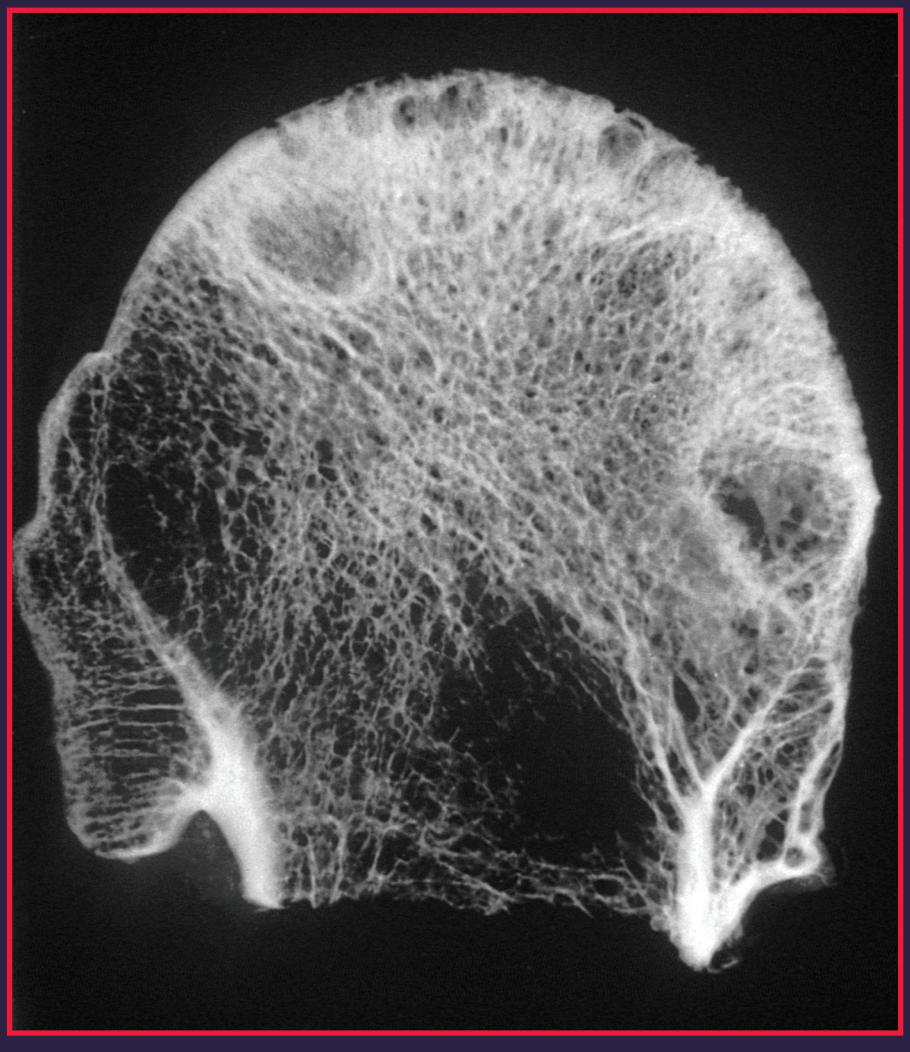
Therapeutic Strategies in RHEUMATOLOGY

M. Doherty



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1

Early arthritis

Jackie Nam, Edith Villeneuve, Paul Emery

INTRODUCTION

Rheumatoid arthritis (RA) is the most common type of inflammatory arthritis, affecting about 1% of the population. It typically presents between the ages of 40 and 50 years, affecting twice as many women as men. Untreated, it results in joint destruction, functional impairment and increased mortality [1]. In recent years, with the availability of effective therapies and the use of early intensive treatment strategies, disease outcomes have improved considerably [2–6]. Studies confirm that all therapies – monotherapy, combination therapies with disease-modifying antirheumatic drugs (DMARDs) and the newer biological agents – work better in early disease than in established RA. Further improvements are achieved with regular monitoring of disease activity and escalation of therapy if optimal disease control is not obtained. The goal of treatment is no longer simply symptom control but early suppression of inflammation and aiming for remission (a low disease activity state that, if sustained, is neither damaging nor disabling) [7].

Although rheumatologists agree that these patients should be seen and treated at the earliest opportunity and optimal disease control should be achieved, a number of issues remain. These include the choice of initial therapy, patient criteria for combination therapy and the use and timing of the newer biological agents [8]. Treating patients with early undifferentiated inflammatory arthritis and preventing the development of RA is another therapeutic strategy under investigation.

THE RATIONALE FOR EARLY THERAPY [9]

Joint damage occurs early in the inflammatory process. There is evidence that radiographic damage [10], loss of bone mineral density [11–13] and loss of function [14] occur early. Radiological outcome studies have shown that 70% of patients with recent-onset RA develop bone erosions within the first 3 years [15]. Furthermore, within 3 months of disease onset, 25% of patients have erosions evident on radiographs [16]. Presence of these early erosions predicts the future development of radiographic lesions. Newer imaging techniques, such as magnetic resonance imaging (MRI) and ultrasound, have confirmed evidence of damage within weeks of onset of symptoms [17, 18]. These lesions also correlate reliably with later radiographic erosions [19].

Further evidence suggests that the disease process exists in the preclinical stage, i.e. before the symptoms of RA. Rheumatoid factor (RF) [20] and anti-cyclic citrullinated peptide (anti-CCP) antibodies [21, 22] have been found in patients with RA years before the onset of symptoms. Raised levels of highly sensitive C-reactive protein (CRP) have also been shown

before onset of clinical disease [23]. Complementary to the serological changes, arthroscopy and imaging with ultrasound and MRI help to detect synovitis in clinically normal joints of patients with early RA [24].

Moreover, there is evidence that very early RA may be an immunopathologically distinct phase compared with later disease [25, 26]. Treatment during this period is believed to optimize outcomes in terms of achieving remission and halting disease progression as measured by disease activity and radiographic progression [27]. This suggests that there may be a 'window of opportunity', a period early in the course of the disease when the disease process can be modified or perhaps even reversed with a complete return to normality.

Several studies have tested this very early window of opportunity and suggest that early treatment has a greater effect on disease progression than treatment later on. There is good evidence that patients with recent-onset polyarthritis who receive earlier DMARD treatment have better outcomes with regards to radiographic progression, function and ability to work than those in whom DMARD treatment is delayed by a few months [16, 28–31]. Disease duration at the time of DMARD initiation was shown to be the main predictor of response to treatment in the meta-analysis of 14 randomized controlled trials by Anderson *et al.* [32]. The best response was seen in those with less than 1 year of symptoms at commencement of therapy. Another meta-analysis of 12 studies examined the effect of early DMARD therapy on the long-term radiographic progression in patients with early RA (less than 2 years at presentation). Six were open-label extensions of randomized controlled trials in which patients initially on placebo later started DMARD therapy, and six were observational cohort studies. The average delay between early and late therapy was 9 months. After a median of 3 years of observation, those patients who received early treatment had 33% less radiological progression than those with delayed treatment [33].

In a case–control parallel-group study, clinical and radiological outcomes were significantly better at 3 years in one group of 20 patients with RA who started DMARD therapy 3 months after disease onset (very early) than in a second group of 20 patients with a median disease duration of 12 months at treatment start (early). Remission was achieved in 50% in the very early group compared with only 15% in the early group. The major differences between the two groups occurred within the first year, and especially during the first 3 months of treatment. An unblinded study of a single dose of glucocorticosteroid in 63 patients with mild early inflammatory arthritis (median duration 20 weeks) also found that the strongest predictor of disease remission at 6 months was a disease duration of less than 12 weeks at time of therapy [34].

These studies highlight the need to identify and treat patients with early RA as soon as possible. Early intervention may induce remission, whereas delayed therapy can result in irreversible damage.

ACHIEVING TIGHT CONTROL

Optimal therapeutic response may be achieved by a combination of early therapy and 'tight control' of disease activity. In practice, tight control for RA means that therapy is increased if disease activity is not suppressed below a predefined level (ideally remission).

In the TICORA ('Tight Control for Rheumatoid Arthritis') study [35], 110 patients with RA of less than 5 years' duration were randomly assigned to an intensive treatment in order to reach a low disease activity state, defined as an original disease activity score (DAS) of less than 2.4, or to regular clinical care. Patients in the tight control group were examined monthly and DMARD therapy was escalated, according to a predefined strategy, if the DAS was above 2.4. Those in the routine care group were seen every 3 months without formal assessment or feedback on disease activity scores, and therapy was adjusted according to the clinical judgement of the rheumatologist. After 18 months of follow-up, the intensive-treatment group had a significantly higher rate of remission (DAS < 1.6, 65%

vs. 16%; $P < 0.001$) and developed less radiographic damage than the control group. In the intensive-treatment group there was also a higher treatment retention rate, a lower rate of discontinuation owing to side-effects and lower costs per patient (based on lower admission costs) than in the routine care group over the 18 months of observation. Of note, however, more intra-articular steroids were used in the intensive-treatment group.

The CAMERA (Computer-Assisted Management of Early Rheumatoid Arthritis) trial [36] also showed intensive treatment and monitoring to be more beneficial than routine care. A total of 299 patients with early RA were randomized to intensive treatment or routine treatment, with oral methotrexate (MTX). If necessary, therapy was changed to subcutaneous MTX and ciclosporin was added to achieve disease control. Patients in the intensive-treatment group were seen more frequently in clinics, and dosages were adjusted based on predefined criteria and tailored to achieve remission using a computer-assisted programme. At 2 years, results showed that more patients in the intensive-management group achieved sustained remission for at least 3 months than in the routine care group (50% vs. 37%; $P < 0.03$). Median area under the curve for all clinical variables (erythrocyte sedimentation rate [ESR], early morning stiffness, visual analogue scale for pain, visual analogue scale for general well-being, number of swollen joints and number of tender joints) were significantly better in the intensive-management group than in the routine care group. Patients in the intensive-management group also used less non-steroidal anti-inflammatory drugs (NSAIDs) than the routine care group.

Further trials have also shown better outcomes where intensive care was based on regular monitoring of disease activity and treatment to target [6, 37].

Regular monitoring of disease activity and adverse events, therefore, should guide decisions on choice and changes in treatment strategies. This includes both traditional DMARDs and biologicals. Monitoring of disease activity should include tender and swollen joint count, patient's and physician's global assessment, ESR and CRP [38]. Arthritis activity should be assessed at 1- to 3-month intervals, aiming for 'remission' or 'low disease activity' as defined by available scores [39–42]. Structural damage should be assessed using radiographs and may be done every 6–12 months during the first few years. Functional assessment (e.g. the Health Assessment Questionnaire [HAQ]) can be used to complement the disease activity and structural damage monitoring.

THERAPEUTIC OPTIONS

GLUCOCORTICOIDS

Several randomized controlled trials and systematic reviews have shown that systemic low-dose glucocorticoids, typically prednisolone ≤10mg/day, were effective in relieving short-term signs and symptoms in patients with established RA [43–45]. Furthermore, despite controversial data [46, 47], several studies have shown that glucocorticoids – either alone or in combination with other DMARD therapy – are effective in slowing radiographic progression in early and established RA [2, 3, 48–52].

In a recent randomized controlled trial, 45 patients with RA and symptom duration of less than 1 year were randomized to receive MTX alone, MTX plus intravenous (i.v.) methylprednisolone (MP) 1 g, or MTX plus infliximab (3 mg/kg) infusions on day 0 and weeks 2, 6, 14, 22, 38 and 46. At week 22 the clinical response rates, according to the American College of Rheumatology 20% improvement criteria (ACR20), the ACR50 and ACR70, were significantly higher in both groups receiving i.v. MP and infliximab than those receiving MTX. At week 52, remission was achieved in 40% of patients in the MTX group and in 70% of the patients in the i.v. MP or infliximab group. HAQ scores improved significantly over time in all groups, with patients receiving i.v. MP showing a significantly greater improvement than patients receiving MTX alone. The combination therapy groups also showed a greater

reduction in MRI-detected synovitis and bone oedema. The progression of MRI-detected erosions, however, was greater in patients treated with MTX plus i.v. MP than in those who received MTX plus infliximab [53].

The use of intra-articular steroids has also been shown to be of benefit. From the 2-year follow-up data of the Ciclosporin–Methotrexate Steroid Treatment in Rheumatoid Arthritis (CIMESTRA) study [54], betamethasone injections resulted in 50% of patients achieving remission (DAS28 < 2.6), and 70% of patients had no progression in the Sharp–van der Heijde scores.

Concerns are often raised about the side-effects of glucocorticoids. Evidence suggests the side-effect profile depends on the dose used and the disease which is being treated. A review of the published literature has shown that in RA, low doses of glucocorticoids may have very few side-effects [55]. Those known to occur in other diseases treated with higher doses of glucocorticoids may not occur when low-dose glucocorticoids are used to treat RA. These include increased cardiovascular risk [56, 57], lipid abnormalities [58] and osteoporosis [59].

Newer glucocorticoids and glucocorticoid analogues that will target inflammatory tissues or specific gene activations are under investigation to obtain the anti-inflammatory effect of the drug with minimal or no increased risk of adverse reactions [60].

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Disease-modifying antirheumatic drugs have an effect on the disease process within weeks to months of commencing treatment. Methotrexate, sulfasalazine (SSZ) and leflunomide [61] are commonly used DMARDs. They have been shown to improve clinical outcomes and to delay radiological progression. Less commonly used agents include azathioprine, gold and ciclosporin. Among the DMARDs, MTX is considered the anchor drug and is generally used first in patients at risk of developing persistent or erosive disease because of its relatively beneficial safety profile [62], clinical and radiological efficacy [63, 64], and its beneficial properties in treatment combinations with biological agents [4, 5, 65]. Leflunomide and SSZ have similar clinical efficacy and are considered the best alternatives.

Despite early treatment, substantial structural damage may still occur in some early patients with RA treated with DMARDs alone [66]. In a cohort of patients with very early RA, with symptom duration of less than 3 months, 64% developed erosive disease by 3 years.

COMBINATION DISEASE-MODIFYING ANTIRHEUMATIC DRUG THERAPY [67]

Another therapeutic strategy in the treatment of RA is the early use of combination therapy with conventional DMARDs. Most of the evidence is based on studies of patients with early or established RA and has been extrapolated to the management of early arthritis.

Several studies have addressed the issue of whether initial combination therapy of early RA confers benefit over more conservative strategies. In the COBRA (Combination Therapy in Early Rheumatoid Arthritis) trial, a combination of MTX (7.5 mg weekly), SSZ (2 g/day) and prednisolone (starting with 60 mg/day and tapering over 6 months) resulted in long-term effects on radiographic progression, compared with SSZ monotherapy in 155 patients with RA of duration under 2 years [2, 68]. These results were consistent with those from the FIN-RACo (Finnish Rheumatoid Arthritis – Combination Therapy) study, in which 197 patients with onset of RA within 2 years were randomly assigned to receive either a four-drug regimen with MTX, SSZ, hydroxychloroquine (HCQ) and prednisolone (maximum doses: 15 mg/week, 2 g/day, 300 mg/week and 10 mg/day, respectively) or a single DMARD [3, 69, 70] for 2 years. After 18 months, a greater proportion of the combination group was less likely to have radiographic progression, and the work disability rate was lower than for patients on monotherapy. In neither study was there an arm with DMARD monotherapy plus steroids. Although, in the latter study, steroid was permitted in the single-treatment

group; this was introduced later, at up to 93 weeks from baseline. The effects achieved in the combination treatment arms may therefore be attributed, at least in part, to the use of steroids rather than the combination of DMARDs alone.

To establish whether a combination of SSZ and MTX may be superior to either drug alone in patients with early RA with suboptimal response to SSZ, the MASCOT (Methotrexate and Sulfasalazine Combination Therapy) study, a randomized controlled study of step-up DMARD treatment, was designed by Capell and colleagues [71]. At 6 months, 191 of 687 (28%) patients had a DAS < 2.4 on SSZ alone. Of the remaining patients, 165 took part in the second phase of the study and were randomized to receive SSZ alone, MTX alone or a combination of the two. The DAS at 18 months was significantly lower in those who received combination treatment than in those who received either SSZ or MTX; monotherapy arms did not differ. Clinical improvement, as measured by the European League Against Rheumatism (EULAR) and ACR scores, favoured combination therapy. In the combination group, SSZ-only and MTX-only groups, the ACR20 responses were 48%, 32% and 33% respectively, the ACR50 responses were 25%, 10% and 7%, respectively, and the ACR70 responses were 13%, 7% and 4%, respectively. No increase in toxicity was seen. These results provide evidence for the use of this combination in patients inadequately treated with monotherapy.

Early parallel triple therapy has been compared with step-up therapy within an intensive disease management regimen. Ninety-six patients with early RA (mean disease duration 11.5 months) were randomized to receive step-up therapy (with SSZ monotherapy, then sequentially adding MTX and HCQ) or parallel triple therapy (SSZ/MTX/HCQ) [72]. Patients were assessed monthly for 12 months. If their disease activity score in 28 joints (DAS28) was ≥ 3.2, the dosage of DMARDs was increased according to protocol, and swollen joints were injected with triamcinolone acetonide. Both groups showed substantial improvements in disease activity and functional outcome. At 12 months, the mean decrease in the DAS28 score was 4.0 (step-up therapy group) versus 3.3 (parallel therapy group) ($P = 0.163$). No significant differences in the percentages of patients with DAS28 remission (step-up therapy group 45% vs. parallel triple therapy group 33%), or ACR20 (77% vs. 76%, respectively), ACR50 (60% vs. 51%, respectively) or ACR70 (30% vs. 20%, respectively) responses were seen. Radiological progression was similar in both groups. This study shows that control of disease activity can be achieved using conventional DMARDs as part of an intensive disease management strategy. Within this setting, step-up therapy is as effective as parallel triple therapy.

Similar benefits of the more intensive approach over 'conservative' treatment have been demonstrated by some studies [73]. However, others comparing MTX/SSZ combination with single agents [74, 75] were unable to identify better outcomes for any treatment arm over the other. Results from the Behandel Strategieën (BeSt) study demonstrated that after a failure of MTX 25 mg/week, adding SSZ to MTX resulted in an original DAS of 2.4 or less in only 22% of patients. An equally low response was obtained when switching from MTX to SSZ [76].

Taken together, some benefit is seen with the use of combination DMARD therapy with or without steroids, at least for the clinical course. The COBRA [2] and FIN-RACo [69] trials also reported radiographic benefits in the more intensive-treatment groups. However, not all of the studies compared radiographic progression, and in others deterioration still occurred with respect to radiological scores.

BIOLOGICAL THERAPY [77]

An alternative approach to managing patients with early arthritis is to target the subgroup of patients with very early synovitis who are at high risk of developing RA with potent anti-inflammatory therapy. Tumour necrosis factor alpha (TNF-α) is a cytokine that is central to the inflammatory cascade. It has pleiotropic effects driving the immune response, with

powerful modulatory effects on many aspects of cellular and humoral immunity [78, 79], and has an important role in persistence of early RA [80].

The concept that intensive interventions early in the course of persistent arthritis may improve clinical activity and profoundly affect long-term radiographic progression is supported by several recent randomized controlled trials with anti-TNF agents in early RA (Table 1.1). In patients with a disease duration of less than 3 years, the use of a TNF blocking drug (adalimumab, etanercept or infliximab) – especially in combination with MTX – revealed an increased rate of clinical remission and slowing of radiographic progression compared with MTX monotherapy [5, 65, 81, 82]. These data are consistent with those from several randomized controlled trials in established RA [4, 83, 84]. In addition, at least for infliximab, it has been demonstrated that, even in cases in which clinical activity was not optimally suppressed ('poor response'), radiographic progression appeared to be significantly retarded in comparison with MTX [85].

PREMIER (a trial of lifestyle interventions for blood pressure control) examined the efficacy of adalimumab and MTX combination therapy compared with adalimumab or MTX alone. Rapidly, clinical response was achieved with adalimumab, and the combination therapy group achieved the highest proportion of responses [65]. The ERA trial compared etanercept at two different doses or MTX as monotherapy. Patients receiving etanercept monotherapy also had a more rapid clinical response [82]. The ASPIRE (Active-Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset) trial assessed the efficacy of infliximab at different doses with MTX versus MTX alone in MTX-naive patients with early RA. Patients treated with infliximab and MTX had a more rapid clinical improvement in terms of their HAQ scores and achieved higher 1-year clinical responses and remission rates (defined by a DAS28 score < 2.6) and less radiographic progression [86].

In the Combination of Methotrexate and Etanercept (COMET) study, the first major study looking at remission as the primary end-point in patients with early RA, patients with symptom duration of less than or equal to 2 years were randomized to MTX or MTX and etanercept. At week 52, remission as defined by a DAS28 < 2.6 was achieved in 48.4% with MTX plus etanercept versus 25.9% with MTX alone ($P < 0.001$) (Figure 1.1). Radiographic progression at week 52 was also significantly lower in the group receiving combination therapy (Figure 1.2). No differences were seen between the two groups in terms of serious adverse events, serious infections or malignancies. No cases of tuberculosis were reported in either group [87].

Anti-TNF agents, therefore, provide rapid control of inflammation and have proven efficacy both in terms of clinical outcomes and regarding reduction of structural damage in early disease. They are, however, substantially more expensive than traditional DMARDs, limiting their widespread use in early disease. Selecting patients with poor prognostic factors may improve this cost–benefit balance [88]. These factors include a positive serum test for RF, the presence of anti-CCP antibodies, early radiographic evidence of erosive disease, impaired functional status and persistently active synovitis with high levels of disease activity [86].

INDUCTION WITH BIOLOGICALS AND MAINTENANCE WITH CONVENTIONAL DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Induction with biologicals and maintenance with conventional DMARDs is another therapeutic strategy. This concept was introduced in a placebo-controlled study by Quinn *et al.* [5]. The study demonstrated that patients with early RA and poor prognostic factors treated with infliximab and MTX showed a significant reduction in synovitis and developed fewer erosions on MRI at 12 months than patients treated with MTX alone. Furthermore, the functional and quality of life benefits obtained in patients treated with infliximab after 1 year was sustained at 2 years without further infliximab infusion (Figure 1.3).

Table 1.1 Trials comparing the efficacy of methotrexate, tumour necrosis factor inhibitors and combination tumour necrosis factor inhibitors and methotrexate in early rheumatoid arthritis

					Clinical outcomes at year 1				*Radiographic outcome (mean change in total Sharp scores from baseline)*	
Trial	*Treatment regimen*	*Number of patients*	*Disease duration*	*Follow-up (weeks)*	*ACR20*	*ACR50*	*ACR70*	*Remission (DAS28 <2.6)*	*Year 1*	*Year 2*
ERA [82, 95]	MTX + placebo	632	<3 years	54	65	45	22	–	0.47	1.3
	ETN 10 mg twice a week				60	35	15	–	1.03	3.2[a]
	ETN 25 mg twice a week				72	50	25	–		
ASPIRE [81]	MTX + placebo	1049	≥3 months and ≤3 years	54	54	32	21	15	3.7*	
	MTX + IFX 3 mg/kg				62	46[a]	33	21	0.5*[a]	
	MTX + IFX 6 mg/kg				66	50[a]	37[a]	31[a]	0.4*[a]	
PREMIER [65]	MTX	799	<3 years	104	63	46	28	21	5.7	10.4
	ADA 40 mg every other week				54	41	26	23	3.0[a]	5.5[a]
	MTX + ADA 40 mg every other week				73[b]	62[ab]	46[ab]	43[ab]	1.3[a]	1.9[ab]
COMET [87]	MTX	542	≥3 months and ≤2 years	52	67	49	28	28	2.44	
	MTX + ETN				86[a]	71[a]	48[a]	50[a]	0.27[a]	

ACR20, American College of Rheumatology 20% improvement criteria; ACR50, ACR 50% improvement criteria; ACR70, ACR 70% improvement criteria; ADA, adalimumab; ETN, etanercept; IFX, infliximab; MTX, methotrexate.

*van der Heijde modification.

[a]$P<0.001$ vs. MTX and placebo.

[b]$P<0.001$ vs. adalimumab alone.

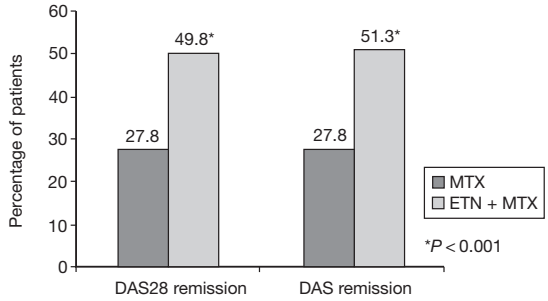

Figure 1.1 Percentage of patients achieving DAS28 remission (primary end-point) and DAS remission at week 52 in the groups receiving MTX versus MTX plus etanercept (ETN) [87]. Source: presentation at ACR, 2007, P. Emery.

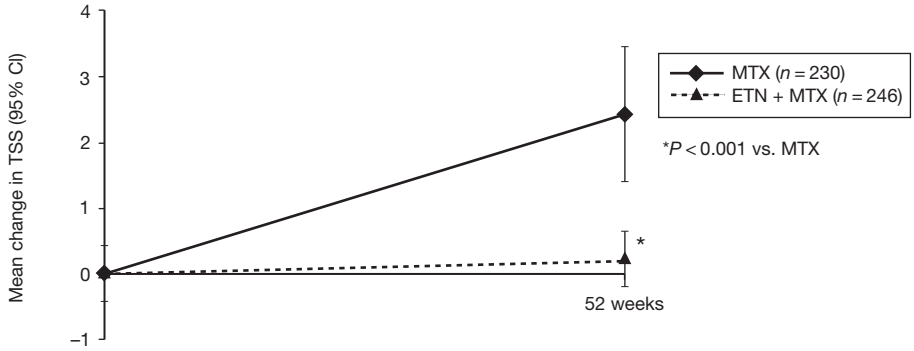

Figure 1.2 Comparison of the change in the modified total Sharp score (TSS) at 52 weeks between the group receiving MTX and the group receiving MTX plus etanercept (ETN) [87]. *n*, number of patients in each treatment group. Source: presentation at ACR, 2007, P. Emery.

COMPARISON OF TREATMENT OPTIONS

One study which compares the use of these various therapeutic options and addresses the optimal treatment paradigms for early RA is the BeSt trial. This multicentre single-blinded trial of 508 patients with RA and less than 2 years of symptoms compared four treatment strategies, including a sequential monotherapy (group 1), step-up combination therapy (group 2), a triple step-down strategy with MTX, SSZ and high-dose prednisolone (group 3) and infliximab plus MTX (group 4) [6]. Treatment was adjusted at 3-monthly intervals with a goal of achieving a DAS of 2.4 or less.

The two groups with initial intensive treatment (groups 3 and 4) showed a more rapid clinical response and a better radiographic outcome than groups 1 and 2. At 2 years, progression of joint damage was less in groups 3 and 4 (median Sharp–van der Heijde scores of 2.0, 2.0, 1.0 and 1.0 in groups 1, 2, 3 and 4, respectively; $P = 0.004$). In addition, fewer treatment adjustments were required in groups 3 and 4 to achieve suppression of disease activity and, after 2 years of treatment, approximately 50% of patients in group 4 were able to stop treatment with infliximab and maintain remission. By year 3, 15% of patients were in remission taking no DMARDs. No significant differences in toxicity were noted between the groups. At 4 years of follow-up, 455/508 patients were still in BeSt and 49% were in clinical

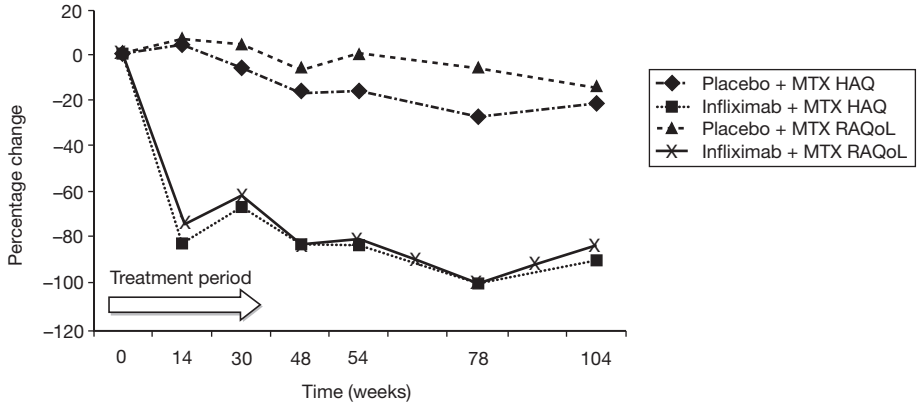

Figure 1.3 Percentage change in the median functional and quality-of-life scores over time in patients with poor-prognosis early RA [5]. HAQ, Health Assessment Questionnaire; MTX, methotrexate; RAQoL, rheumatoid arthritis quality of life. Source: Quinn MA *et al.* Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005; 52:27–35.

remission (DAS < 1.6), with similar disease control across all groups. A small number (11%) of patients were able to successfully discontinue all therapies and were in treatment-free remission. In group 4, 51% of subjects were able to successfully discontinue infliximab with a mean infliximab period of 35 months. Overall, less radiographic progression was seen in those treated with infliximab than those in the other groups.

This study shows that good clinical outcomes were obtained in all patients irrespective of the initial treatment group, reinforcing the importance of early intervention and tight control in the treatment of RA. This strategy of frequent evaluation of disease activity and change of therapy to achieve low disease activity resulted in a sustained clinical and functional benefit for up to 4 years [89].

Further analysis from the BeSt trial comparing patients who received initial infliximab treatment (group 4) with patients receiving infliximab at a later stage (groups 1–3) showed that 56% of patients in group 4 were able to successfully stop infliximab compared with only 15% in the other groups at 2 years. This suggests that, by achieving remission within the 'therapeutic window of opportunity', patients may require less treatment later in the disease course [77].

A systematic review examined 23 head-to-head trials and compared the effectiveness and harms of the various disease-modifying agents for RA [90]. Similar clinical efficacy was found among synthetic DMARDs (limited to MTX, leflunomide and SSZ) and among anti-TNF agents (adalimumab, etanercept and infliximab). Monotherapy with anti-TNF agents resulted in better radiographic outcomes than did MTX alone, but no important differences in clinical outcomes (e.g. the ACR20, 50 and 70 response criteria) were found. Clinical response rates and functional outcomes were better with the various combinations of biological agents plus MTX compared with monotherapy with either MTX or biological agents alone. In patients whose monotherapy failed, combination therapy with synthetic DMARDs improved response rates. The comparative evidence, however, was not sufficient to firmly conclude which combination or therapeutic strategy was superior to the others for the early treatment of RA. In the trials that were reviewed, the numbers and types of short-term adverse events were similar for biological and synthetic DMARDs.

Newer biological therapies with different modes of action have been used in established RA. These include rituximab, a B-cell-depleting agent; abatacept, an inhibitor of T-cell co-stimulatory pathways; and tocilizumab, an interleukin 6 receptor antagonist. Clinical studies are ongoing to define their role in early disease.

PREVENTION OF RHEUMATOID ARTHRITIS

The goalpost for 'early' continues to move towards earlier diagnosis and treatment of patients with inflammatory arthritis. In randomized clinical trials, patients with early RA were included if they had a diagnosis of RA for less than 3 years. A survey from Europe and the USA, however, found that the majority of rheumatologists defined early RA as symptom duration less than 3 months [91]. Targeting early arthritis even before diagnosis of RA at the stage of undifferentiated inflammatory arthritis (UIA) is another area of research as a treatment strategy for obtaining better outcomes in RA. There is evidence which suggests treating undifferentiated arthritis (UA) with glucocorticosteroid, MTX or biological agents may delay or prevent development of RA.

An approach for patients who present with very early inflammatory arthritis (less than 12 weeks of symptoms) may be to give a single dose of glucocorticosteroid to provide rapid improvement symptoms and demonstrate the reversibility of disease. Green *et al*. [34] demonstrated the possible reversibility of early arthritis by treatment with glucocorticosteroid injections before diagnosis of RA. Results of an open study of 100 patients with UA suggest that a single dose of intramuscular or intra-articular steroids may induce remission [92].

In the PROMPT (Probable Rheumatoid Arthritis: Methotrexate versus Placebo Treatment) study, the first double-blind, randomized, controlled trial addressing early DMARD therapy in patients with UA before the stage of fulfilling ACR criteria for RA, 110 patients were randomized to treatment with MTX or placebo for 12 months. Outcomes at 30 months showed that MTX may delay the development of RA; this was mainly seen in the subgroup of patients who demonstrated the presence of anti-CCP antibodies [93].

In a recent study, Saleem *et al*. [94] evaluated the ability of TNF antagonist therapy to produce remission and prevent progression to RA in patients with poor prognosis UA. Seventeen patients with UA of less than 12 months' duration having relapsed after a single parenteral glucocorticosteroid injection were recruited into a double-blind, placebo-controlled trial of infliximab or placebo monotherapy administered at weeks 0, 2, 6 and 14. MTX was added at week 14 if no clinical response was achieved. The primary outcome was clinical remission at week 26. At week 14, the infliximab group had greater improvements in CRP and HAQ, but by week 26 there was just a trend favouring infliximab for early morning stiffness, tender joint count, swollen joint count and HAQ; there was no significant difference in DAS28 between the two groups. Furthermore, only three patients were in clinical remission (two infliximab, one placebo). By week 52, 100% (10/10) of patients in the infliximab group and 71% (5/7) of patients in the placebo group had developed RA. In this study, the use of a short course of TNF antagonist therapy in patients with poor-prognosis UA provided modest short-term relief but did not prevent the development of RA [94].

Managing patients in the earliest stages of inflammatory arthritis is an area of ongoing research. Further studies may enable one to assess the factors and therapeutic options that will influence the development and prevention of RA.

CONCLUSION

With effective therapies and advances in treatment strategies, the outcomes of patients with RA continue to improve. Studies have shown that early therapy with disease-modifying agents together with treatment escalation to achieve tight control results in significant clinical

and radiographic benefits with a potential for (drug-free) remission or reduced biological or DMARD dependence. In determining optimum treatment strategies, issues such as drug safety and cost-efficacy will need to be taken into consideration. The biological agents, in particular TNF blockers, have been shown to be highly effective in the treatment of early RA but are more expensive than conventional DMARDs. With cost constraints, a pragmatic therapeutic option may be initial DMARD therapy, with steroids as adjunctive therapy, and early intervention with biological agents for those with poor prognostic features or inadequate disease control.

Treating patients with early inflammatory arthritis, or intervention in the preclinical stages for the prevention of RA, remains an area of interest and may be the way of the future.

TREATMENT STRATEGIES: PRACTICAL POINTS

- Early therapy with disease-modifying agents is the cornerstone of treatment for early RA.
- Disease activity should be monitored regularly, escalating treatment to achieve optimal disease control.
- Early use of TNF-blocking agents has been shown to improve clinical and radiographic outcomes in RA and may provide an opportunity for (drug-free) remission. Treatment with these agents should be considered early in the disease course, particularly if patients have an inadequate response to conventional DMARD therapy.

FURTHER RESEARCH

Areas for further research include:

- studies with an appropriate design to determine comparative effectiveness and cost-effectiveness of different therapeutic strategies;
- the effect of the temporary use of intensive treatments, such as biological agents in early arthritis, to assess whether prevention of erosions and cure (in terms of long-term, possibly drug-free, remission) of the disease is possible; and
- therapeutic strategies in early undifferentiated arthritis to prevent RA.

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