinical cohorts were treated with methotrexate, and had 1-5 tender or swollen joints and an ESR <28 mm/hour (89) [up to 40% of patients have a normal ESR at their first visit (95)]. This observation suggests that methotrexate may be sufficient therapy for many, if not most, patients with RA, and/or that inclusion criteria for clinical trials might be broadened to be more generalizable.

Efficacy of methotrexate in "head-to-head" comparisons with biological agents: Methotrexate is the "anchor" drug

Several recent clinical trials compared methotrexate with TNF-blockers and/or a combination of TNF-blockers with methotrexate. In these trials, patients received methotrexate at the start of the study rather than being partial responders and continuing methotrexate.

The ERA clinical trial to compare etanercept to methotrexate in early RA patients with less than 3 years of disease (40, 93) was discussed above and is presented in greater detail elsewhere in this supplement (96). The results indicated superiority of etanercept over methotrexate in ACR 20, 50 and 70 responses at some time points, and in slowing the progression of total Sharp radiographic scores (40, 93). Many of these results are statistically significant, but differences between etanercept and methotrexate are rather small, and their clinical significance is not established. Furthermore, patients in the ERA trial were selected for severity of RA, as fewer than 20% of 232 patients with less than 3 years of disease in one clinical setting met the inclusion criteria (92).

Therefore, etanercept may be superior to methotrexate in patients who have severe clinical activity, i.e. 20-30% of patients. However, such patients are a minority of all patients with RA in several sites, including Norway (97). It is possible that most patients could do as well with methotrexate, possibly in combination with hydroxychloroquine and/or sulfasalazine (98-100).

In the ASPIRE trial which, like the ERA trial, involved patients with < 3 years disease duration, methotrexate was compared to a combination of methotrexate and infliximab. The combination was significantly superior to methotrexate monotherapy in all endpoints – clinical, radiological and functional (101). In the TEMPO trial, results of which were briefly presented at a EULAR Satellite symposium, patients with long-standing RA were treated with methotrexate, etanercept or a combination of the two agents, and the combination was the most superior regimen.

Thus, while monotherapy of biological agents may be only marginally superior to methotrexate monotherapy (and might even be less so if methotrexate were combined with intermediate dose glucocorticoids), the combination of methotrexate with TNF blockers appears to convey the maximal therapeutic effects currently obtainable, at least in patients selected for having severe RA. In such an approach, methotrexate again serves as the "anchor" with which a biological agent can be combined for greater efficacy. Given that methotrexate may interfere primarily with IL-1 pathways (102), the combined blockade of IL-1- and TNF-mediated pathologies may constitute one of several explanations for the significant efficacy observed by this type of combination therapy.

Conclusion

The data presented above indicate a trend to increasing use of methotrexate as the primary "anchor drug" for the treatment of RA, both as monotherapy and in combination therapies with other DMARDs or biologicals, including one report that methotrexate was the first DMARD used in more than 80% of patients with early RA. These findings reflect the superior efficacy and safety of methotrexate compared to other DMARDs. Nonetheless, at least 20-50% of patients do not continue methotrexate for longer than 5 years, and therapy generally involves a lifetime commitment, since the dysregulation that characterizes RA remains poorly understood and without any therapies. Therefore, there is clearly a need for additional DMARDs and biological therapies to control RA in many patients at this time, although methotrexate remains the anchor therapy for most patients.

References

1. RAGAN C: Rheumatoid arthritis: The natural history of the disease and its management. *Bull NY Acad Med* 1951; 27: 63-74.
2. FORESTIER J: Rheumatoid arthritis and its treatment by gold salts. *J Lab Clin Med* 1935; 20: 827-40.
3. MULTICENTRE TRIAL GROUP: Controlled trial of D(-)penicillamine in severe rheumatoid arthritis. *Lancet* 1973; 1: 275-80.
4. MAKSYMOWYCH W, RUSSELL AS: Antimalarials in rheumatology: Efficacy and safety. *Semin Arthritis Rheum* 1987; 16: 206-21.
5. PAULUS HE: Antimalarial agents compared with or in combination with other disease-modifying antirheumatic drugs. *Am J Med* 1988; 85 (Suppl. 4A): 45-52.
6. HANNONEN P, MÖTTÖNEN T, HAKOLA M, OKA M: Sulfasalazine in early rheumatoid arthritis. *Arthritis Rheum* 1993; 36: 1501-9.
7. LIPSKY PE: Remission-inducing therapy in rheumatoid arthritis. *Am J Med* 1983; 75 (Suppl. 4B): 40-9.
8. 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.
9. SCOTT DL, GRINDULIS KA, STRUTHERS GR, COULTON BL, POPERT AJ, BACON PA: Progression of radiological changes in rheumatoid arthritis. *Ann Rheum Dis* 1984; 43:8-17.
10. 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.
11. WOLFE F, HAWLEY DJ: Remission in rheumatoid arthritis. *J Rheumatol* 1985; 12: 245-52.
12. EMERY P, SALMON M: Early rheumatoid arthritis: Time to aim for remission? *Ann*

Rheum Dis 1995; 54: 944-7.
13. WEINBLATT ME: Rheumatoid arthritis: Treat now, not later ! (editorial). *Ann Intern Med* 1996; 124: 773-4.
14. 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.
15. PINCUS T, GIBOFSKY A, WEINBLATT ME: Urgent care and tight control of rheumatoid arthritis as in diabetes and hypertension:better treatments but a shortage of rheumatologists. *Arthritis Rheum* 2002; 46: 851-4.
16. LIGHTFOOT RW JR: Treatment of rheumatoid arthritis. *In* MCCARTY DJ (Ed.): *Arthri - tis and Allied Conditions*. Philadelphia, Lea & Febiger, 1985: 668-76.
17. MIKKELSEN WM, DODGE H: A four-year follow-up of suspected rheumatoid arthritis: the Tecumseh, Michigan, community health study. *Arthritis Rheum* 1969; 12: 87-91.
18. 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.
19. PINCUS T, CALLAHAN LF: Prognostic markers of activity and damage in rheumatoid arthritis: Why clinical trials and inception cohort studies indicate more favorable outcomes than studies of patients with established disease. *Br J Rheumatol* 1995; 34: 196-9.
20. PINCUS T, CALLAHAN LF: What is the natural history of rheumatoid arthritis ? *Rheum Dis Clin North Am* 1993; 19: 123-51.
21. WOLFE F: The natural history of rheumatoid arthritis. *J Rheumatol* 1996; 23 (Suppl. 44): 13-22.
22. PINCUS T: The paradox of effective therapies but poor long-term outcomes in rheumatoid arthritis. *Semin Arthritis Rheum* 1992; 21:2-15.
23. WILSKE KR, HEALEY LA: Remodeling the pyramid – A concept whose time has come. *J Rheumatol* 1989; 16: 565-7.
24. FRIES JF: Reevaluating the therapeutic approach to rheumatoid arthritis: The "saw-tooth" strategy. *J Rheumatol* 1990; 17 (Suppl. 22): 12-5.
25. 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.
26. PINCUS T: Rheumatoid arthritis: A medical emergency ? *Scand J Rheumatol* 1994; 23 (Suppl. 100): 21-30.
27. MORELAND LW, BRIDGES JR SL: Early rheumatoid arthritis: A medical emergency ? *Am J Med* 2001; 111: 498-500.
28. HOFFMEISTER RT: Methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1972; 15 (Suppl.): S114 (abstr.).
29. HOFFMEISTER RT: Methotrexate therapy in rheumatoid arthritis:15 years experience . *Am J Med* 1983; 75 (Suppl. 6A): 69-73.
30. MACKENZIE AH: Liver biopsy findings after methotrexate (MTX) therapy for rheumatoid arthritis (RA). *J Rheumatol* 1974; 1 (Suppl.): 73 (abstr.).
31. WILKE WS, CALABRESE LH, SCHERBEL AL: Methotrexate in the treatment of rheumatoid arthritis. *Cleve Clin Q* 1980; 47: 305-9.
32. WILLKENS RF, WATSON MA, PAXSON CS: Low dose pulse methotrexate therapy in rheumatoid arthritis. *J Rheumatol* 1980; 7: 501-5.
33. STEINSSON K, WEINSTEIN A, KORN J, ABELES M: Low dose methotrexate in rheumatoid arthritis. *J Rheumatol* 1982; 9: 860-6.
34. WEINBLATT ME, COBLYN JS, FOX DA *et al.*: Efficacy of low-dose methotrexate in rheumatoid arthritis. *N Engl J Med* 1985; 312: 818-22.
35. TUGWELL P, BOMBARDIER C, GENT M *et al.*: Low-dose cyclosporin versus placebo in patients with rheumatoid arthritis. *Lancet* 1990; 335: 1051-5.
36. ZEIDLER HK, KVIEN TK, HANNONEN P *et al.*: Progression of joint damage in early active severe rheumatoid arthritis during 18 months of treatment: Comparison of low-dose cyclosporin and parenteral gold. *Br J Rheumatol* 1998; 37: 874-82.
37. STRAND V, TUGWELL P, BOMBARDIER C *et al.*: Function and health-related quality of life: Results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. *Arthritis Rheum* 1999; 42: 1870-8.
38. SMOLEN JS, KALDEN JR, SCOTT DL *et al.*: Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: A double-blind, randomised, multicentre trial. *Lancet* 1999; 353: 259-66.
39. 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.
40. BATHON JM, MARTIN RW, FLEISCHMANN RM *et al.*: A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000; 343:1586-93.
41. 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.
42. BRESNIHAN B, ALVARO-GRACIA JM, COBBY M *et al.*: Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum* 1998; 41: 2196-204.
43. COHEN S, HURD E,CUSH J *et al.*: Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate:Results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; 46: 614-24.
44. RAU R, HERBORN G, SANDER O *et al.*: Long-term treatment with the fully human anti-TNF-antibody D2E7 slows radiographic disease progression in rheumatoid arthritis. *Arthritis Rheum* 1999; 42, S400 (Abstr. 1978).
45. WEINBLATT ME, KEYSTONE EC, FURST DE *et al* .: Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003; 48: 35-45.
46. SOKKA T, PINCUS T: Contemporary disease modifying antirheumatic drugs (DMARD) in patients with recent onset rheumatoid arthritis in a US private practice: Methotrexate as the anchor drug in 90% and new DMARD in 30% of patients. *J Rheumatol* 2002; 29: 2521-4.
47. WILLKENS RF, WATSON MA: Methotrexate: A perspective of its use in the treatment of rheumatic diseases. *J Lab Clin Med* 1982; 100: 314-21.
48. THOMPSON RN, WATTS C, EDELMAN J, ESDAILE JM, RUSSELL AS: A controlled two-centre trial of parenteral methotrexate therapy for refractory rheumatoid arthritis. *J Rheumatol* 1984; 11: 760-3.
49. WEINSTEIN A, MARLOWE S, KORN J, FAROUHAR F: Low-dose methotrexate treatment of rheumatoid arthritis: Long-term observations. *Am J Med* 1985; 79: 331-7.
50. WILLIAMS HJ, WILLKENS RF, SAMUELSON CO JR *et al.*: Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis: a controlled clinical trial. *Arthritis Rheum* 1985; 28: 721-30.
51. 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.
52. WEINBLATT ME, KAPLAN H, GERMAIN BF *et al.*: Methotrexate in rheumatoid arthritis. A five-year prospective multicenter study. *Arthritis Rheum* 1994; 37: 1492-8.
53. KREMER JM, PHELPS CT: Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis: Update after a mean of 90 months. *Arthritis Rheum* 1992; 35: 138-45.
54. KREMER JM: Safety, efficacy, and mortality in a long-term cohort of patients with rheumatoid arthritis taking methotrexate: Follow-up after a mean of 13.3 years. *Arthritis Rheum* 1997; 40: 984-5.
55. SANY J, ANAYA JM, LUSSIEZ V, COURET M, COMBE B, DAURES JP: Treatment of rheumatoid arthritis with methotrexate: A prospective open long-term study of 191 cases. *J Rheumatol* 1991; 18: 1323-7.
56. MARAVIC M, BOLOGNA C, DAURES JP, JORGENSEN C, COMBE B, SANY J: Radiologic progression in early rheumatoid arthritis treated with methotrexate. *J Rheumatol* 1999; 26: 262-7.
57. 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.
58. 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.
59. BUCHBINDER R,HALL S, SAMBROOKPN *et al.*: Methotrexate therapy in rheumatoid

arthritis: A life table review of 587 patients treated in community practice. *J Rheumatol* 1993; 20: 639-44.
60. WLUKA A, BUCHBINDER R,MYLVAGANAM A *et al*.: Longterm methotrexate use in rheumatoid arthritis: 12 year follow-up of 460 patients treated in community practice. *J Rheumatol* 2000; 27: 1864-71.
61. KRAUSE D, SCHLEUSSER B, HERBORN G, RAU R: Response to methotrexate treatment is associated with reduced mortality in patients with severe rheumatoid arthritis. *Arthritis Rheum* 2000; 43: 14-21.
62. CHOI HK, HERNÁN MA, SEEGER JD, ROBINS JM, WOLFE F: Methotrexate and mortality in patients with rheumatoid arthritis: A prospective study. *Lancet* 2002; 359: 1173-7.
63. CHOI HK, SEEGER JD, KUNTZ KM: A cost effectiveness analysis of treatment options for methotrexate-naive rheumatoid arthritis. *J Rheumatol* 2002; 29: 1156-65.
64. YAZICI Y, ERKAN D, PAGET SA: Monitoring methotrexate hepatic toxicity in rheumatoid arthritis: Is it time to update the guidelines? *J Rheumatol* 2002; 29: 1586-9.
65. YAZICI Y, ERKAN D, PAGET SA: Monitor for methotrexate, etanercept, infliximab and anakinra associated adverse events by rheumatologists. *Arthritis Rheum* (in press).
66. ALETAHA D, SMOLEN JS: Laboratory testing in rheumatoid arthritis patients taking disease-modifying antirheumatic drugs:Clinical evaluation and cost analysis. *Arthritis Rheum* 2002; 47: 181-8.
67. ALETAHA D, SMOLEN JS: The rheumatoid arthritis patient in the clinic:comparing more than 1300 consecutive DMARD courses. *Rheumatology* 2002; 41: 1367-74.
68. HOEKSTRA M, VAN EDE AE, HAAGSMA CJ, VAN DE LAAR MAFJ, HUIZINGA TWJ: Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. *Ann Rheum Dis* 2003; 62: 423-6.
69. SUAREZ-ALMAZOR ME, SOSKOLNE CL, SAUNDERS LD, RUSSELL AS: Use of second line drug for the treatment of rheumatoid arthritis in Edmonton, Alberta. Patterns of prescription and long-term effectiveness. *J Rheumatol* 1995; 22:836-43.
70. PAPADOPOULOS NG, ALAMANOS Y, PAPADOPOULOS IA, TSIFETAKI N, VOULGARI PV, DROSOS AA: Disease modifying antirheumatic drugs in early rheumatoid arthritis: A long-term observational study. *J Rheumatol* 2002; 29: 261-6.
71. RIISE T, JACOBSEN BK, GRAN JT: Changes in therapy of rheumatoid arthritis during the period 1979 to 1996. *Scand J Rheumatol* 2001; 30: 199-202.
72. KLAUKKA T, KAARELA K: Methotrexate is the leading DMARD in Finland. *Ann Rheum Dis* 2003; 62: 494-6.
73. KAY EA, PULLAR T: Variations among rheumatologists in prescribing and monitoring of disease modifying antirheumatoid drugs. *Br J Rheumatol* 1992; 31: 477-83.
74. JOBANPUTRA P, WILSON J, DOUGLAS K, BURLS A: A survey of British rheumatologists' DMARD preferences for rheumatoid arthritis. *Rheumatology* 2003; 42: 1-5.
75. MAETZEL A, BOMBARDIER C, STRAND V, TUGWELL P, WELLS G: How Canadian and US rheumatologists treat moderate or aggressive rheumatoid arthritis: A survey. *J Rheumatol* 1998; 25: 2331-8.
76. MIKULS TR: The changing face of rheumatoid arthritis therapy: Results of serial surveys. *Arthritis Rheum* 2000; 43:464-7.
77. PAULUS HE, RAMOS B, WONG WK *et al*.: Equivalence of the acute phase reactants C-reactive protein, plasma viscosity, and Westergren erythrocyte sedmientation rate when used to calculate American College of Rheumatology 20% improvement criteria or the disease activity score in patients with rearly rheumatoid arthritis. Western Consortium of Practicing Rheumatologists. *J Rheumatol* 1999; 26: 2324-32.
78. SOKKA T, WILLOUGHBY J, YAZICI Y, PINCUS T: Databases of patients with early rheumatoid arthritis in USA. *Clin Exp Rheumatol* 2003; 21 (Suppl. 31):S146-S153.
79. GIARA REGISTRY STUDY GROUP: Aggressive rheumatoid arthritis registry in Italy. Characteristics of the early rheumatoid arthritis subtype among patients classified according to the ACR criteria. *Clin Exp Rheumatol* 2003; 21 (Suppl. 31):S129-S132.
80. BUKHARI MAS, WILES NJ, LUNT M *et al.*: Influence of disease-modifying therapy on radiographic outcome in inflammatory polyarthritis at five years: Results from a large observational inception study. *Arthritis Rheum* 2003; 48: 46-53.
81. ALETAHA D, SMOLEN JS: Effectiveness profiles and dose dependent retention of traditional disease modifying antirheumatic drugs for rheumatoid arthritis. An observational study. *J Rheumatol* 2002; 29: 1631-8.
82. ALETAHA D, SMOLEN JS: DMARD use in early rheumatoid arthritis. Lessons from observations in patients with established disease. *Clin Exp Rheumatol* 2003; 21 (Suppl. 31): S169-S173.
83. 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.
84. 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.
85. LIPSKY PE, VAN DER HEIJDE DMFM, CLAIR EW *et al*.:Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000; 343: 1594-602.
86. BOERS M: Add-on or step-up trials for new drug development in rheumatoid arthritis: A new standard? *Arthritis Rheum* 2003; 48: 1481-3.
87. PAULUS HE: The use of combinations of disease-modifying antirheumatic agents in rheumatoid arthritis. *Arthritis Rheum* 1990; 33: 113-20.
88. SCOTT DL, FARROW S, YEO SI: Early developments in combination therapy. *Clin Exp Rheumatol* 1999; 17: S8-S12.
89. SOKKA T, PINCUS T: Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or American College of Rheumatology criteria for remission. *J Rheumatol* 2003; 30: 1138-46.
90. BERGSTROM U, BOOK C, LINDROTH Y, MARSAL L, SAXNE T, JACOBSSON L: Lower disease activity and disability in Swedish patients with rheumatoid arthritis in 1995 compared with 1978. *Scand J Rheumatol* 1999; 28: 160-5.
91. SOKKA TM, KAARELA K, MÖTTÖNEN TT, HANNONEN PJ: Conventional monotherapy compared to a "sawtooth" treatment strategy in the radiographic procession of rheumatoid arthritis over the first eight years. *Clin Exp Rheumatol* 1999; 17: 527-32.
92. SOKKA T, PINCUS T: Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis. *Arthritis Rheum* 2003; 48: 313-8.
93. GENOVESE MC, BATHON M, MARTIN RW *et al*.: Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002; 46: 1443-50.
94. ST CLAIR EW, WAGNER CL, FASANMADE AA *et al*.: The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: Results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; 46: 1451-9.
95. WOLFE F, MICHAUD K: The clinical and research significance of the erythrocyte sedimentation rate. *J Rheumatol* 1994; 21: 1227-37.
96. BATHON JM, GENOVESE MC: The Early Rheumatoid Arthritis (ERA) Trial comparing the efficacy and safety of etanercept and methotrexate. *Clin Exp Rheumatol* 2003; 21 (Suppl. 31): S195-S197.
97. KVIEN TK,UHLIG T, KRISTIANSEN IS: Criteria for TNF-targeted therapy in rheumatoid arthritis: Estimates of the number of patients potentially eligible. *Drugs* 2001; 61: 1711-20.
98. O'DELL JR, HAIRE CE, ERIKSON N *et al*.: Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996; 334:1287-91.
99. MÖTTÖNEN T, HANNONEN P, LEIRISALO-REPO M *et al*.: Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: A randomised trial. FIN-RACo trial group. *Lancet* 1999; 353: 1568-73.
100. 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.
101. SMOLEN J, EMERY P, BATHON J *et al*.: Treatment of early rheumatoid arthirtis with infliximab plus methotrexate or methotrexate alone:Preliminary results of the ASPIRE trial. *Ann Rheum Dis* 2003; 62: S64.
102. SEITZ M, ZWICKER M, LOETSCHER P: Effects of methotrexate on differentiation of monocytes and production of cytokine inhibitors by monocytes. *Arthritis Rheum* 1998; 41: 2032-8.