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Treating very early rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) is common and leads to joint damage due to persistent synovitis. The persistence of inflammation is maintained by hyperplastic stromal tissue, which drives the accumulation of leukocytes in the synovium. Aggressive treatment after the first 3–4 months of symptoms, with either disease modifying anti-rheumatic drugs or anti-tumor necrosis factor (TNF)- α therapy, reduces the rate of disease progression. However, it rarely switches off disease such that remission can be maintained without the continued need for immunosuppressive therapy. There is increasing evidence that the first few months after symptom onset represent a pathologically distinct phase of disease. This very early phase may translate into a therapeutic window of opportunity during which it may be possible to permanently switch off the disease process. The rationale for, and approaches to, treatment within this very early window are discussed.

Keywords

rheumatoid arthritis; early arthritis; synovitis; therapy; remission; DMARD; anti-TNF- α therapy

INTRODUCTION

Early inflammatory arthritis is remarkably common. However, in up to half of patients the disease resolves spontaneously over a few months.^{1,2} In the rest, the processes driving the natural resolution of inflammation are disrupted, leading to a switch to chronic persistent disease characterised by the accumulation of large numbers of lymphocytes, macrophages and fibroblasts in the synovium. Rheumatoid arthritis (RA) is the most prevalent of the persistent inflammatory arthritides, affecting 0.81% of adults in the UK.³ The disease typically manifests as a symmetrical peripheral inflammatory polyarthritis that leads to joint destruction and may be associated with extra-articular features. RA causes significant disability^{4,5} and enhanced mortality, predominantly related to accelerated cardiovascular disease.^{6,7}

In the 1980s treatment decisions in RA were guided by a 'pyramid approach', with non-steroidal anti-inflammatory drugs (NSAIDs) being used as initial therapy, and disease

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modifying anti-rheumatic drugs (DMARDs) being added later, usually after the development of erosive disease. The development of this therapeutic approach was based on two assumptions. First, that RA was a benign, non-life threatening disease, in which damage occurred late. Secondly, that DMARDs were too toxic for wide-spread use. Identifying that these assumptions were false⁸ led to an important shift in the management of RA in the early 1990s. It became apparent that bone erosion, an important feature of established RA, actually began early in the course of disease⁹ and was due to active synovitis.^{10–12} These and other observations led to the use of DMARDs and anti-tumor necrosis factor (TNF)- α therapy earlier in the course of RA to limit damage by reducing the cumulative inflammatory burden to which patients were exposed.^{13,14} Nevertheless, therapy was restricted to patients in whom it was clear that established RA had developed (typically with symptoms of more than 3 months duration) and in whom the chances of the disease resolving spontaneously were slim.

Over the last 5–10 years we, and others, have shown that the persistence of chronic inflammation in the rheumatoid synovium is associated with hyperplastic stromal tissue, which inhibits leukocyte apoptosis leading to the accumulation of inflammatory cells in the joint.^{15–19} Once symptoms have been present for more than 3 months the immunopathological processes operating in the rheumatoid synovium appear to become stereotyped and become very similar in patients with markedly different disease durations. Therapy after the first 3 months of symptoms with conventional DMARDs (reviewed in Smolen et al)²⁰ as well as with drugs targeting TNF- α ^{21,22}, reduce disease activity and so limit the development of damage, but do not cure RA. However, there is accumulating evidence that the very early phase of synovitis in patients destined to develop RA (within the first 12 weeks of symptoms) represents a pathologically distinct stage of disease.^{23–26} This suggests that late disease is not just more of early disease and gives, for the first time, a clear rationale for suggesting that very early intervention may have a *qualitatively* different effect compared with later intervention – a genuine therapeutic window of opportunity during which the potential for therapies to permanently switch off inflammation needs to be explored.^{27,28} In this article we will discuss those studies that have treated RA patients with symptoms of less than 2 years duration, review why intervention within this time frame fails to switch off inflammation permanently and outline the rationale and prospects for intervention within the first 3 months of symptoms.

THE TREATMENT OF ‘EARLY’ RA

The time frames within which the effects of therapy have been studied in most trials of ‘early’ intervention in RA have been somewhat arbitrarily defined and have been based on the principle of ‘the earlier the better (assuming the patient has definitely developed RA)’.

Most trials of ‘early’ therapy have chosen a maximum symptom duration of 2 years. Therapeutic approaches studied to date have included intra-articular and systemic steroid, DMARD monotherapy, DMARD combination therapy and anti-TNF- α therapy (either alone or in combination with DMARDs); these approaches in each case were compared with less aggressive approaches to treatment.

Early studies compared the pyramid approach of escalating therapy in early RA with early DMARD introduction.^{29,30} A Dutch study assessed outcomes in patients with RA of <12 months duration who were randomised to receive therapy with either NSAID, hydroxychloroquine, intramuscular gold or oral methotrexate.³⁰ Patients treated with initial DMARD therapy showed a significantly greater rate of improvement in disability, pain, joint scores and erythrocyte sedimentation rate (ESR). In the early 1990s attention shifted from whether patients with established RA of less than 1–2 years duration should commence

DMARD therapy at diagnosis or have delayed treatment, to whether initial combination therapy was better than initial DMARD monotherapy in this period and whether after initial induction therapy the intensity of treatment could be reduced while maintaining the benefits of initial rapid disease control. The landmark COBRA trial explored this 'step-down bridge' approach.³¹ In that study, combination therapy was compared with sulphasalazine monotherapy in patients with RA of <2 years duration (median duration 4 months). Patients in the combination group were treated with oral prednisolone (initially at 60 mg daily tapered over 6 weeks to 7.5 mg daily and then stopped after 28 weeks), oral methotrexate (which was stopped after 40 weeks) and sulphasalazine. Patients treated with combination therapy had significantly less disease activity compared with the monotherapy group. However, this was only apparent while the steroid was being given and disease activity in the groups converged once steroid had been withdrawn at 28 weeks. Nevertheless, the difference in cumulative disease activity between the groups was associated with less radiological deterioration in the combination group by week 56. Importantly, a 5-year follow-up of patients in this trial showed that initial combination therapy resulted in a sustained suppression of the rate of radiological progression independent of subsequent treatment³² implying that early combination therapy had lasting beneficial effects. The FIN-RACo trial compared a combination regimen (sulphasalazine, methotrexate, hydroxychloroquine and low dose prednisolone) that was maintained over the study period with monotherapy (sulphasalazine alone) in patients with RA of <2 years duration (mean duration 8 months).³³ Of the patients who received combination therapy, 37% were in drug maintained remission after 1 year compared with 18% of patients on monotherapy. As in the COBRA trial, 5-year follow-up of patients in the FIN-RACo study showed that the early use of combination therapy reduced the rate of radiological progression in peripheral joints between 2 and 5 years, compared with the rate seen in patients treated with single therapy, although treatments for the two groups were unrestricted after the first 2 years of the study.³⁴ Similarly, in another study of RA of <12 months duration, intra-articular steroid therapy as an adjunct to methotrexate treatment led to better control of synovitis and a slowing in the rate of the development of erosions.¹²

However, not all studies have shown a benefit from 'early' combination therapy. A study of patients with RA of <12 months duration and with poor prognostic indicators, compared a combination of methotrexate, cyclosporin A and intra-articular steroid with sulphasalazine alone.³⁵ The combination therapy group achieved a more rapid improvement in swollen and tender joint counts and inflammatory markers during the first few weeks of the study, probably related to the higher initial use of steroid in this group. However, by week 48 there was no significant clinical or radiological difference between groups. Similarly, a study of patients with RA of <12 months duration showed no benefit of combined methotrexate and sulphasalazine compared with each treatment alone.³⁶ In addition, a few studies have shown no long-term benefit from initial combination therapy.^{37,38} For example, the 5-year follow-up of patients in the study by van der Heide et al. failed to show a significant difference in radiological progression between early DMARD therapy and the pyramid approach to treatment.³⁷ However, in that study more patients in the NSAID group were treated with oral and intra-articular steroid than in the DMARD group, so the real therapeutic differences between the groups may not have been sufficiently large to translate into clinical effects at 5 years. The use of such steroid additions to trial therapies is a major confounding factor.

Those studies that have shown benefit from early combination therapy have used steroids, albeit in different regimens.^{12,31,33} Steroids certainly allow a more rapid control of synovitis than conventional DMARDs, explaining their incorporation in step-down regimes. The use of steroid in the medium to long-term, however, remains controversial. Several studies suggest that oral steroids reduce the risk of development of erosions in patients with early

RA^{39,40} and there is a clear biological rationale for this.⁴¹ However, data from the WOSERACT study does not support this clinical benefit.⁴²

In conclusion, many studies of patients with established RA of <1–2 years duration show that initial combination DMARD therapy (often with a steroid) leads to better control of disease activity and a reduction in the progression of erosions compared with monotherapy. In addition more aggressive therapy within the first 1–2 years of disease may slow the rate of subsequent disease progression.

There is increasing interest in the treatment of ‘early’ RA with anti-TNF- α drugs. Several studies have shown that the antagonism of TNF- α within the first 3 years of symptoms leads to better disease control compared with regimens that do not include anti-TNF- α drugs.^{43–45} However, it remains unclear if the use of these agents earlier in disease will have superior efficacy. Emery et al. addressed this issue in a pilot study of five patients with poor prognosis RA and disease of <1 year duration (mean 7 months).⁴⁶ Patients were treated with high dose infliximab (10 mg/kg at weeks 0, 2, 6 and 10) together with methotrexate. ‘Remission’ was induced in only one patient (who required maintenance therapy with methotrexate). In a follow-up study, 20 RA patients (disease <1 year duration; mean 7 months) were randomised to therapy with infliximab plus methotrexate or placebo plus methotrexate for 46 weeks after which time infliximab was withdrawn and patients were treated with methotrexate alone until week 104.⁴⁷ The use of infliximab was associated with improved clinical and radiological outcomes but not with the induction of remission that could be maintained without ongoing methotrexate therapy.

Similarly, the BeSt trial looked at patients with RA of <2 years duration (median duration 23 weeks).⁴⁸ Aggressive therapy with regimens that included either infliximab and methotrexate or high dose prednisolone together with methotrexate and sulphasalazine was associated with improved clinical and radiological outcomes compared with a less aggressive initial approach to therapy (sequential monotherapy or a step-up approach).⁴⁸ Of those patients initially treated with infliximab, 50% were eventually able to stop anti-TNF- α therapy because of persistently low disease activity (DAS₄₄ 2.4 for at least 6 months). However, those patients were maintained on methotrexate monotherapy and the issue of the induction of remission that could be maintained without drug was not addressed in that study.

Therefore, even with potent regimens (anti-TNF- α and methotrexate) it appears unlikely that permanent drug-free remission can be induced in patients with established RA once symptoms have been present for more than 3 months.

WHY IS IT SO DIFFICULT TO PERMANENTLY SWITCH OFF RHEUMATOID SYNOVITIS IN PATIENTS WITH SYMPTOMS OF MORE 3 MONTHS DURATION: LESSONS FROM PATHOLOGY

Physiological inflammation is not a stable state. During the early stages of a local inflammatory response, large numbers of leukocytes are recruited from peripheral blood into the inflamed tissue. In the absence of extrinsic stimuli such inflammation resolves and the tissue reverts to normal. Resolution is mediated by the cessation of recruitment of further inflammatory cells and the clearance of unwanted effector cells. The clearance of inflammatory cells results, at least in part, from the loss of local stromal derived survival signals that lead to apoptosis and the subsequent phagocytosis of dead cells. The resolution of such inflammatory responses is an active and coordinated process involving the ordered production of anti-inflammatory mediators such as lipid-derived lipoxins and resolvins.⁴⁹ In

chronic inflammation, this resolution phase becomes disordered and fibroblast activation and hyperplasia contribute to the persistence of the inflammatory infiltrate.^{15–19} In synovium from patients with established RA, infiltrating lymphocytes are frequently organised into microstructures that resemble the lymphoid aggregates found in secondary lymphoid organs.⁵⁰ The chronically inflamed rheumatoid synovium is, therefore, a highly stable microenvironment which inappropriately mimics many of the structural and functional features of lymphoid tissue.⁵¹

The mechanisms underlying the maintenance of persistent inflammation have been relatively well defined. Fibroblast derived interferon (IFN)- β , for example, mediates T cell survival by upregulating levels of the anti-apoptotic mitochondrial protein Bcl-X_L.¹⁶ In addition to IFN- β , other fibroblast related mechanisms facilitating T cell survival are likely to operate in established RA. For example, exposure of CD4⁺ve T cells to stromal derived factor (SDF) 1 α (produced by synovial fibroblasts) renders T cells less susceptible to apoptosis induced by anti-CD3 stimulation⁵² as well as to cytokine deprivation induced apoptosis.⁵³ Furthermore, fibroblasts inhibit neutrophil apoptosis via IFN- β ⁵⁴ and also keep B cells alive through contact dependent interaction involving vascular cell adhesion molecule 1 (VCAM-1)/CD106.⁵⁵ Although the inhibition of T-cell apoptosis by stromal cells at sites of chronic inflammation contributes to T-cell accumulation, it cannot be the only mechanism because cells should be able to leave the joint during the resolution of inflammation even if their death is inhibited. In fact, work from our group and others suggests that inflammatory cells are actively retained in the joint through the upregulation of the chemokine receptor chemokine (C-X-C motif) receptor 4 (CXCR4) by stromal-derived transforming growth factor (TGF)- β .¹⁹ Within the established rheumatoid synovium, T cells play an important contact-dependent role in driving TNF- α production by synovial macrophages.^{56,57}

This goes some way to explaining why anti-inflammatory therapies used when disease is established, and the fibroblast layer expanded, do not eliminate disease. Thus, in established RA, many therapeutic interventions that lead to the elimination of inflammatory leukocytes from the synovium have been used with transient success, from intra-articular steroid injections to thoracic-duct drainage.^{58–60} However, eventually the leukocytes return to repopulate the hyperplastic stromal environment and associated with this there is a recurrence of symptoms.

Is the pathology of very early RA, with symptoms of less than 3 months duration, different from that found in later disease? If so, this would provide a rational basis for proposing that therapy within the first 3 months might do more than can be achieved with the use of immunosuppressive therapy in established RA. In other words, it might be possible to switch off inflammation permanently rather than just controlling it. However, if the pathology of very early and established RA is the same, it is difficult to see why initiating a treatment very early should switch off the disease process when the same drug(s) given later are unable to do so. Despite the importance of this question little work has been done in this area. Tak et al have compared RA patients with symptoms of less than 1 year duration with patients with longer standing disease. Immunohistological analysis of the synovium, including an assessment of the expression of interleukin (IL)-1 β , TNF- α and IL-6, as well as infiltration with CD4⁺ve and CD8⁺ve cells, CD22⁺ve B cells, CD38⁺ve plasma cells, mast cells, macrophages and fibroblasts did not reveal any differences between early (mean disease duration 6 months) and longstanding RA.⁶¹ In addition, subgroup analysis comparing histological scores in patients with a disease duration of <6 months and those with disease of 7–12 months duration did not yield any statistically significant differences. However, it is unclear whether there were differences between patients with very early synovitis (<3 months) and established disease. In another study expression of IFN- γ , IL-10

and IL-12 mRNA in synovial fluid mononuclear cells was also similar between 11 early RA patients (median disease duration 10 weeks, range 6–31 weeks) and 11 patients with established RA (median disease duration 14 years, range 3–39 years).⁶²

Unfortunately, very few groups have studied the pathology of RA within the first few weeks of symptom onset. Indeed, because patients with a symptom duration of less than 6 weeks cannot fulfil 1987 American Rheumatism Association (ARA) classification criteria for RA⁶³, any study of early disease that limits itself to patients who have already fulfilled these criteria will exclude those with very early synovitis who subsequently develop RA. Important contributions to the understanding of *very early* synovial lesions were made in the 1970s and 1980s by Schumacher et al^{23,24} and Konttinen et al.²⁵ In patients with very early RA (synovitis of <3 months duration) Konttinen et al described very large numbers of macrophages with neutrophils often present in patchy infiltrates.²⁵ This contrasted with patients with established RA where large numbers of plasma cells and T cells were present. In work from Schumacher's group, synovial biopsies were taken from 24 patients with a disease duration of less than 2 months, six of whom eventually developed RA.²³ In all six RA patients, vascular changes were noted to be prominent and plasma cells and lymphoid aggregates were absent. The absence of lymphoid aggregates in very early RA (within 6 weeks after the onset of disease symptoms) has been noted in a more recent study from that group.⁶⁴ We have studied the immune and stromal cell processes present soon after the initiation of RA by assessing a panel of T cell, macrophage and stromal cell related cytokines in the synovial compartment of patients with synovitis of <12 weeks duration.²⁶ Patients with very early inflammatory arthritis who subsequently developed RA had a distinct, but transient, synovial cytokine profile. The levels of a range of T cell, macrophage and stromal cell related cytokines (IL-2, IL-4, IL-13, IL-15, basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF)) were significantly elevated in these patients, within 3 months after symptom onset. This profile was not seen in synovitis that resolved, or in early synovitis that persisted but that did not develop into RA. In addition, this profile in very early RA was transient and was not seen in established RA patients or after the first few months in patients who developed RA. The first 3 months of symptoms in RA thus represents a biologically distinct phase of the disease. The very early phase of RA, within 3 months of symptom onset, is characterised by very low levels of lymphocyte and neutrophil apoptosis within the synovial compartment (unpublished observations). It is likely that the high levels of common- γ chain cytokines (IL-2, IL-4 and IL-15) and of granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) that we have reported in the very early rheumatoid lesion contribute to lymphocyte and neutrophil survival in this phase of disease, allowing accumulation of these cells. In addition, other cytokines present in the very early rheumatoid lesion may play a role in the development of the microenvironment required for persistence. IL-13, for example, induces proliferation and CD154 (CD40 ligand) expression in lung fibroblasts^{65,66} and is important in inducing fibrosis in T helper Type 2 (Th2)-mediated diseases such as schistosomiasis.⁶⁷ In addition, both IL-4 and IL-13 protect synoviocytes against nitric oxide (NO)-induced apoptosis.⁶⁸ The pro-survival and proliferative effects of these cytokines may thus be important in the development of the expanded fibroblast network that occurs during early disease and which characterises established RA.¹⁷ The presence of significant levels of the autocrine synovial fibroblast growth factors, bFGF and EGF⁶⁹, would clearly support this process. Th2-type cytokines have additional effects on synovial fibroblasts, which may be relevant in very early RA. Cultured synovial fibroblasts have a global gene expression profile that is quite different from that of lymph node and tonsil fibroblasts.⁷⁰ However, the addition of IL-4 to synovial fibroblasts dramatically modulates their gene expression profile, which converges with that of fibroblasts from secondary lymphoid tissue.⁷⁰ The synovial environment in early RA may modulate fibroblast function leading to the production of

factors facilitating the formation of the lymphoid aggregates that characterise established RA.⁷¹

VERY EARLY THERAPY WITHIN THE FIRST 3 MONTHS OF SYMPTOMS

The first 12 weeks of symptoms represents a potentially important therapeutic window in patients with very early synovitis destined to develop RA. However, treating patients within this phase presents three challenges: (1) getting patients with symptoms of such short duration to clinic; (2) predicting which patients with very early synovitis will develop RA and thus require treatment; (3) determining how such patients should be treated.

Capturing patients with very early synovitis

Until relatively recently patients with RA were seen by rheumatologists many months after the onset of their symptoms. In the 1980s the median delay from symptom onset to referral to secondary care was over 20 months in a teaching hospital in Glasgow, UK.¹³ Over the last 20 years there has been a dramatic reduction in this delay; between 1994–97 the median time from symptom onset to GP referral was 4 months and from GP referral to hospital clinic appointment was 1 month.¹³ Nevertheless, most patients with RA are still seen in rheumatology clinics more than 3 months after the onset of symptoms. Using a variety of strategies, early arthritis clinics have facilitated access of patients with early synovitis to rheumatological care. In Austria, for example, a nationwide public information campaign encouraged patients with symptoms and signs of inflammatory arthritis to contact their primary care provider.⁷² In Birmingham, UK, and Leiden, Holland, approaches have focused more on the primary care providers, who have been targeted with regular letters highlighting the importance of early referral, and on workshops focusing on the recognition of early synovitis. In addition, the primary care teams have been provided with a rapid-access system through which patients are evaluated by a rheumatologist within 1–2 weeks of referral.^{73,74}

Distinguishing patients who will develop RA from those whose disease will resolve

The frequent spontaneous remission of synovitis in patients with symptoms of <3 months duration means that a therapeutic approach targeting all patients with very early synovitis will needlessly expose many patients to potentially toxic therapies. The ability to distinguish resolving disease from synovitis that persists and develops into RA is thus essential in the management of very early RA. Recently, a model has been developed using seven variables including clinical criteria and a range of autoantibodies to predict persistence in patients with synovitis of <2 years duration.⁷⁵ Each variable was ascribed a weighted score and the probability of persistence in an individual patient was determined by their total score. The maximum weights were given to sero-positivity for anti-cyclic citrullinated peptide antibody (anti-CCP Ab) and, perhaps not surprisingly, a symptom duration of >6 months. Similarly Emery's group showed that the best predictor of persistence in patients with synovitis of <1 year duration was a symptom duration of >12 weeks.⁷⁶ However, using disease duration to predict whether patients will develop RA is unhelpful if the aim is to treat patients within the first 12 weeks of symptoms. A number of studies have addressed the utility of measurement of anti-CCP Ab in the prediction of the development of RA.^{74,75,77,78} In patients with synovitis of 3 months duration, a combination of sero-positivity for rheumatoid factor (RF) and anti-CCP Ab had a specificity of 97%, with a sensitivity of 63%, for the prediction of the development of a persistent inflammatory arthritis fulfilling criteria for RA.⁷⁴ The very high specificity of this combination of autoantibodies is supported by data from Smolen et al.⁷⁹ The presence of anti-CCP Ab is also a predictor of severe disease.^{80,81} The presence of the anti-CCP Ab and RF in patients with very early synovitis can thus identify with very high specificity those who will develop RA and who are likely to have severe disease –

precisely the group in which one would want to intervene as early as possible. The relatively low sensitivity of the assay (approximately 60%) is of some concern. Relying on this autoantibody combination to define those who should be managed with early aggressive therapy will mean that a proportion of patients who will develop RA will be excluded from such therapy. Consequently a prognostic test with a higher sensitivity, whilst maintaining a very high specificity, remains an important goal.

How should very early patients be treated

Very few published studies have addressed the issue of therapy within the first few months of symptom onset. In a retrospective subgroup analysis of results from the FIN-RACo trial, patients were more likely to enter remission if single DMARD therapy (usually sulphasalazine) was started within 4 months of symptom onset compared with the later institution of therapy.⁸² In a prospective parallel group trial in which the observer, but not the treating rheumatologist or patient, was blinded to therapy, patients with very early RA (median disease duration 3 months) were compared with RA patients of longer duration disease.⁸³ Patients were treated with a DMARD once a diagnosis of RA was made, with the type and dose of DMARD being left to the discretion of the treating rheumatologist. Sulphasalazine monotherapy was the most frequent initial DMARD, with methotrexate monotherapy being the next most popular option. Patients with very early RA had a significantly greater reduction in disease activity and in the rate of radiological progression than patients in whom treatment was commenced later in the course of disease. Neither of these studies used very intensive remission inducing regimes. Two ongoing European placebo-controlled randomised trials (STIVEA and SAVE) are comparing the effects of low dose intramuscular depomedrone injections in patients with very early synovitis. The STIVEA trial is assessing the effects of 240 mg of depomedrone given over 3 weeks to patients with synovitis of <10 weeks duration. In the SAVE trial the effect of 120 mg depomedrone is being assessed in patients with synovitis of <16 weeks duration. The aim of these studies is to assess whether the early use of steroid can induce remission and the results are awaited with great interest. However, these studies target a broad range of patients many of whom will have had a self-limiting disease. Indeed it is an appreciation of the fact that up to 50% of patients with early synovitis will spontaneously enter remission that is likely to have limited the potency of the therapeutic approaches adopted to date in relatively unselected cohorts of patients with very early inflammatory arthritis.

An alternative approach to this problem is to target the subgroup of patients with very early synovitis who are at high risk of the development of RA with potent anti-inflammatory therapy. The choice of agent to be used within this phase of disease is currently the subject of much debate. There is a strong rationale for the short term use of anti-TNF- α therapy and high-dose steroid. TNF- α has pleiotropic effects driving the immune response occupying a central position in the inflammatory cascade, with a powerful modulatory effect on many aspects of cellular and humoral immunity.^{84,85} Indeed, data from our group suggests that macrophages, a significant source of TNF- α , are important in maintaining the transient persistence that characterises very early RA. Antagonism of this cytokine together with the pleiotropic effects of high dose steroid would provide a potent immunosuppressive regimen in very early disease. Recent studies have shown that targeting CD20 has good therapeutic effects in established disease⁸⁶ and it is tempting to suggest that this would also be a possible means to prevent the switch to chronic disease in early RA, because of the powerful diagnostic potential of RF and anti-CCP Ab. However, it is unlikely that the B cell alone is at the core of sustaining the disease process and it is likely that, if used, anti-B cell therapies would form part of a broader anti-inflammatory strategy. In addition, data from our group suggests that very early RA is associated with the presence of activated IL-2 producing T cells in the joint.²⁶ This raises the possibility that agents such as (a fusion protein

comprising the extracellular domain of cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and a fragment of the Fc domain of human immunoglobulin (Ig)1) which are of benefit in established RA⁸⁷, may also be useful in the very early phase of disease. Studies involving these agents within the first few months of symptoms will go some way to assessing whether the pathologically distinct nature of very early disease translates into a therapeutic window.

FUTURE DIRECTIONS

As the last 15 years have seen a move towards the introduction of DMARDs (singly or in combination) within the first year of disease, the next 5 years are likely to see studies assessing the effects of therapy within the first few months of symptoms. A desire to introduce therapy earlier in the course of disease will stimulate research into predictors of the development of RA in patients with very early synovitis in an attempt to improve on the sensitivities of current tests.

Studies in early disease have so far tested therapeutic strategies that have been found to be effective in established RA. The pathological mechanisms involved in the initiation of RA appear to be distinct from those driving the persistence of established disease. Defining these mechanisms in early disease will suggest multiple potential targets, which may include T cells, fibroblasts, macrophages and B cells. It is likely that the therapeutic potential of these targets will be tested in small scale pilot studies using robust short-term measures such as synovial tissue quantity and vascularity measured by high frequency ultrasound⁸⁸ and MRI.⁸⁹ Further assessment of candidate therapies that proved successful in initial pilot studies will need to include assessment of the long-term effects of treatment, including whether drug-free remission can be maintained.

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Practice points

- Once it is clear that a patient has developed rheumatoid arthritis (RA), disease modifying anti-rheumatic drug (DMARD) therapy should be introduced immediately. This controls synovitis and slows the rate of subsequent disease progression.
- Using anti-cyclic citrullinated peptide (CCP) antibody and rheumatoid factor (RF), it is now possible to predict with a very high specificity which patients with very early synovitis (within the first 3 months of symptoms) will develop RA. Consequently these patients can be targeted with anti-inflammatory therapies as soon as they present to clinic.
- Several studies suggest that the very early phase of disease (within 3 months of symptom onset) may be pathologically distinct from established RA. This pathologically distinct phase may represent a therapeutic window during which the disease is particularly amenable to anti-inflammatory therapies.

Research agenda

- Despite the very high specificity of the combination of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibody in predicting the development of rheumatoid arthritis (RA) in patients with very early synovitis, the sensitivity of this assay is limited (approximately 60%). Approaches to the prediction of outcome that improve on this sensitivity are required.
- Ongoing studies are assessing the effects of currently available anti-inflammatory therapies within the first 3 months of symptom onset.
- Defining the pathological mechanisms operating in very early RA may suggest novel potential targets.