Treatment of early rheumatoid arthritis

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Rheumatoid arthritis is common and leads to joint damage due to persistent synovitis. Aggressive treatment within the first few years after symptom onset, with either disease-modifying antirheumatic drugs or antitumor necrosis factor therapy, reduces the rate of disease progression. There is increasing interest in the concept that the first few months after symptom onset represent a pathologically distinct phase of disease and that this translates into a therap eutic window of opportunity during which it may be possible to switch off the disease process. The rationale for, and difficulties associated with, treatment within this window are discussed.

Keywords: anti-TNF therapy, DMARD, early arthritis, rheumatoid arthritis, synovitis, therapy

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Early inflammatory arthritis is remarkably common. 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 characterized 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 an early study, Scott and colleagues reported that more than half of RA patients recruited in the mid-1960s were either dead or severely disabled after 20 years [8]. This period of observation encompassed a time when treatment decisions in RA were guided by a 'pyramid approach', with nonsteroidal anti-inflammatory drugs (NSAIDs) being used as initial therapy, and disease-modifying antirheumatic drugs (DMARDs) being added later, usually after the development of erosive disease. Since the early 1990s there has been an important shift in the management of RA. This has involved the use of DMARDs, alone or in combination, and antitumor necrosis factor (TNF) therapy much earlier in the disease [9,10]. This review will focus on the rationale for this shift in therapeutic approach, the results of trials of early therapy and potential future developments in this area.

The rationale for early treatment

Bone erosion, an important feature of established RA, begins early in the course of disease and is due to active synovitis [11,12]. There is a clear relationship between the time-averaged extent of synovitis at a joint and the development of new erosions [13]. In a community-based cohort of patients with inflammatory arthritis (who typically have milder disease than patients in hospital-based cohorts), erosions were evident in the hands or feet in 36% of patients within the first 2 years of disease [14]. Bone edema on magnetic resonance imaging (MRI) is now recognized as a very early bone change in RA, occurring as a consequence of synovitis and preceding the development of erosions [15]. Bone edema was seen in 35% of the metacarpophalangeal joints of RA patients with a disease duration of less than 1 year [15]. In addition to this articular damage, accelerated cardiovascular disease is seen relatively early in the course of disease. In a community-based study, patients with rheumatoid factor (RF)-positive inflammatory arthritis, followed for a median disease duration of 6.9 years, had a significantly enhanced mortality, with cardiovascular disease being the most common cause of death [16]. The observation that joint damage and extra-articular disease occurs early in RA, and that the former, at least, is a direct consequence of active synovitis, led to the hypothesis that reducing the cumulative inflammatory burden to which patients are exposed by early aggressive treatment would reduce joint damage. In addition to this rationale for early treatment, there has been growing interest in the concept that the very early phase of RA may represent a window of opportunity – a period in which therapy has

an effect that is qualitatively superior to that which can be achieved at a later stage of disease. This may involve either resetting the rate of disease progression (which can be maintained at a slower rate once initial aggressive induction therapy is replaced with a less aggressive maintenance regimen) or switching the disease off altogether.

Does a therapeutic window of opportunity exist, and if so, how long does it last?

The answers to these questions are important. If such a window exists, patients should be treated within it. However, if the window is of very short duration (i.e., only a few months) two significant problems arise. Firstly, mechanisms need to be put in place to capture patients with very early synovitis. Secondly, patients with very early synovitis who will develop RA need to be distinguished from patients whose disease will resolve.

Until relatively recently patients with RA were seen by rheumatologists many months after the onset of their symptoms. In a teaching hospital in Glasgow, UK, in the 1980s, the median delay from symptom onset to referral to secondary care was over 20 months [9]. Over the last 20 years there has been a dramatic reduction in this delay; between 1994 and 1997 the median time from symptom onset to general practitioner (GP) referral was 4 months and from GP referral to hospital clinic appointment was 1 month [9]. Nevertheless, most patients with RA are still seen in rheumatology clinics more than 3 months after the onset of symptoms. Delays take place at one or more of the following levels:

- Initial presentation of the patient to the primary care provider
- Referral by the primary care provider after initial consultation by the patient
- Assessment in secondary care after referral from primary care

The introduction of early arthritis clinics, predominantly in the UK and mainland Europe, has facilitated access of patients with early synovitis to rheumatologic care by targeting one or more of these delays. In Austria, for example, a nationwide public information campaign encouraged patients with symptoms and signs of inflammatory arthritis to contact their primary care provider [17]. In Birmingham, UK, and Leiden, The Netherlands, approaches have focused on the primary care providers who have been targeted with regular letters highlighting the importance of early referral and 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 to 2 weeks of referral [18,19].

The frequent spontaneous remission of synovitis of less than 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. In one of the first studies to address this, a combination of seropositivity for RF and an erythrocyte sedimentation rate (ESR) of more than 30 mm/h in patients with symmetrical polyarthritis of 6 months' duration or less had a specificity of 94%, but a sensitivity of only 69%, for the development of persistent synovitis [1]. More 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 less than 2 years' duration [20]. Each variable was ascribed a weighted score and the probability of persistence in an individual patient determined by their total score. The maximum weights were given to seropositivity for antibodies to cyclic citrullinated peptide (anti-CCP Ab) and, perhaps not surprisingly, a symptom duration of more than 6 months. Similarly, the Leeds group showed that the best predictor of persistence in patients with synovitis of less than 1 year's duration was a symptom duration of more than 12 weeks [21]. However, using disease duration to predict whether patients will develop RA is unhelpful if one wants to treat patients within the first 12 weeks of symptoms. A number of studies have addressed the utility of measuring anti-CCP Ab for the prediction of the development of RA [19,20,22,23]. In patients with synovitis of 3 months' duration or less, a combination of seropositivity for RF and anti-CCP Ab had a specificity of 97%, with a sensitivity of 63%, for the prediction of a persistent inflammatory arthritis fulfilling criteria for RA [19]. The presence of anti-CCP Ab is also a predictor of severe disease [24,25]. The presence of anti-CCP Ab and RF in patients with very early synovitis can thus identify with high specificity patients who will develop RA and who are likely to have severe disease.

It is therefore possible to see patients very early (i.e., within the first 12 weeks of symptoms) and to predict who will develop RA. Is there any evidence that the pathology of very

early RA is different from later disease? If so, this provides a rational basis for a therapeutic window during which treatment might be curative. If not, 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 induce this effect. Despite the importance of this question, little work has been done on the pathologic correlates of a potential therapeutic window. An important contribution to the understanding of early synovial lesions was made in the 1970s by Schumacher and Kitridou [26]. Synovial biopsies were taken from 24 patients with a disease duration of less than 2 months. Nine of these turned out to have transient, self-limiting synovitis, and six developed RA. In all six RA patients, vascular changes were prominent with widespread congestion and erythrocyte extravasation. In addition, varying degrees of lymphocyte infiltration and lining cell proliferation were seen, although the nature of the synoviocytes making up the expanded lining layer was not fully investigated. Whilst lining cell hyperplasia was not generally as prominent in patients with self-limiting arthritis as in very early RA, there were no clear differences between the synovium of patients in these groups using conventional hematoxylin and eosin staining. In another study comparing RA patients with disease of less than 1 year's and more than 5 years' duration, no differences were seen in the levels of expression of interleukin (IL)-1β, TNF-α or IL-6, or infiltration with $CD4^+$ cells, $CD8^+$ cells, $CD22^+$ B-cells, $CD38^+$ plasma cells, mast cells, macrophages or fibroblasts [27]. Subgroup analysis suggested that there were no differences between patients with a disease duration of less than 6 months and patients with a disease duration of 7 to 12 months, although it remained unclear whether there were differences between patients with very early synovitis (<3 months) and established disease. The authors have studied 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 less than 12 weeks' duration [28]. 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, -4, -13, -15, basic fibroblast growth factor and epidermal growth factor) were significantly elevated in these patients, within 3 months of 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 early RA was transient and was not seen in established RA patients or after the first few months in patients with early RA. The first 3 months of symptoms in RA thus represents a biologically distinct phase of the disease, an observation which supports the concept that this phase may represent a well defined therapeutic window.

The treatment of early disease

The effects of early aggressive DMARD & steroid therapy

Initial clinical trials of early therapy were designed without clear consideration of whether the pathology of early RA differed from that of established disease. Thus the time frames, or potential windows of opportunity, chosen to test are sometimes much broader than the authors' recent study of the pathology of very early RA would suggest was appropriate [28]. Most trials of early therapy have chosen a maximum symptom duration of 1 year, with some adopting even longer cut offs (up to 3 years). Therapeutic approaches adopted to date, and studied within these time frames, have included intra-articular and systemic steroids, DMARD monotherapy, DMARD combination therapy, monotherapy with anti-TNF agents and combination therapy with anti-TNF agents; these approaches being compared with a less aggressive approach to treatment.

Early studies compared the pyramid approach in early RA with early DMARD introduction [29,30]. A Dutch study assessed outcomes in patients with RA of less than 12 months' duration who were randomized to receive therapy with either NSAID, hydroxycholoroquine, 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 ESR. In the early 1990s, attention moved from whether patients with RA of less than 1 to 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 of time and whether after initial induction therapy the intensity of treatment could be reduced with the benefits of initial rapid disease control being maintained. The landmark COmbinatietherapie Bij Reumatoide Artritis (COBRA) trial explored this 'step-down bridge' approach [31]. In this study, combination therapy was compared with

sulfasalazine monotherapy (2 g daily) in patients with RA of less than 2 years' duration (median duration: 4 months). Patients in the combination group were treated with oral prednisolone (initially at 60 mg daily tapered in 6 weekly steps to 7.5 mg daily, then discontinued after 28 weeks), oral methotrexate (7.5 mg weekly then discontinued after 40 weeks) and sulfasalazine (2 g daily). Patients treated with combination therapy had a significant improvement in disease activity compared with the monotherapy group. However, the difference between groups was only apparent while the steroid was being given; disease activity in the groups converged once steroid had been withdrawn. Nevertheless, the difference in cumulative disease activity between the groups was associated with less radiologic deterioration in the combination group over the 56 weeks of the trial. The FINnish Rheumatoid Arthritis Combination therapy (FIN-RACo) trial compared a combination regimen that was maintained over the study period with monotherapy in patients with RA of less than 2 years' duration (mean duration: 8 months) [32]. This trial compared sulfasalazine (initially 1 g daily, increased if necessary to 2 g daily), methotrexate (initially 7.5 mg weekly, increased if necessary to 10 mg weekly), hydroxychloroquine (300 mg daily) and low-dose prednisolone (5 mg daily) used in combination against sulfasalazine alone (2 g daily, increased if necessary to 3 g daily). A total of 37% of patients who received combination therapy were in drug-maintained remission after 1 year, compared with 18% of patients on monotherapy. In addition, there was significantly less atlanto-axial disease in the combination therapy group at 2 years [33]. Similarly, in another study of RA of less than 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 [13].

However, not all studies showed a benefit from early combination therapy. A study of patients with RA of less than 12 months' duration and with poor prognostic indicators, compared a combination of methotrexate, ciclosporin A and intra-articular steroid with sulfasalazine alone [34]. Whilst 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 (likely related to the higher initial use of steroid in this group), by week 48 there was no significant clinical or radiologic difference between groups. Similarly, a study of patients with RA of less than 12 months' duration showed no benefit of a combination of methotrexate and sulfasalazine when compared with each treatment alone [35].

In conclusion, in many studies of patients with RA of less than 1 to 2 years' duration, initial combination DMARD therapy leads to better control of disease and a reduction in the progression of erosions compared with monotherapy. Those studies that have shown benefit from early combination therapy have used steroids, albeit in different regimens [13,31,32]. However, the precise role for steroids in early RA remains to be determined. Steroids certainly allow a more rapid control of synovitis than conventional DMARDs, explaining their incorporation in step-down regimens. The use of steroid in the medium- to long-term, however, remains controversial. Whilst Kirwan and colleagues have suggested that oral steroid reduces the risk of development of erosions in patients with early RA [36], data from the West Of Scotland Early Rheumatoid Arthritis Corticosteroid Therapy (WOSERACT) study does not support this [37]. These studies themselves raise two important questions. Does therapy within the first 1 to 2 years of disease reset the rate of subsequent disease progression, and is the rate of disease progression persistently slowed if the aggressive therapy is withdrawn?

The long-term articular effects of early aggressive therapy

A 5-year follow-up of patients in the COBRA trial showed that an intensive 6 months of combination therapy resulted in a sustained suppression of the rate of radiologic progression independent of subsequent antirheumatic therapy [38]. Similarly, 5-year follow-up of patients in the FIN-RACo study showed that the early use of combination DMARD therapy reduced the rate of radiologic 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 [39]. In addition, the cumulative duration of work disability was significantly lower after 5 years in the combination therapy group in the FIN-RACo study [40].

In contrast, several studies have not shown a long-term benefit of initial combination therapy. The 5-year follow-up of patients in the study of van der Heide and colleagues failed to show a significant difference in radiologic progression

between early DMARD therapy and the pyramid approach to treatment [41]. However, in this 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 to clinical effects at 5 years. In addition, a follow-up of the study of Dougados and colleagues showed no structural benefit at 5 years after initial therapy with the methotrexate and sulfasalazine combination when compared with either drug used as monotherapy [42]. However, this is perhaps not surprising as there was no advantage of this combination therapy even at 1 year. Thus, combination DMARD therapy within the first 2 years of disease may slow the rate of disease progression compared with monotherapy but it certainly does not switch the disease off.

Anti-TNF therapy in early RA

There is increasing interest in the treatment of early RA with anti-TNF drugs. Trials published to date have looked at patients with disease of up to 3 years' duration, although ongoing studies are assessing the effects of these drugs at an earlier stage. In patients with active RA of 3 years' duration or less, the use of twice-weekly subcutaneous etanercept led to a significant improvement in disease activity over the first 6 months and a significant slowing in the rate of development of erosions compared with the effect seen with methotrexate therapy [43]. In a 2 year, open-label extension to this study, in which patients continued to receive the therapy to which they had been randomized, there were fewer erosions in the etanercept group compared with the methotrexate group [44]. Whilst this study demonstrated that etanercept was superior to methotrexate in early RA, recent data from the Trial of Etanercept and Methotrexate with radiographic Patient Outcomes (TEMPO) has shown that methotrexate plus etanercept is superior to etanercept alone in reducing disease activity and joint damage [45]. However, TEMPO included patients with a disease duration of up to 20 years and the effect of methotrexate plus etanercept in early RA has not been studied. A post hoc subgroup analysis of patients with RA of 3 years' duration or less in the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) study showed that infliximab combined with methotrexate reduced the rate of structural damage when compared with the placebo plus methotrexate combination [46]. A similar conclusion was drawn from the recent Active-controlled Study of Patients Receiving Infliximab for the treatment of Rheumatoid arthritis of Early onset (ASPIRE), which only included patients with disease of 3 years' duration or less [47]. In this study, therapy with methotrexate plus infliximab was associated with significantly reduced radiologic progression and improved disease activity and physical function compared with methotrexate alone. The effects of adalimumab have also been assessed in patients with RA of less than 3 years' duration in the Premier study [48]. To date, results have been published only in abstract form but suggest that the combination of adalimumab and methotrexate is associated with significantly reduced disease activity when compared with either therapy alone throughout the 2 years of the study [48]. The observation that a more potent therapeutic approach, antagonizing TNF within the first 3 years of symptoms, leads to better disease control is important but perhaps not surprising.

The antagonism of TNF-α earlier in disease is only now being studied. Emery and colleagues have addressed this issue in a pilot study of five patients with poor prognosis RA and a disease of less than 1 year's duration (mean: 7 months) [49]. 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). This suggested that within this time frame the introduction of anti-TNF therapy would not switch off disease. Nevertheless, this issue needs to be formally addressed and studies are underway to do this.

Initial combination versus step-up therapy

Whilst much current data suggests that early combination therapy is better than monotherapy, a recent survey of UK rheumatologists revealed that only 2% would use combination DMARD therapy in the management of a newly presenting RA patient [Wilson J, Pers. Commun.] [50]. Many adopted a step-up approach, using combination therapy if synovitis was not controlled with initial DMARD monotherapy. The BeSt trial comparing monotherapy, with step-up therapy, with step-down therapy, with early anti-TNF-α use addresses this issue [51]. Patients with RA of less than 2 years' duration were treated with sequential monotherapy (methotrexate, followed by sulfasalazine followed by leflunomide), or step-up therapy from methotrexate (with the sequential additions of sulfasalazine and then hydroxycholroquine), or step-down therapy (methotrexate plus sulfasalazine

plus prednisolone 60 mg tapered to 7.5 mg), or methotrexate plus infliximab. Although currently reported only in abstract form, results suggest that initial treatment with combination therapy or with methotrexate plus infliximab lead to a significantly greater and more rapid reduction in disability, as well as significantly less radiologic damage than sequential monotherapy or step-up therapy. Publication of results from this trial is awaited with interest.

The effects of very early therapy

The trials of early therapy discussed thus far have included patients with RA of up to 1, 2 and even 3 years' duration. However, the window within which early RA is distinguishable from established RA at a pathologic level is much shorter than this. Few published studies have addressed the issue of therapy within the first few months of disease. In a retrospective subgroup analysis of results of the FIN-RACo trial, patients were more likely to enter remission if therapy was started within 4 months of symptom onset compared with later therapy [52]. 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 disease duration [53]. Patients were treated with DMARD once a diagnosis of RA was made, the type and dose of DMARD being left to the discretion of the treating rheumatologist. Sulfasalazine 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 radiologic progression than patients in whom treatment was commenced later in the course of disease. However, the criteria by which patients were diagnosed as having RA in the very early group were unclear and interpretation of the data are complicated by the fact that the rate of spontaneous remission will be higher in patients with early inflammatory arthritis compared with patients with synovitis of longer disease duration. Ongoing randomized trials are comparing the effects of intramuscular depomedrone injections with placebo within the first 3 months of symptoms. It is anticipated that the effects of anti-TNF therapy will also be assessed within this window in patients at very high risk of the subsequent development of severe RA. These studies will go some way to assessing whether the pathologically distinct nature of very early disease correlates with a therapeutic window.

Early treatment & mortality

Mortality secondary to accelerated cardiovascular disease is increased in patients with established RA [54–56]. The mechanisms underlying this are unclear, although it is likely that the systemic inflammatory response accelerates atherogenesis by accentuating established and novel risk factor pathways [57]. An effect of systemic inflammation on the vascular endothelium may play an important role. Endothelial dysfunction is an early event in atherosclerosis. Patients with RA have evidence of endothelial dysfunction [58] and this is reversed with anti-inflammatory therapies, as has previously been shown for vasculitis [58,59]. Treating patients with RA earlier and more aggressively with anti-inflammatory therapy may thus reduce their atherosclerotic burden. Circumstantial support for this comes from a study that showed that mortality amongst RA patients who presented early was lower than in those who presented late [60]. In addition, patients with severe RA who responded to methotrexate had a significantly lower mortality than patients in whom disease control was not achieved [61]. The extent to which inflammation needs to be controlled in order to eliminate or reduce the inflammation-associated cardiovascular risk in RA remains uncertain but it is likely that the early and tight control of synovitis will reduce the enhanced cardiovascular mortality associated with RA. In addition to the control of joint disease, the treatment of comorbidity, and lifestyle interventions, are important in the prevention of cardiovascular disease. These include the cessation of smoking, the introduction of an exercise programme (which may benefit the joints as well as the cardiovascular system [62]) and the active management of hypertension and dyslipidemia. Statins are widely used for the control of dyslipidemia. In addition to their lipid-lowering properties these drugs have potent anti-inflammatory effects in animal models [63–65] and reduce disease activity in RA [66]. Although not assessed in early disease, their use at this stage may reduce cardiovascular risk and control synovitis; this warrants investigation.

From clinical trials to clinical reality: comorbidity, compliance & cost

The applicability of results from clinical trials to clinical practice is often limited by the design of the trials [67]. Exclusion criteria adopted in clinical trials are an important example of this. Thus, most early arthritis trials have excluded

patients with serious comorbidity [31,32,43] and patients who the investigators suspected would be unable to comply with study protocols [31,32]. At Vanderbilt University fewer that 20% of consecutive RA patients were eligible to take part in trials over a 15-year period [68]. Although combination DMARD therapy has not been shown to be associated with greater toxicity than monotherapy in early RA, the exclusion of patients with significant comorbidity (which is common in early RA [69]) and of patients regarded as being unable to comply with polypharmacy may have contributed to this effect.

Many of the drugs used in early RA, such as anti-TNF agents, are expensive; in many healthcare environments their use will need to be justified on economic grounds. The early use of a drug that switches off disease and converts a chronic illness into a curable one will have a favorable health economic profile even if the drug is very expensive. Although the subject of active investigation, there is no current evidence for such an effect of very early therapy. A second scenario, in which an expensive induction regimen that allows the maintenance of remission with less expensive drugs may also be cost beneficial. In this case, direct short-term costs need to be weighed against potential reduced direct long-term costs (e.g., reduced rate of joint replacement surgery) and reduced indirect long-term costs (e.g., reduced productivity loss by patients and carers).

Outlook

As the last 15 years has seen a move towards the introduction of DMARDs (singly or in combination) within the first year of disease, the next 5 years are likely 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 early synovitis in an attempt to improve on the sensitivities of current tests, which stand at about 60%.

Even with potent biologic agents, an American College of Rheumatology (ACR)50 response is currently only obtained in approximately 50% of patients within the first 3 years of disease. The prediction of response to therapy, allowing treatment to be targeted to those likely to respond, is thus an important research goal. For example, the response to etanercept in patients with RA of 3 years' duration or less has recently been shown to be influenced by genetic variation in the HLA-DRB1 region [70]. Patients with two copies of the shared epitope were significantly more likely to achieve an ACR50 response at 12 months (odds ratio: 4.3; 95% confidence interval: 1.8–10.3). In addition, two extended haplotypes which included HLA-BRB1 alleles *0404 and *0401 (both of which encode the shared epitope) and six single nucleotide polymorphisms in the lymphotoxin α-TNF region were associated with a particularly favorable response to treatment [70].

Studies in early disease have so far tested therapeutic strategies that have been found to be effective in established RA. The pathologic 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 that 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 ultrasound [71] and MRI [72], which are more sensitive to change than joint scores derived from plain radiographs. Further assessment of candidate therapies successful in initial pilot studies will need to include clinically relevant outcomes such as measures of pain and disability as well as an assessment of the long-term effects of therapy on end points such as cardiovascular mortality.

Highlights

- Rheumatoid synovitis causes joint damage and this commonly occurs within the first year of disease.
- Tight control of synovitis with disease-modifying antirheumatic drugs (DMARDs) or anti-tumor necrosis factor (TNF) therapy within the first few years of disease reduces the rate of progression of damage.
- It is now possible to predict, within the first few months of symptoms, which patients will progress to develop rheumatoid arthritis (RA).
- It has recently been shown that the first few months of symptoms represent a pathologically distinct window in the development of RA.
- Studies are underway to assess whether this pathologically distinct window represents a phase during which therapy can switch off disease.

Conflicts of interest

Karim Raza holds a research grant funded by Wyeth and has been paid honoraria by both Wyeth and Pfizer. Christopher D Buckley holds a research grant funded by Wyeth and has been paid honoraria by Wyeth, Schering Plough and Celltech.

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