Review

The Michael Mason prize: early rheumatoid arthritis—the window narrows

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Abstract

RA is a chronic disease in which synovitis drives joint destruction. Immunomodulatory therapy in the established phase of disease limits synovitis, and slows the rate of joint destruction, but is not curative. Increasing evidence suggests that the very early phase of RA, within the first few months after the onset of symptoms, represents a pathologically distinct and temporally transient window during which outcomes can be more effectively modulated by therapy. Furthermore, recent data show that we can accurately predict the development of RA in patients with very early synovitis, using clinical and serological measures. This makes very early targeted treatment a realistic possibility. However, it remains the case that the majority of patients with very early synovitis delay for prolonged periods before seeking medical help. Effective public engagement, to reduce this delay, is the key to translate advances in the fields of pathology, prognostication and therapy into benefit for patients with new onset RA.

Key words: Rheumatoid arthritis, Early synovitis, Joint aspiration, Anti-citrullinated protein/peptide antibody, Cytokines, Apoptosis, Prediction, Outcome, Delay, Help-seeking behaviour.

Introduction

‘The earlier the better’ is a principle applied almost universally by physicians in the context of the initiation of therapy. In oncology, early disease is widely recognized to be qualitatively and quantitatively different from late disease. The smaller tumour burden, and the fact that mechanisms allowing metastatic spread may not yet have developed, mean that clinical outcomes, including the likelihood of cure, dramatically improve the earlier therapy is commenced. For cancer this is recognized not only by clinicians but is also firmly embedded in the psyche of the general population and is championed by the Department of Health whose targets make early access to therapy a key priority.

It is now clear that articular outcomes in RA, including the development of bone and cartilage destruction, are determined by a simple formula: disease activity over time equals damage. For many years, rheumatologists have recognized that a reduction in cumulative inflammatory burden associated with early therapy may limit both articular and extra-articular manifestations of RA [1–4]. Furthermore, recent studies have provided tantalizing insights into the concept that very early RA may be qualitatively as well as quantitatively different from late RA with the rate of long-term disease progression being reset with a short course of early intensive therapy [1, 5–7]. Indeed, the first 3 or 4 months after the onset of symptoms may well represent a distinct therapeutic window [8]. Understanding the pathobiological processes operating during this phase of disease is thus a key goal. Achieving it will shed light on new therapeutic targets and strategies, and will lead to new approaches in predicting the development of RA in patients with early synovitis [1, 9].

Pathogenic mechanisms in very early RA

Physiological inflammation is not a stable state. During the early stages of a local inflammatory response, large numbers of leucocytes 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 which leads to apoptosis and 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 [10]. In chronic inflammation, this resolution phase becomes disordered and fibroblast activation and hyperplasia contribute to the persistence of the inflammatory infiltrate [11–15]. In synovium from patients with established RA, infiltrating lymphocytes are frequently organized into microstructures that resemble the lymphoid aggregates found in secondary lymphoid organs [16]. The chronically inflamed rheumatoid synovium is, therefore, a highly stable microenvironment that inappropriately mimics many of the structural and functional features of lymphoid tissue [17].

The mechanisms underlying the maintenance of persistent inflammation have been relatively well defined. Fibroblast-derived IFN-β, for example, mediates T-cell survival by up-regulating levels of the anti-apoptotic mitochondrial protein Bcl-XL [13]. 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+ T cells to CXCL12 (SDF-1α; produced by synovial fibroblasts) renders T cells less susceptible to apoptosis induced by anti-CD3 stimulation [18] as well as to cytokine deprivation-induced apoptosis [19]. Furthermore, fibroblasts inhibit neutrophil apoptosis via IFN-β [20] and GM-CSF [21], and also keep B cells alive through contact-dependent interactions involving VCAM-1/CD106 [22]. Although the inhibition of lymphocyte apoptosis by stromal cells at sites of chronic inflammation contributes to lymphocyte accumulation, it cannot be the only mechanism, because cells should be able to leave even if their death is inhibited. In fact, work from our group and others suggest that inflammatory cells are actively retained in the joint by stromal-derived chemokines, including CXCL12 [15, 23]; in the context of T cells, this is facilitated through the up-regulation of the chemokine receptor CXCR4 by stromal-derived TGF-β [15]. Rheumatoid synovial fibroblasts are themselves activated through a number of mechanisms. These include cytokines derived from infiltrating inflammatory cells, such as TNF-α and IL-17 [21], but importantly also through the engagement of toll-like receptors, integral components of the innate immune response [24]. This, to a certain extent, explains why anti-inflammatory therapies used when the disease is established, and the fibroblast layer expanded, do not eliminate the 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 IA steroid injections to thoracic-duct drainage [25–27]. However, eventually the leukocytes return to repopulate the hyperplastic stromal environment and there is a recurrence of symptoms associated with this.

Is the pathology of very early RA, within the first few months of symptom onset, different from that found in later disease? Despite the importance of this question, little work has been done in this area. Seminal work from Schumacher’s group in the 1970s spearheaded the study of the synovium in patients with synovitis of only a few months’ duration, though methodologies available to study immunopathological mechanisms were limited at the time [28, 29]. More recently, in work from the Amsterdam Medical Centre, RA patients with symptoms of <1 year’s duration have been compared with patients with longer standing disease. Immunohistological analysis of the synovium, including an assessment of expression of IL-1β, TNF-α and IL-6, as well as infiltration with CD4+ and CD8+ cells, CD22+ B cells, CD38+ plasma cells, mast cells, macrophages and fibroblasts did not reveal any differences between early (mean disease duration 6 months) and long-standing RA [30]. In addition, subgroup analysis comparing histological scores in patients with a disease duration of <6 months, and those with a disease of 7–12 months’ duration did not yield any statistically significant differences. However, it remained unclear whether there were differences between patients with very early synovitis and established disease. In another study, expression of IFN-γ, IL-10 and IL-12 mRNA in SF mononuclear cells was also similar between 11 early RA patients [median disease duration 10 (range 6–31) weeks] and 11 patients with established RA [median disease duration 14 (range 3–39) years] [31]. However, difficulty accessing patients with very short symptom durations and in obtaining biological material from small joints, which are typically involved early in RA, have hampered research in this area.

In Birmingham, we have addressed these issues by actively engaging with primary care to facilitate rapid patient referral and developing minimally invasive ultrasound guided approaches to collect SF [32] from the earliest clinically apparent lesions. Using these approaches, we have shown that the first 3 months after the onset of symptoms represents a pathologically distinct and temporally transient phase of the disease, characterized by a cytokine profile that is different from that in established RA and other very early synovitides [33]. The role of these characteristic cytokines in early RA is unclear but certain cytokines (e.g. fibroblast growth factor and epidermal growth factor) may contribute to the expansion of the stromal network that mediates the persistence of inflammation and drives joint destruction. Other cytokines (e.g. IL-2, -15, G-CSF and GM-CSF) may inhibit leucocyte apoptosis which is a characteristic of the very early rheumatoid lesion [34]. In addition, a number of chemokines [CCL2 (MCP1), CCL3 (MIP1-α), CCL4 (MIP1-β) and CCL5 (RANTES)] were identified in the very early rheumatoid lesion that may contribute to the recruitment of monocytes and lymphocytes [33]. There remains a pressing need to define the cellular sources of these cytokines and chemokines, and the pro-inflammatory and pro-fibrotic mechanisms operating in the rheumatoid joint within the first few months of symptom onset. The development of minimally invasive ultrasound guided approaches to the collection of tissue [35] represents an important advance in this area and this

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approach is now being used by several groups to study tissue from patients at the earliest clinically apparent phase of disease.

**Prediction of the development of RA in patients with very early synovitis**

Prediction of the development of RA in patients with very early synovitis is essential to allow early targeted therapy. Although the biological characteristics operating within the joint have helped elucidate mechanisms of disease, they have not, as yet, contributed significantly to predictive algorithms. The inhibition of leucocyte apoptosis is a generic feature of all early synovitis destined to persist rather than a specific feature of early RA per se [34]. The distinctive cytokine profile may prove to be useful in routine practice, but in patients reported to date it appears to be a feature of those who are anti-citrullinated protein/peptide antibody (ACPA) positive [33], and it is unclear whether the profile is seen in ACPA-negative RA. We, and subsequently others, have shown that sero-positivity for RF and ACPA is highly specific for the development of RA in patients with synovitis of <3 months’ duration [36, 37]. However, the sensitivity of this combination is low and a more accurate test is needed. Recently, this has become available in the form of a predictive algorithm developed in Leiden [38] and validated in cohorts of patients with early undifferentiated arthritis from Birmingham, Leiden and Berlin [39]. Principles established in other inflammatory diseases and cancer suggest that the incorporation of variables derived from understanding pathogenic mechanisms into these clinical algorithms will allow them to be refined and increase their accuracy in the prediction of both diagnostic outcome and disease severity [40, 41]. Nevertheless, we can currently accurately predict, in a proportion of early synovitis patients, those who will develop RA and are increasingly able to identify pathogenic mechanisms operating at the earliest stages of disease. This opens the way for clinical trials in selected patient groups to test the ability of early targeted interventions to significantly modulate the course of disease.

**Accessing patients with very early synovitis**

Patients will only benefit from these important advances if they present to medical attention early, and it is crucial that we do not overlook this as we further our understanding of pathobiology and therapy in very early RA. Data from our group, and subsequently others, highlight that patients with a new onset of RA delay for an average of 3 months before seeing their general practitioner [42, 43]. The reasons for this are illuminating but depressing. In a recent study, many patients reported that they did not know anything about RA at the time of symptom onset, did not recognize that their symptoms were indicative of a potentially serious underlying pathology and were unaware of the need for, and benefit of, early treatment [44]. Interestingly, certain demographic characteristics are associated with longer delay. For example, patients of South Asian origin delay in seeking advice for longer periods than patients from other ethnic backgrounds [45], a finding that has been reported in other diseases [46]. The rheumatological community now needs to effectively communicate the fact that RA is not a benign disease and ensure that patients with new onset synovitis are equipped with the knowledge to make appropriate decisions about seeking medical help in order to benefit from the huge and ongoing clinical and scientific advances in the field of very early RA.

**Rheumatology key messages**

- The first symptomatic months represent a pathologically distinct phase of RA and a potentially important therapeutic window.
- Useful algorithms exist to predict the development of RA in patients with early synovitis.
- Delay in seeking medical help remains an important barrier to early intervention for RA.

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