Window of opportunity in early rheumatoid arthritis: Possibility of altering the disease process with early intervention

M.A. Quinn, P. Emery

Academic Unit of Musculoskeletal Disease, Department of Rheumatology, Leeds General Infirmary, Leeds, United Kingdom.
Mark A. Quinn, MBChB MRCP, Lecturer in Rheumatology; Paul Emery, MA MD FRCP, ARC Professor of Rheumatology.

Please address correspondence to:
Professor Paul Emery, Academic Unit of Musculoskeletal Disease, Department of Rheumatology, 1st Floor, Leeds General Infirmary, Great George Street, Leeds, LS13EX, United Kingdom.
E-mail: p.emery@leeds.ac.uk

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ABSTRACT

Therapeutic strategies for the treatment of rheumatoid arthritis (RA) have changed significantly in the last decade. The emphasis is now on early intervention with the aim of preventing disability and irreversible damage. Advocates of early intervention would suggest an alteration in the disease process, not just debulking of inflammatory disease. The data would at least support attenuation of the disease process with aggressive early therapy. Further research is required to elucidate the scientific mechanisms involved and their impact on the pathological progress of RA.

Introduction

The concept of a "window of opportunity" for therapeutic intervention in rheumatoid arthritis was first hypothesized in the early 1990s (1). The hypothesis is based on the existence of a time frame within which there is a disproportionate response to therapy, resulting in long-term sustained benefits or more importantly the chance of "cure". It is an attractive approach to the management of a persistent, progressive, damaging, inflammatory disorder.

Historically damage predicted therapy

Until the 1990s, the conventional approach to treatment of RA had been a protocol which started with the least toxic and least effective therapies, e.g. analgesics and NSAIDs, followed by more effective but what were thought to be more toxic drugs, e.g. corticosteroids and disease modifying antirheumatic drugs (DMARDs), i.e. the classic treatment pyramid. It was common practice that DMARDs were only initiated when patients had demonstrable radiological damage and so had 'justified their treatment.' This treatment approach was based on the notion that RA in general is 'mild', with joint damage and disability occurring slowly. However, radiological outcome studies have demonstrated that damage occurs early in disease and 90% of patients have radiological evidence of damage by the end of 2 years of symptoms (2). More recent studies using imaging techniques such as magnetic resonance imaging (MRI) and ultrasonography (US) have confirmed evidence of damage within weeks of the onset of symptoms (3, 4). Moreover these lesions correlate reliably with later radiographic erosions (5). Damage therefore occurs even earlier than was first thought and waiting for evidence of radiographic damage prior to intervention can no longer be justified.

Inflammation causes damage

C-reactive protein (CRP) is regarded as a surrogate marker of inflammatory disease. There is a plethora of data in the literature relating high levels of CRP to radiographic (6-8) and functional (9) outcomes as well as localised and systemic bone density loss (10-12). This becomes more clinically relevant when time integrated values for CRP are considered (13). Despite these data, it has been suggested that damage may occur in the face of control of inflammatory disease (14). However, imaging has helped elucidate the relationship of inflammatory disease with bone damage. MRI studies have shown a direct correlation between synovial volume and erosive changes (15) and evidence of a threshold effect, below which damage does not occur. This concurs with recent data where damage occurs only in clinically affected joints (16). From these data therefore there appears no dissociation of inflammatory disease with radiographic damage and inflam-

matory disease should be the primary therapeutic target.

Early therapy is effective

There is a body of evidence from therapeutic studies in early RA to support the early use of DMARD therapy. The majority of studies demonstrate a quantitative benefit in clinical outcome and show delayed introduction of DMARD therapy to be detrimental. Moreover there is some evidence to suggest the best predictor of response to therapy is symptom duration. Anderson J *et al.* demonstrated in an analysis of 1435 patients from 11 different studies that disease duration was of foremost importance in predicting response to DMARD therapy (17). Patients presenting with less than 1 year disease duration showed response in 53%, whereas later groups 1-2 yrs, 2-5 yrs,5-10 yrs and > 10 yrs showed diminished response measured by ACR20 with disease duration.

The opportunity for functional improvement may also be lost with delayed introduction of therapy. In a study of 440 patients, patients treated early (< 2 yrs) showed a significant improvement in function, measured by the Health Assessment Questionnaire (HAQ), whereas patients with a longer disease duration showed little reversibility of their impairment (18). Similarly when early treatment was compared to delayed therapy after 8 months with oral gold, clinical benefit and sustained radiological improvement was demonstrated after 5 years follow up (19). Van der Heide compared DMARD treatment with NSAID alone and delayed introduction of DMARD. All clinically relevant variables were improved at 1 year. No significant difference however was detected in radiographic progression. This may have been due to a significantly greater number of non-DMARD treated patients discontinuing therapy, a greater use of intra-articular corticosteroid in the non-DMARD group or a Type 2 statistical error (20). Other studies looking at any DMARD use versus NSAID or no therapy, strongly favour DMARD use with respect to the long-term disability index (21) and also the deformed/damaged joint and radiographic score (22). In considering qualitative rather than quantitative improvement in outcome less data are available. However, in a study of 448 RA patients, patients that presented with less than 5 years of disease maintained a lower mortality ratio over 21.5 years of follow up when compared to late presenters (23). Early introduction of therapy therefore would appear the most effective therapeutic approach, but debate continues with respect to whether true alteration of disease process or just debulking of inflammatory disease is taking place.

Can disease process be altered with early intervention ?

Searching for evidence to support alteration of disease process, five studies are highlighted and each offers an alternative approach and interpretation of efficacy.

Cure in mild inflammatory disease

Green *et al*. studied 63 patients with mild early inflammatory arthritis, defined as synovitis ≥ 2 joints with < 12 months of symptoms, longitudinally for 6 months (24). Mild disease was defined as one of the following: (a) duration of symptoms less than 3 months irrespective of the pattern of disease; (b) asymmetrical disease; or (c) symmetrical MCP joint disease, but with a low prognostic severity score based on predictors of poor outcome in terms of function and radiographic damage. The aims of the study were to determine the factors that predict persistence of inflammation 6 months following corticosteroid therapy and to assess the ability of the ACR criteria to select these patients.

There was sufficient uncertainty about the outlook of these patients that a temporary delay in DMARD therapy was felt to be ethical. The initial treatment was with a single dose of corticosteroids given either intramuscularly (120 mg methylprednisolone or 80 mg if <60 kg) or intra-articularly. The factors associated with outcome at 6 months were subsequently examined. In this group the best predictor of persistence was disease duration (12 weeks). With disease < 12 weeks the chance of remission was increased 5-fold. In analysing the sero-negative group for rheumatoid factor (RF) separately, patients in possession of the shared-epitope (SE) were significantly more likely to have persistent disease. This suggests that in the RF negative sub-group, the SE may be of greater value. It has already been suggested that the SE is associated with persistence rather than induction of arthritis (25). No patients RF + SE positive entered remission. After 12 weeks classic features of RA were more predictive with all but 1 patient with symmetrical MCP synovitis having persistent disease. Interestingly there was a trend for patients with a high CRP with very early disease to enter remission. Here greater than 50% patients entered remission with a single dose of corticosteroid. ACR classification criteria were not predictive of persistence and duration of symptoms alone was the best predictor of outcome. If we consider these patients to be RA patients in evolution then this may be preliminary evidence to suggest intervention at this very early stage truly alters the disease process.

Disease duration predicts remission rate with monotherapy

Mottenen *et al*. studied the impact of the delay from the onset of symptoms to institution of DMARD therapy on remission rates in 195 patients with RA (26). In this further analysis of the FIN-RACo cohort, only disease duration significantly predicted remission rates in the monotherapy arm using a cut off of 4 months symptom duration ($p = 0.01$). No other recognised prognostic variable emerged in the logistic regression model. Perhaps also of interest here is that symptom duration did not predict remission in the combination therapy arm, suggesting aggressive therapy may abolish the impact of conventional prognostic factors. Boers *et al.* have found similar in that the prognostic impact of the SE was abolished in the aggressive arm in the COBRA study (27). These data suggest that disease duration should be an important factor when considering therapeutic approaches in RA patients.

Long-term benefit from short-term intervention with conventional therapies

The ultimate aim of therapy remains remission. In attempting remission induction the COBRA study group reported a step down therapeutic approach of sulphasalazine (SSA) + methotrexate (MTX) + prednisolone versus SSA alone (26). Significant radiographic benefits were seen at 80 weeks, yet disease activity was comparable in the two groups after the steroid therapy was stopped. Importantly a follow up study analyzing rate of radiographic progression between groups over the subsequent 4-5 years after the initial 56-week study period demonstrated a reduction in radiographic progression rate in the combination therapy arm (29). The findings are significant due to the sustained apparent benefit from 6 months early aggressive therapy. This may be a debulking effect, but such a long-term benefit is suggestive of an alteration in disease process.

Rapid and sustained disease control with biologics

More recently a placebo-controlled study in poor prognosis early RA using infliximab and MTX versus MTX alone demonstrated significant differences in functional outcome, quality of life and MRI erosion scores at 12 months (30). There were significant differences in the ACR responses at 12 months (ACR50 77% vs 40%) However, after withdrawal of study drug and 12 months further observation, no patient demonstrating response to infliximab had flare of their disease requiring additional DMARD and median disease activity score was maintained at remission levels. In this study not only was structural damage improved but disease activity benefits were seen early and sustained, not only at 12 months but at 2 years. Even more importantly functional and quality of life differences remain at 2 years. This was without further infliximab therapy. This study of anti-TNF for the first time has shown that early use of anti-TNFα produces sustained benefits in the important disease parameters of function and quality of life. This differs from the studies of conventional DMARDs where structural damage is prevented, but patient based assessments are not improved.

Long-term benefit from continued biologic therapy

In the Enbrel ERA study 632 patients with early, active RA were randomised to receive either twice weekly etanercept (10mg or 25mg) or weekly oral MTX (mean dose 19mg/ week) for 1 year in a double blind manner. Thereafter 512 patients continued to receive their randomised therapy (open-label) for a further year. The 12-month paper showed rapid disease activity control with etanercept, which converged between groups by the 12-month time point (31). At 12-months there was a significant difference in Sharp erosion score in favour of the 25mg etanercept group, but not for total score or joint space narrowing. With 12 months further follow up significant benefits were demonstrated in total Sharp and erosion scores and also functional improvement (32). A greater number of patients achieved ACR 20 response in the etanercept 25 mg group at 24 months. Importantly here benefits are seen in the second year after rapid and sustained suppression of disease activity with continued therapy, suggesting an important role of early suppression of inflammatory disease. However this therapeutic benefit was only seen with continued use of etanercept. If it is assumed that etanercept is a better therapy than methotrexate alone, the increasing significant benefits that were seen were due to an incremental effect over time.

Previously it was thought that more aggressive treatment regimens, usually combination therapies with corticosteroids, reduced damage for the duration of suppression of inflammation, and once stopped disease returned to previous levels. However, COBRA and early data using infliximab suggest, there is evidence for a qualitative change in the disease mechanisms. It is clear that initial aggressive regimens result in debulking of disease with improvement in damage and early outcome, and although the disease process continues, it appears somewhat attenuated.

The pathological mechanisms to explain these data are not fully understood, but raise the question of a "therapeutic window" that may be exploited to gain maximum effect of therapy. Also a very early "window of opportunity"may exist (< 12 weeks symptoms) where early intervention may alter the propensity to persistence and therefore offer the opportunity of cure. These avenues need further research to fully understand the pathological processes behind these findings, but the evidence for a therapeutic "window of opportunity" continues to develop.

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