

The therapeutic approach of early intervention for rheumatoid arthritis: what is the evidence?*

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Abstract

Objective. The concepts of early intervention and early arthritis clinics for the management of rheumatoid arthritis (RA) were introduced almost a decade ago. The evidence for these is diverse and the best therapeutic approach remains vehemently debated. This review addresses these issues.

Methods. The MEDLINE database was searched to identify relevant papers satisfying inclusion criteria for disease duration and no previous use of disease-modifying anti-rheumatic drugs (DMARDs). Where possible, evidence was obtained from randomized controlled trials. We selected the most relevant topics to best justify early therapeutic intervention in RA.

Results. The benefit of DMARDs over placebo and delayed therapy is unquestionable from the studies presented, with reduction in bone damage and preservation of function. Through prevention of disability, early treatment should be the most cost-effective approach. The evidence presented supports the use of DMARDs when the diagnosis of RA is first made. Delay in treatment may result in irreversible damage. There is insufficient evidence to recommend combination therapy for all patients at disease onset. Further research into newer therapies is required before their routine first-line use is recommended.

Conclusions. Early therapeutic intervention in RA reduces long-term disability and joint damage. Optimal management appears to be the early identification of non-responders and targeted combination therapy. Biological therapies have the potential to revolutionize the treatment of early RA.

KEY WORDS: Early rheumatoid arthritis, Combination therapy, Corticosteroids, DMARDs, Anti-TNF- α agents.

It is believed that rheumatoid arthritis (RA) is the most common, potentially treatable cause of disability in the Western world [1]. Early disease represents a potential window of opportunity for therapeutic intervention and the principle of early treatment in RA is now widely accepted in routine clinical practice. But what is the evidence for this? The following review looks at the evidence supporting early treatment and the consequences of delay in producing adequate disease suppression.

What is true early disease?

Patients who satisfy the 1987 American College of Rheumatology (ACR) classification criteria for RA [2]

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and who have a very short disease duration may show a qualitative change in their outcome if they are treated at presentation [3] (see later). However, the very early diagnosis of RA can be difficult, as the disease may be indistinguishable from conditions such as postviral arthropathies, early spondyloarthritis and other self-limiting arthritides that may satisfy the 1987 ACR criteria [4]. The critical issue is to predict persistence, and symptom duration greater than 12 [3] or 14 [5] weeks appears to be the best single predictor of those that have been examined. Therefore, a symptom duration of at least 12 weeks may be more appropriate for ACR classification criteria than the currently recommended 6 weeks if the specificity of these criteria is to be improved.

For the purposes of clinical trials, early disease has been taken as a symptom duration of less than 2 yr (more conventionally, a time point of 5 yr) with no previous therapy with disease-modifying anti-rheumatic drugs (DMARDs) or corticosteroids. A case could be made for shorter disease duration, but in practice this would exclude many studies. This duration has been chosen because, at the end of this period, the majority of patients have incurred significant damage when treated

conventionally. Patients who have received DMARD therapy previously are excluded because such treatment may affect the immunological and pharmacological parameters.

Why is early disease so important?

Damage occurs early

There is considerable evidence that radiographic damage, loss of function [6] and loss of bone mineral density, both axial [7] and peripheral [8, 9], occur very early in the disease process. In early RA (less than 6 months of symptoms), up to 40% of patients have erosive disease at presentation [10]. Even with the early arthritis clinic approach, 25% of patients have radiographic erosions at presentation [11]. New imaging techniques have demonstrated that bone changes occur even earlier than was first thought. Bone oedema, the MRI precursor to erosions, can be seen in patients after only 4 weeks of symptoms [12]. Ultrasound (US) can also demonstrate erosions before they are evident on plain radiography [13].

Subclinical disease

Both US and MRI [14] are able to demonstrate the presence of synovitis in early RA patients in joints that are normal on clinical examination. In an early oligoarthritis cohort, US has also shown subclinical synovitis to be widespread, with up to 50% of patients actually having polyarticular disease, and the presence of subclinical disease correlates with persistence and a less favourable outcome [15]. Macro- and microscopic data from arthroscopy in clinically normal knees of RA patients support these findings [16], as does blind synovial biopsy [17]. These results question the sensitivity of clinical examination for the detection of low-grade synovitis and therefore true early disease. Synovitis is likely to be much more widespread at presentation than is indicated by conventional clinical examination. Findings using imaging may have consequences for the future development of diagnostic criteria for RA.

Remission is rare

Remission implies a state of low disease activity that, if sustained, is neither damaging nor disabling, and it remains the ideal outcome of therapy in RA. However, the definition of remission is complex and often confusing, and may not be accurate as it is most often dependent on clinical examination, which is unreliable according to the results of imaging studies [14]. Definitions vary from 'no active disease on examination' to the rigorous ACR remission criteria. The interpretation is further confused by the use of drugs—DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs) or even simple analgesics. The number of patients whose disease remits spontaneously without therapy is unknown. As evidence accumulates that non-treatment is harmful, it becomes ethically difficult to study untreated patients

with active RA. Whichever definition is applied, the prevalence of remission remains low and is inherently different in very early disease compared with established RA [3].

Using the definition of no arthritis on examination and no DMARD for 3 months, Harrison *et al.* [18] found that only 5% of patients entered sustained remission among 258 patients with early RA in primary care, which may or may not have been DMARD-induced, during 2 yr of follow-up. Similarly, in a study of 183 patients in secondary care, only 7% of patients entered sustained remission over 5 yr with routine care, where remission was defined as four of the five ACR criteria satisfied, fatigue being excluded [19]. From their results, Harrison *et al.* also concluded that it was not possible to produce a predictive model for remission that would be useful in clinical decision-making. Remission in patients with RA is rare and is unpredictable at the outset of disease. Furthermore, it has also been hypothesized that the good prognosis group that do well, including those who enter spontaneous remission, represent a disease that is a separate entity and is distinguishable from RA by the primary disease site [20]. Therefore, spontaneous remission without treatment in patients with established persistent disease may be so rare as to be virtually non-existent in true RA. Conversely, true RA may always be persistent.

What evidence is there to support early treatment?

The C-reactive protein (CRP) is used as a surrogate marker of inflammation, and the progression of radiographic damage [21–23], loss of function and bone mineral density correlate well with persistent elevation of CRP. Suppression of CRP results in at least stabilization of these parameters [6, 7, 24, 25]. This reinforces the paradigm of inflammation \times time = damage.

According to longitudinal MRI studies in early RA, synovitis appears to precede bone oedema and subsequent erosions. Erosions do not occur in the absence of synovitis [12]. More importantly, it has been demonstrated that if synovitis is adequately suppressed by a single dose of an intra-articular (i.a.) corticosteroid, MRI shows reduced bone oedema and the absence of new bony lesions over 3 months [26]. It therefore appears that adequate suppression of synovitis prevents the progression of bone damage. The presence of subclinical synovitis may explain previous papers describing the progression of radiographic damage despite what appears to be adequate suppression of clinical disease [27]. This can also be explained by the accepted lag between the time of true damage and the appearance of radiographically detectable erosions. Reversibility of functional loss may also be lost with time. Patients treated early (within 2 yr) showed a significant improvement in function, assessed with the Health Assessment Questionnaire, when compared with later disease groups in a study of 440 patients [28] (see later).

For patients who present rapidly to rheumatologists, the outcome is better than for those presenting late. Anderson *et al.* [29] demonstrated, in an analysis of 1435 patients from 11 studies, that disease duration was of foremost importance in predicting the response to DMARD therapy [29]. Of patients presenting with a disease duration less than 1 yr, 53% showed a response, whereas later groups (disease duration 1–2, 2–5, 5–10 and >10 yr) showed a diminishing response as disease duration at presentation increased. In a study of 448 RA patients, those who presented with disease of less than 5 yr duration maintained a lower mortality ratio over 21.5 yr of follow-up compared with late presenters [30]. Other studies looking at any DMARD use *vs* NSAID or no therapy, strongly favour DMARD use with respect to long-term disability index [31] and deformed/damaged joint and radiographic score [32].

DMARD treatment is not necessarily more toxic

In practical terms, 90% of patients diagnosed with RA are treated with DMARDs within 3 yr of diagnosis [1]; therefore, the majority of patients are eventually subjected to potential DMARD toxicity. NSAIDs have been compared with DMARDs by calculating a toxicity index derived from symptoms, abnormal laboratory measurements and hospitalizations related to treatment [33, 34]. The comparisons show that some commonly used NSAIDs have toxicity indices considerably greater than those of intramuscular (i.m.) gold and hydroxychloroquine (HCQ) and comparable to those of methotrexate (MTX) and azathioprine. In context, the toxicity of DMARDs is no worse than that of long-term NSAID use. From this evidence, delaying the use of DMARDs on toxicity grounds is unfounded.

Published studies in early RA

A number of placebo-controlled, delayed therapy and comparison studies further support the case for early treatment in RA. We have attempted to identify the best available evidence for each DMARD in early disease. The MEDLINE (1966 to present) database was searched using the terms 'rheumatoid arthritis', 'early rheumatoid arthritis', 'DMARD therapy' and 'early treatment'. Studies were excluded if disease duration was greater than 2 yr and patients had received previous DMARD treatment (except for studies involving new therapies). Where possible, category 1b evidence was sought using methods defined by Shekelle *et al.* [35]. Further papers were identified by cross-referencing from papers identified from the original searches.

There are no meta-analyses of therapy in early RA.

Placebo-controlled studies

There are a number of pieces of evidence to support early DMARD therapy which show that long-term

placebo-controlled studies produce unacceptable irreversible damage in the placebo-treated arm [36] and may therefore be unethical. It has been suggested that the use of placebo in RA clinical trials is ethical as long as standards of care are maintained [37]. However, the authors believe that the evidence that prolonged exposure to unsuppressed inflammation is damaging is unequivocal, and to expose a patient to this when effective interventions are available remains unethical. This should be considered seriously when future RA studies are being designed.

In published placebo-controlled studies (Table 1), sulphasalazine (SSA) has been shown to improve the clinical outcome over 12 months and reduce radiological damage [10, 38]. HCQ also improves the clinical outcome but has not been shown to reduce radiological damage when compared with placebo. Part of the problem is that a group of patients with mild disease and little radiological progression was studied [39].

Delayed treatment

Other studies have compared early *vs* delayed use of DMARDs. Studies using oral gold have shown both clinical benefit and sustained radiological improvement up to 5 yr in favour of early intervention [40]. When the use of i.m. gold was compared at different stages of disease, early use produced the most improvement in functional status [28] (Table 2).

Van der Heide *et al.* [41] compared DMARD treatment with NSAID treatment alone and the delayed introduction of DMARD treatment. All clinically relevant variables were improved at 1 yr. However, no significant difference was detected in radiographic progression. This may have been due to a significantly greater number of non-DMARD-treated patients discontinuing therapy, greater use of i.a. corticosteroid treatment in the non-DMARD group or a type 2 statistical error.

Comparator studies

An increasing number of studies have compared one DMARD with another in an attempt to demonstrate greater effectiveness. SSA was shown to reduce radiographic progression significantly in a double-blind trial when compared with HCQ [42] over 48 weeks, but the study failed to demonstrate a significant difference in clinical outcome measures [43]. A comparison of cyclosporin (CyA) with chloroquine shows a trend to improved efficacy and similar tolerability with chloroquine [44], and when CyA was compared with i.m. gold, CyA demonstrated better tolerability and comparable retardation of radiographic progression [45]. When SSA was compared with i.m. gold, a trend to a greater effect on radiographic progression over 12 months was demonstrated in favour of SSA. However, the analysis was not done on an intention-to-treat basis and survival of the drugs at 12 months was 60 and 52% respectively [46] (Table 3). Van Jaarsveld *et al.* [47] compared different treatment strategies: a mild *vs* a potent DMARD with a long lag-time compared with a potent DMARD with

TABLE 1. Placebo-controlled trials in early RA

Study	Patients	Study design	Study duration (months)	ACR RA	Mean disease duration (months)	Drug	Main outcome
Australian Multicentre Study Group, 1992 [38]	105, non-erosive, DMARD-naive	Rpct	6	ARA	<12 only	SSA	Reduction in STJC, ESR/CRP, RF, RI and EMS ($P < 0.05$)
Borg <i>et al.</i> , 1988 [63]	138, DMARD-naive	Dbrpct	24	ARA	11	Oral gold	Reduction in STJC, XR, HAQ, functional score ($P < 0.05$)
Davis <i>et al.</i> , 1991 [39]	104 ^a , DMARD-naive	Dbrpct	12	ARA	14	HCQ	Reduction in RI, synovitis score, ESR, EMS and GS ($P < 0.05$)
Hannonen <i>et al.</i> , 1993 [10]	80 (40% erosive), DMARD-naive	Dbrpct	12	Yes	5	SSA	Reduction in STJC, RI, PGA, pain and GS ($P < 0.05$)
HERA Study Group, 1995 [64]	120, DMARD-naive	Dbrpct	8	Yes	9 (all <24)	HCQ	Reduction in STJC, HAQ, EMS, pain and GS ($P < 0.05$)

^aMild RA classified as disease affecting hands and feet only, CRP <20 or ESR <30.

ACR RA, ACR list of criteria for RA, 1987; ARA, pre-1987 classification criteria for definite/classical RA as given by ARA; Dbrpct, double-blind, randomized, placebo-controlled trial; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate; GS, grip strength; HAQ, Health Assessment Questionnaire; PGA, patient's global assessment; RF, rheumatoid factor; RI, Ritchie index; Rpct, randomized, placebo-controlled trial; STJC, swollen, tender joint count; XR, radiographic progression.

TABLE 2. Delayed treatment trials in early RA

Study	No. patients	Study design	Study duration (months)	ACR RA	Mean disease duration (months)	Drug	Main outcome
Buckland-Wright <i>et al.</i> , 1993 [65]	23	Pct	18	Not stated	8	I.m. gold vs 6 months delay	Reduced XR at 6/12 weeks ($P < 0.05$)
Egsmose <i>et al.</i> , 1995 [40]	75	Dbrpct	60	ARA	11	Oral gold vs 8 months Rx delay	Reduction in STJC, HAQ, XR ($P < 0.05$)
Munro <i>et al.</i> , 1998 [28]	440	Pt	60	ARA	0–24, 24–60, 60+	I.m. gold	Reduction in HAQ, 0–24 months ($P < 0.05$)
Van der Heide <i>et al.</i> , 1996 [41]	238	Prt	12	Yes	<12	DMARD	Reduction in STJC, HAQ, ESR and pain ($P < 0.05$)

ACR RA, ACR list of criteria for RA, 1987; ARA, pre-1987 classification criteria for definite/classical RA as given by ARA; Dbrpct, double-blind, randomized, placebo-controlled trial; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; Pt, placebo trial; Prt, placebo randomized trial; Rpct, randomized, placebo-controlled trial; Rx, treatment; STJC, swollen, tender, joint count; XR, radiographic progression.

a short lag-time. The potent DMARDs were significantly superior at 12 months according to joint score, remission rates and radiographic progression, but only radiographic progression was still significantly superior at 24 months. MTX followed by SSA appeared to offer the best outcome, and their tolerability better than that of the other strategies.

Further evidence for targeted aggressive treatment is gained from Stenger *et al.* [24]. By identifying a high-risk group of early RA patients and treating this group with an aggressive strategy, it was possible to reduce the rate of radiographic progression of this group to the rate seen in low-risk patients.

Combination therapy

An increasing trend has been towards the use of combination therapy in early disease in the hope of complete suppression of synovitis and reductions in radiographic damage, disability and deformity. The results on the whole are consistent [48] (Table 4).

Dougados *et al.* [49] and Haagsma *et al.* [50] report studies looking at the MTX + SSA combination vs the single components alone. The results showed good tolerability but failed to show a significant difference in clinical and radiographic variables between the groups, despite a trend to favour the combination arm. In both studies MTX showed similar efficacy to SSA when used as monotherapy.

Further evidence to support the inclusion of corticosteroid in a chosen combination comes from Mottenen *et al.* [51]. Greater remission rates were achieved at 12 months and a significant reduction in radiographic damage was seen at 24 months in the combination group. However, the ACR 20 responses were not significantly different between the two groups.

The ultimate aim remains remission. The COBRA study group reported a step-down therapeutic approach of SSA + MTX + prednisolone vs SSA alone [52]. Although significant radiographic benefits were seen at 80 weeks, disease activity was comparable in the two groups after the steroid therapy was stopped. There was

TABLE 3. DMARD comparison studies in early RA

Study	No. patients	Study design	Study duration (months)	ACR RA	Mean disease duration (months)	Drug	Main outcome
Menninger <i>et al.</i> , 1998 [66]	174, erosive	Dbprt	36	ARA	23.9	MTX vs i.m. gold	Reduction in STJC, pain, function, ESR/CRP and EMS in both groups ($P < 0.05$). Better tolerability with MTX
Nuver-Zwart <i>et al.</i> , 1989 [43] ^a	60, DMARD-naive	Dbprt	11	ARA	12.8	SSA vs HCQ	Reduction in STJC, RI, ESR/CRP, pain, RF, EMS and GS with SSA. Only pain, STJC, RI with HCQ ($P < 0.05$). No significant intergroup differences
Peltomaa <i>et al.</i> , 1995 [46]	128 (70 i.m. gold, 58 SSA)	Pt	12	Yes	6.8	SSA vs i.m. gold	Reduction in RI, ESR/CRP, in both groups ($P < 0.05$) pain (VAS), EMS and GS.
Rau <i>et al.</i> , 1998 [67]	174, erosive + active disease	Dbprt	12	Yes	11.35	I.m. gold vs i.m. MTX	No significant intergroup differences No significant difference in XR. Better tolerability of MTX
Stenger <i>et al.</i> , 1998 [24]	228	Pt	24	Yes	6.9	Aggressive vs step-up Rx	Reduction in CRP AUC and XR with aggressive Rx ($P < 0.05$). Similar tolerability
Van der Heijde <i>et al.</i> , 1989 [42] ^a	60	Dbprt	11	ARA	12.8	SSA vs HCQ	Reduction in XR at 48 weeks ($P < 0.05$)
Van Jaarsveld <i>et al.</i> , 2000 [47]	313	Prt	24	Yes	<12	Strategy I vs II vs III ^b	Reduction in Thompson joint score, XR + higher remission rates at 12 + 24 months XR in II + III ($P < 0.05$)
Zeidler <i>et al.</i> , 1998 [45]	375, erosive + active disease	Prt	18	ACR	11.8	CyA vs i.m. gold	No significant difference in XR, greater reduction in ESR with i.m. gold ($P < 0.05$)

^aSeparate papers from one study.

^bStrategy I, mild DMARD/long lag-time (HCQ replaced by oral gold if needed); strategy II, potent DMARD with long lag-time (i.m. gold replaced by D-penicillamine); strategy III, potent DMARD with short lag-time (MTX replaced by SSA).

ACR RA, ACR list of criteria for RA, 1987; ARA, pre-1987 classification criteria for definite/classical RA as given by ARA; CyA, cyclosporin A; CRP AUC, CRP area under the curve; Dprt, double-blind, randomized, placebo-controlled trial; EMS, early morning stiffness; GS, grip strength; Prt, placebo randomized trial; Pt, prospective trial; RI, Ritchie index; Rx, treatment; STJC, swollen, tender joint count; VAS, visual analogue scale; XR, radiographic progression.

TABLE 4. Combination treatment studies in early RA

Study	No. patients	Study design	Study duration (months)	ACR RA	Mean disease duration (months)	Drug	Main outcome
Boers <i>et al.</i> , 1997 [52]	155, 21% erosive, DMARD-naive	Prt	13	Yes	4	MTX + SSA + pred ^a vs SSA	STJC, HAQ, pain VAS, ESR and PGA, PhGA improved with comb. Rx at 28 weeks ($P < 0.05$), but not significant at 56 weeks. Reduction in XR at 28, 56 + 80 weeks ($P < 0.05$)
Dougados <i>et al.</i> , 1999 [49]	205, DMARD-naive	Prt	12	Yes	2.9, 13.3 symptoms	SSA vs MTX vs MTX + SSA	Similar efficacy of all groups for STJC, HAQ, EMS, CRP/ESR, XR with more adverse events in the combination group
Haagsma <i>et al.</i> , 1997 [50]	105, DMARD-naive	Prt	12	Yes	2.8	SSA vs MTX vs MTX + SSA	Similar efficacy of all groups for DAS, STJC, HAQ, RI, ESR and pain VAS. No significant difference in tolerability
Mottenen <i>et al.</i> , 1999 [51]	199, DMARD-naive	Prt	24	Yes	8, <24	SSA + MTX + HCQ + pred vs SSA + pred	No significant difference in STJC, HAQ, ESR, PGA, PhGA at 24 months. More patients in remission with combination treatment ($P < 0.05$) and ACR 50 at 12 months ($P < 0.05$)
Proudman <i>et al.</i> , 2001 [54]	82, poor prognosis, DMARD-naive, 62% erosive	Prt	11	Yes	8.3	MTX + CyA + i.a. CCS vs SSA	No significant difference in ACR 20/50, remission rates or XR at 48 weeks. Greater reduction in STJC only in combination treatment group ($P < 0.05$)

^aStep-down regime: MTX 7.5 mg weekly for 28 weeks, reducing course of prednisolone, equivalent to 12 mg daily for 28 weeks with SSA 2 g daily continued.

ACR RA, ACR list of criteria for RA, 1987; CCS, corticosteroid; CyA, cyclosporin A; DAS, disease activity score; EMS, early morning stiffness; HAQ, Health Assessment Questionnaire; PGA, patient's global assessment; PhGA, physician's global assessment; pred, prednisolone; Prt, placebo randomized trial; RI, Ritchie index; Rx, treatment; STJC, swollen, tender joint count; VAS, visual analogue scale; XR, radiographic progression.

also a trend to greater bone density loss in the steroid-treated arm. A cost-effectiveness analysis tended to favour the combination group [53]. In an attempt to achieve this in early RA with a poor prognosis, we have used i.a. injection of all active joints and aggressive therapy with MTX + CyA vs SSA and aspiration plus injection of significant joint effusions [54]. Results have again been disappointing, although there was a trend to a lower drop-out rate due to lack of efficacy in the combination group.

More aggressive treatment regimens therefore appear to reduce damage for the duration of suppression of inflammation, but there is no evidence for a qualitative change in the disease mechanisms. Using the oncological analogy, it is clear that initial aggressive regimens result in initial debulking of disease with improvement in damage and alteration of the early outcome, yet the disease process continues. A quantitative improvement can therefore be attained, but the qualitative change in outcome that was hoped for has not yet been demonstrated. Disease activity returns when treatment is reduced.

The role of corticosteroids

The role of corticosteroids remains controversial. However, they are very effective in suppressing both cyclooxygenase-II and cytokines. They also have a number of uses in the management of RA, including the induction of remission, maintenance therapy, and bridge and rescue therapy. Corticosteroids have several modes of delivery. The aim is to use the minimum dose necessary for effective outcome. When a low dose of prednisolone (7.5 mg) was added to conventional DMARD therapy over 2 yr, a significant reduction in bone damage was obtained [55]. When therapy was stopped blindly and the cohort reanalysed at 3 yr, the rate of radiographic progression in the steroid group was similar to that of the placebo arm [56]. As already mentioned, i.a. corticosteroids can suppress synovitis in MCP joints effectively, as demonstrated by MRI [26]. The early benefits seen in the combination studies that use corticosteroids [51, 52, 55] can be explained by the effect of corticosteroids, which is then lost after treatment withdrawal, although benefit is seen for the period of time during which the disease is suppressed. Data published recently suggest that, in very early mild inflammatory arthritis with less than 12 weeks of symptoms, a single corticosteroid dose, either i.m. or i.a., may alter disease persistence and result in remission rates of up to 50% [3]. Corticosteroids are undoubtedly effective, but are limited in use by toxicity, the severity of which is difficult to quantify.

New therapies (Table 5)

For the first time in many years, the rheumatologist has new therapeutic options for the management of RA. Leflunomide, an inhibitor of pyrimidine synthesis, is now licensed and immunotherapies have finally reached the clinic. In established disease, these new therapies

TABLE 5. Studies of new therapies in RA

Study	No. patients	Study design	Study duration (months)	ACR RA	Mean disease duration (months)	Drug	Main outcome
Smolen <i>et al.</i> , 2000 [57]	358	Dbrpct	6	Yes	84 (42% <24)	SSA vs lef vs placebo	Reduction in STJC, PhGA, CRP, XR ($P < 0.05$) for SSA + lef. Reduction in HAQ lef > SSA ($P < 0.05$)
Strand <i>et al.</i> , 1999 [58]	482	Dbrpct	12	Yes	80 (38% <24)	MTX vs lef vs placebo	Reduction in STJC, PGA/PhGA, CRP + XR ($P < 0.05$) Reduction in HAQ lef > MTX ($P < 0.05$)
Bathon <i>et al.</i> , 2000 [59]	632	Dbrpct	12	Yes	12	MTX vs Et 10 mg vs Et 20 mg	Reduction in Sharp erosion score ($P < 0.05$) at 12 months
Emery <i>et al.</i> , 2000 [61]	82	Dbrpct	12	Yes	<36	MTX ± infliximab ^a	All infliximab arms: reduction in XR ($P < 0.05$) vs placebo

^aFive arms: MTX + placebo; MTX + infliximab 3 mg/kg 8 weekly; MTX + infliximab 3 mg/kg 4 weekly; MTX + infliximab 10 mg/kg 8 weekly; MTX + infliximab 10 mg/kg 4 weekly.

^bNot significant for in MTX + infliximab 3 mg/kg 8 weekly.

AUC, area under curve; Dbrpct, double-blind, randomized, placebo-controlled trial; Et, etanercept; HAQ, Health Assessment Questionnaire; lef, leflunomide; PGA, patient's global assessment; PhGA, physician's global assessment; Pct, placebo randomized controlled trial; STJC, swollen, tender joint count; XR, radiographic progression.

have proven to be as effective as or more effective than existing medications.

Leflunomide has demonstrated efficacy and tolerability similar to SSA in a cohort of 358 patients (42% with <2 yr disease duration, 47% DMARD-naive), with a more rapid rate of onset and significantly greater reduction in functional disability ($P < 0.05$) over 24 weeks [57]. When compared with MTX over 52 weeks in 482 patients (38% with <2 yr disease duration, 43% DMARD-naive), similar efficacy and a significant functional improvement in favour of the use of leflunomide use was demonstrated [58].

The tumour necrosis factor blocking agents are now available. The majority of studies to date assess their safety and efficacy in established RA. Studies in early disease are now emerging. In a study of 632 patients with active early RA (<3 yr), etanercept showed a significant improvement in clinical outcome when this was measured as the area under the curve for ACR improvement, but failed to reach significance when the more accepted and conventional ACR improvement criteria were used in a comparison with MTX over 12 months [59]. There was a significant reduction in erosion score for the higher dose of etanercept (25 mg) at 6 and 12 months, but there was no significant difference in total radiographic score using the modified Sharp method at 12 months. The greatest benefit was seen in the first 6 months, when the rapid action of etanercept (25 mg) produced significant improvement in clinical and radiographic measures. In a subanalysis of early patients (<3 yr) from the ATTRACT study [60], in which patients resistant to MTX received either MTX + placebo or MTX + infliximab 3 mg or 10 mg/kg every 4 or 8 weeks, significant radiographic improvement was seen in all infliximab-treated patients [61]. Radiographic progression was effectively halted in the infliximab-treated patient group. Such inhibition of bone damage has not been demonstrated with existing DMARDs. There was a trend towards improved clinical and functional outcome but this was not significant because of small numbers in each group.

At this stage there is insufficient evidence to assess fully the impact of these new agents in the management of early RA. However, immunotherapies may have the potential to revolutionize early treatment. Further evidence to establish this is required.

Discussion

The benefit of early treatment in RA is clearly supported by published data. Properly conducted studies, with the majority of currently used DMARDs, demonstrate both clinical improvement and retardation of radiographic damage, although evidence suggests X-ray changes are insensitive and lag considerably behind inflammatory activity [12]. Studies using newer techniques of joint assessment, such as MRI and US, have shown greater sensitivity and a close temporal correlation with inflammatory activity and damage progression.

Whereas it is straightforward to demonstrate the benefits of early intervention and suppression of inflammation, how best to achieve this is more difficult to assess. There are several inherent difficulties. Corticosteroids have a profound and dramatic early effect when used in therapeutic regimes, yet toxicity generally occurs late. RA itself is heterogeneous and so, unfortunately, is the response of the patient to therapy. What conclusions can be made?

Multiple treatment strategies have been tried: step-up, step-down, bridge, combination and monotherapy in addition to several variants. No strategy has been proved to be consistently better than another for all patients. A significant factor is the high proportion of good responders to monotherapy alone who are not further improved by complex therapeutic regimes and for whom the additional cost of extra therapy cannot be justified [54]. The same effect means that, at present, there is insufficient evidence to recommend the routine first-line use of biological agents. The therapeutic regimen currently being assessed by our unit involves the routine use of first-line monotherapy. Poor responders are identified early in order to limit the development of irreversible damage. Such patients are targeted with escalating combination therapy, continued poor responders receiving biological agents. The priority for treatment should be rapid and sustained suppression of inflammation.

It must be remembered that most data presented are from randomized trials in which the use of adjunct corticosteroid—i.a., i.m. or oral—is restricted, and this does not reflect true general rheumatology practice. Studies of the effectiveness of monotherapy and combination therapy with judicious use of adjunct corticosteroids compared with the new biological agents are required. The availability of these agents has had a major impact on the management of established RA, with marked improvement in quality of life and conventional measures of disease activity. It is likely that health economic issues will dominate in the determination of future optimal therapeutic regimes for early RA [62].

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