Disease-modifying anti-rheumatic drug therapy and structural damage in early rheumatoid arthritis

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ABSTRACT
The appearance of measurable structural damage in rheumatoid arthritis (RA) is an indicator of disease severity and future disability. Disease-modifying anti-rheumatic drugs (DMARDs) used in combination appear to be more effective than monotherapies at reducing the rate of progressive joint damage during randomized controlled trials. In clinical practice, however, combination DMARD therapy is still largely reserved for patients who have failed to respond to monotherapy. High dose corticosteroid, when given in early disease with combination DMARD therapy, may continue to ameliorate disease severity and progression for years after discontinuation of the high dose. To date, no DMARD combination has totally arrested joint damage in all patients with early RA. Future randomised controlled trials should always include prospective radiographic data as a primary outcome measure.

Introduction

Conventional radiographs are an important objective measure of disease progression in rheumatoid arthritis (RA), and are recommended as a disease outcome measure by the American College of Rheumatology (ACR) (1). Several studies have demonstrated that erosions occur during the first two years of disease (2-4). Furthermore, the rate of joint damage may be greatest during the first two years of disease (5). In a long-term longitudinal study of radiographic progression in RA, Wolfe and Sharp showed a more linear progression over time. A substantial number of these patients had received early DMARD therapy, however, which may have affected the natural history of the joint progression in this cohort (6). As joint damage in RA is related to long-term functional disability (7), these studies provide a rationale for effective early treatment. Although more sensitive imaging techniques such as MRI are now available (8), radiographs remain the standard measure of bone and joint damage due to issues of convenience, access and cost. Most recent randomized clinical trials investigating treatment strategies in early RA have included measures of radiographic progression and are the focus of this review.

Changing strategies of DMARD use in the treatment of early RA

Since the early 1990s, an increased understanding of the long-term consequences of RA has led to significant changes in management (9). The mortality (10-14), morbidity (12) and economic cost (15) in established disease have been well described. Significant functional impairment and loss of earnings are also features of poorly controlled early disease (16, 17).

In RA, a disease modifying anti-rheumatic drug (DMARD) is defined as a pharmacological agent that has the ability to retard the rate of progressive joint damage and associated disability, which occur as a result of persistent disease activity. Delayed introduction of DMARD therapy has been shown to correlate with a poorer outcome in several clinical trials (18, 19), whilst patients receiving early DMARD therapy demonstrate an improved outcome (19-24).

The pathogenesis of RA is incompletely understood. Moreover, the mechanisms of action of all conventional DMARDs with efficacy in RA are unknown. It is widely held, however, that the course of RA proceeds through a number of defined phases. A pre-clinical initiation event is required to prime the immune system to respond to self-antigens. This is followed by the clinical disease phase, where synovial inflammation precedes and may overlap with a joint destruction phase. A fourth phase may be considered outcomes, which include such phenomena as

work disability, joint replacement surgery and premature death. Sustained remission in RA is rare (25, 26). Furthermore, the capacity of disease modifying therapy to change disease outcomes is greatly reduced after joint damage has occurred (27). By treating arthritis in the very early clinical period, it was hoped that increased rates of remission could be achieved. Previous studies have demonstrated that DMARDs slow the radiographic progression of structural damage in established RA (28-32). In treating early RA, the rationale is to slow or arrest joint damage completely.

Comparatively few studies have evaluated the effects of DMARD medication on the clinical course of early RA. A full interpretation of their composite findings is hampered by variations in the duration of follow up and the difficulty in making direct comparisons between the differing study designs. The DMARDs that have been studied, whether as monotherapies, or in combination, against placebo or other DMARD regimes are discussed below.

Monotherapy
Gold salts
Gold salts were introduced as therapeutic agents for the treatment of infectious disease, including tuberculosis, in the 19th century. Their successful application in treating the articular manifestations of rheumatic fever by Lande in 1927, and the hypothesis of a link between RA and mycobacteria, led to its more widespread use for the treatment of rheumatic diseases (33). Although the mechanism of action is not known, its efficacy in established RA is well documented (34, 35). There have been a number of comparator studies in early arthritis of the effects of parenteral gold sodium thiomalate (GSTM) versus intramuscular methotrexate (MTX) (36), oral sulphasalazine (SSZ) (37) and cyclosporin A (CYA) (38). All studies showed that, despite improvements in other clinical parameters, new erosions continued to occur. No statistically significant superior effects between GSTM and any of the comparator DMARDs were demonstrated.

Antimalarials
The antimalarial drugs, which include chloroquine phosphate and hydroxychloroquine, have been used in the treatment of RA and SLE for more than 50 years (39). Hydroxychloroquine and chloroquine phosphate have been favored by clinical rheumatologists and have been shown to be successful in reducing joint inflammation and stiffness in early RA, with a relatively low risk of side effects (40-42). However, no radiographic information is available from any of these studies.

Sulphasalazine
SSZ has been used for the treatment of inflammatory arthritis and inflammatory bowel disease for more than fifty years. It is a conjugate of 5-aminosalicylic acid and the sulphonamide sulfapyridine (43). Although the mechanism of action in arthritis is unknown, it has multiple immunomodulatory effects. SSZ therapy decreases the production of IgM rheumatoid factor (44), suppresses T cell responses (45), and inhibits the binding of tumour necrosis factor to its membrane receptor (46). SSZ successfully retards the development of joint erosions and improves the parameters of disease activity in established RA (28, 29).

Two studies have assessed the effect of SSZ in early arthritis. One randomized control trial compared SSZ with diclofenac sodium in 117 patient with early RA (47). Patients treated with SSZ showed a significant decrease in new erosion formation over 12 months, compared to diclofenac (mean new erosions per patient 2.3 versus 10.5, respectively). In a randomized controlled trial of SSZ versus placebo, SSZ improved clinical and laboratory parameters of disease activity, but did not retard new erosion formation (48). Patient numbers were small in this study however and the results could have been confounded by the concomitant use of corticosteroids.

Methotrexate
MTX has proven efficacy in the treatment of established RA and is widely considered as the DMARD of choice. It has the most favorable benefit to toxic-

ity ratio in patients remaining on long-term DMARD therapy (49). MTX acts as a folate antagonist by inhibiting tetrahydrofolate reductase. The mechanism of action in the treatment of RA is unknown but appears to be mediated through anti-inflammatory, rather than cytotoxic, actions. Treatment with MTX has been shown to reduce cytokine production through apoptosis of peripherally active T cells (50), to reduce adhesion molecule expression and macrophage numbers in synovial tissue (51), and to reduce collagenase gene expression in rheumatoid synovial tissue (52).

The benefits of MTX in established RA have been well documented in randomized controlled trials (30-32) Uncontrolled trials on patients receiving methotrexate as their first DMARD (53), or in early disease (54), continue to demonstrate radiographic progression. In one study, patients without erosions at first presentation were less likely to develop erosions after 1 year (53). In the absence of any placebo control it cannot be inferred that this effect is due to MTX rather than the more benign course of non-erosive disease.

Only two randomized studies investigating MTX monotherapy in early RA using radiographic evaluation as an outcome measure have been completed. In one long-term follow-up trial of 174 patients randomized to intramuscular MTX or GSTM, patients receiving MTX had higher radiographic scores after 3 years than patients who had received GSTM, although the difference was not significant (36). Two-year radiographic outcomes from an etanercept versus MTX study in early RA demonstrated that a Sharp score of zero was maintained over 2 years in 86% of patients receiving etanercept 25 mg twice weekly compared to 65% of MTX-treated patients (55). Some patients from both treatment groups demonstrated continuing progressive joint damage.

Leflunomide
Leflunomide is a novel antirheumatic drug, which arrests the cell cycle through inhibiting *de novo* pyrimidine synthesis in rapidly dividing cells (56).

A number of studies have shown that leflunomide is superior to placebo and other DMARDs in retarding new joint damage in RA (56-58). These studies were not restricted to early arthritis and no sub-analyses of disease outcomes for patients with early disease were provided.

Cyclosporin A
Cyclosporin A (CYA) exerts its potent immunosuppressive effects mainly through the inhibition of T cell activation and has a wide range of clinical indications (59). Although its hypertensive and nephrotoxic side effects limit its widespread use in RA, it has been relatively well studied in the treatment of early disease (38, 40, 60, 61). CYA significantly reduced erosion formation after 12 months of treatment when compared with a control group receiving other DMARD monotherapy (60). In a 42-month study of CYA versus MTX, radiographic progression increased equally in both treatment groups. Stable radiographic scores were found in 71% of patients receiving CYA over the study period (n=37). All patients received concurrent prednisolone therapy so the results may be due to combination therapy rather than a CYA effect alone (62).

Glucocorticoids
Glucocorticoids have been an important therapeutic option for the rapid control of the symptoms and signs of RA for several decades (63). Possible mechanisms of actions of glucocorticoids in RA include inhibition of macrophage function, antigen presentation and class II molecule expression (52), and reduction in adhesion molecule expression (64). In addition to reducing acute inflammation, glucocorticoids have been shown to retard erosion formation in studies of early RA, although the evidence is conflicting. Low dose prednisolone has been shown to retard radiographic progression when employed as monotherapy in early RA (65). Similar results were found when continuous low dose prednisolone therapy (7.5 mg/day) versus placebo, was included in addition to conventional DMARD treatment (66).

After a third year of follow-up during which all steroid therapy was discontinued, a rate of progression similar to that of placebo was resumed (67). No evidence of a flare in disease activity following withdrawal of prednisolone therapy was seen, and patients who had previously received prednisolone continued to maintain a lower Larsen score.
These results suggest that low dose prednisolone has disease-modifying effects for the duration of treatment, but that joint destruction resumes at its previous rate after withdrawal. Another early RA study initially designed to compare the effects of two different NSAIDs noted that patients in both groups who were receiving concomitant corticosteroid therapy had slower rates of radiographic progression. As corticosteroid therapy was not randomized in this study, it is difficult to draw any firm conclusions (68).

Combination therapy
Because the available DMARDs have differing mechanisms of action and limited efficacy as monotherapeutic agents, combination strategies have been advocated in both established and early RA. Although the effects of combination therapy on the pathophysiology of RA is largely unstudied, combination therapy has been shown to be superior to monotherapy at reducing serum TNF alpha levels (69). Various approaches have been investigated, including 'step-up' regimes where DMARDs are sequentially added, and 'step-down' regimes where shorter potent combinations of immunosuppression are followed by strategic withdrawal, according to predefined protocols. A number of different combinations of DMARDs have been tested both with and without concomitant corticosteroids (see Table I).
Marchesoni treated an early RA cohort with MTX and CYA for 6 months followed by step-down treatment with either DMARD alone. Radiographic deterioration continued over the two-year period of follow-up, but at a reduced rate during the second year of follow-up (70). As joint destruction occurred at a faster rate during combina-

tion therapy, it is unlikely that this treatment had any significant additive effect over monotherapy. The slowing of radiographic progression could have been part of the natural history of early disease progression, as observed by van der Heijde (6).
Results from other 'step-down' studies in early RA are variable. Proudman compared the effect of combined MTX, CYA and aggressive intra-articular corticosteroid therapy to SSZ monotherapy and failed to show any statistical improvement in the number of clinically active joints or the rate of radiographic progression over 48 weeks (71). Haagsma found no significant difference in clinical outcome measures when a combination of MTX and SSZ was compared to the effect of the individual compounds, although radiographic data were not examined (72).
A number of other studies in early RA have demonstrated the superior efficacy of combination therapy over monotherapy in retarding radiographic progression, but none demonstrate a halting of joint damage (19, 73, 74). The COBRA trial employed an initial, intensive six-month step-down bridge therapy with sulphasalasine, MTX and a high dose oral prednisolone (60 mg day initially, tapered down to stop at week 28) (19). Patients in the combined arm of the trial had rapid relief of clinical symptoms and sustained, significant reduction in the rates of new joint erosion formation over the next 5 years (75). This could not be explained by differences in DMARD therapy or steroid use after the first year, as the treatment regimes in both groups were roughly comparable. The authors suggest that the combined effects of high dose corticosteroid and DMARDs for 6 months in early disease may have the ability to 'reset'the rate of disease progression even after intensive therapy is reduced.
Surprisingly, none of the combination studies showed any evidence of increased withdrawal from combination therapy as a result of adverse side effects. In general combination therapy was tolerated as well as monotherapy although the incidence of nausea in the combination arm was increased in one

Table I. Randomized control trials of DMARDs in early rheumatoid arthritis.

(Ref.) First author and year	Disease duration	DMARD(s) studied	Effect on radiographic progression	Other outcomes
(48) Hannonen 1993	< 1 year	SSZ 2 gm/day vs. placebo	Non-significant reduction in erosions in SSZ group at 48 weeks	SSZ superior at reducing disease activity measures
(47) Choy 2002	< 1 year	SSZ 2 gm/day vs. diclofenac sodium	SSZ superior to diclofenac at 12 months	
(55) Genovese 2002	< 3 years	MTX (mean dose 19 mg/week) vs. etanercept 10 mg or 25 mg twice weekly	Etanercept 25 mg superior to MTX at 24 months	
(65) Van Everdingen 2002	< 1 year	Prednisolone 5 mg/day vs. placebo	Prednisolone superior to placebo at 12 months	
(66) Hickling 1998	< 2 years	Prednisolone 7.5 mg/day vs. placebo	Prednisolone superior to placebo at 12 months	Radiographic progression resumes after prednisolone discontinued
(61) Zeidler 1998	< 3 years	CYA 3-5 mg/kg/day vs. GSTM 50 mg/wk	No significant difference between groups at 18 months	Patients on corticosteroids developed fewer erosions
(62) Drosos 2000	< 3 years	CYA 3 mg/kg/day vs. MTX 0.15 mg/kg/wk	No significant difference between groups at 42 months	
(60) Pasero 1996	< 4 years	CYA 3 mg/kg/day vs. any other DMARD	CYA superior to other DMARDS at 12 months	
(75) Landewé 2002 (COBRA)	< 2 years	(MTX 7.5 mg/wk + SSZ 2 gm/day + prednisolone 60 mg/day reducing to 7.5 mg/day (maintenance) vs. SSZ 2 gm/day	Combination superior to SSZ monotherapy at 12 months	Sustained reduction in rate of progression continues even after cessation of combination therapy
(74) Gerards 2003	< 3 years	(CYA 2.5-5 mg/day + MTX 7.5 mg/wk) vs. (CYA 2.5-5 mg/day + placebo)	Combination superior to monotherapy at 48 weeks	
(23) Möttönen 2002	< 2 years	(SSZ 1 gm/day + MTX 7.5 mg/wk + HQ 300 mg/day + prednisolone 5 mg/day) vs.(SSZ 2 gm/day ± prednisolone 5 mg/day)	Combination superior to monotherapy at 2 years	Delay in therapy > 4 months after symptom onset in monotherapy group predicted a poorer outcome

SSZ: salazopyrine; MTX: methotrexate; GSTM: gold sodium thiomalate; CYA: cyclosporin A; HQ: hydroxychloroquine.

study (72). Monotherapy treated patients were more likely to discontinue because of lack of efficacy than the combination treated patients (19, 71).

Structural damage continues despite DMARD therapy in early RA

Randomized clinical trials demonstrate, either through direct comparison with placebo or by inference through comparison with another drug, that DMARD therapy has the potential to retard the progression of erosions in early arthritis. Furthermore, joint damage can be reduced still further by intensive induction therapy employing a 'step-down' approach. The exact con- tribution of prednisolone remains unclear. In low doses it appears to have disease-modifying properties for the duration of therapy, whereas at high doses and in conjunction with other DMARDs it may down-regulate the aggressive nature of disease even after corticosteroid therapy has been withdrawn.

No study has demonstrated that traditional DMARD therapy, whether used alone or in combination, can totally arrest progressive joint damage in all early RA patients. The natural history of new erosion formation in early RA, and the lack of an adequate control group in some studies (36, 70), have made it difficult to attribute any change in the rate of joint damage to a therapeutic effect.

Historically, standard rheumatology practice included a period of patient observation in the DMARD-naïve state, followed by case-specific tailoring of disease modifying therapy. With the advent of early aggressive treatment, clinicians no longer accept the benefit of hindsight in identifying patients with more severe disease. Prognostic factors available at the time of diagnosis that have been associated with progressive joint damage in early RA include disease activity scores, IgM rheumatoid factor, elevated C-re-

active protein, HLA-DR4/shared epitope, and the presence and severity of baseline radiographic damage (76).

In clinical practice, however, predictive measures obtained from pooled patient data or AUC analyses are of limited value. The relationship between the levels of acute phase markers and radiographic progression, for example, has been shown to be highly individualized and requires a 6-month period of observation before a case-specific predictive value can be ascribed (77). In a study of 179 patients with early RA, standard radiographs taken within 6 months of disease onset did not correlate with subsequent erosive progression during follow-up, although radiographs taken after 18 months did predict further joint damage (78).

Progressive joint destruction despite improvement in the clinical parameters of disease activity following treatment is well described both in established RA (79, 80) and in many studies of early disease reviewed here. Conventional DMARD therapy does not arrest joint damage in early RA, although it can reduce the rate of progression. As patient responses to currently available treatments vary, reassessment of clinical and laboratory measures early in the treated phase of the disease, may be of greater predictive value than measures obtained during the pre-treatment 'unmodified' stage of disease.

If a truly case-specific approach to DMARD therapy in early RA is to be justified, more reliable prognostic indicators are required at the time of first presentation. An approach using combination therapy for all newly diagnosed patients, followed by early reassessment of clinical responsiveness, may yet offer the best long-term outcome. Combination therapy is superior to monotherapy, but the efficacy in comparison to targeted biologic therapies in early RA remains unknown. Assuming that a proportion of patients with RA will enter a phase of prolonged disease remission following the very early introduction of targeted therapy, and that targeted therapy will not be continued indefinitely in most, it will be intriguing to determine the possible role of conventional DMARDs in maintaining

clinical remission, as well as in preventing further joint damage, after judicious withdrawal of the biologic agent.

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