

Introduction

The science of rheumatoid arthritis: a prelude

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Published: 16 March 2005

Arthritis Res Ther 2005, **7(Suppl 2)**:S1-S3 (DOI 10.1186/ar1720)
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With respect to research advances, rheumatoid arthritis (RA) has evolved from being largely neglected about a dozen years ago to being one of the most fascinating diseases in medicine. There are a variety of reasons for this metamorphosis, mostly related to renewed interest in studying the many biological facets of the disease, to developments in clinical and basic research, and to stimulation by the results obtained. First, RA develops as a combination of an inflammatory process – synovitis – with a ‘semimalignant’ event, namely the transgression of tissue boundaries characteristic of this erosive disease; although the full details of this transformation remain enigmatic, some important aspects have been elucidated [1,2]. Second, RA involves an autoimmune component, the role of which in the pathogenic cascade is at least a disease-aggravating one [3,4], although this is yet to be sufficiently clarified. Autoimmunity frequently precedes the development of clinical symptoms by many years [5], suggesting an essential or at least closely associated role in pathogenesis, but there is also a slow evolution of the disease through states of ‘pre-arthritis’ and ‘very early arthritis’. Third, novel, validated and reproducible techniques have been developed and used to assess changes in clinical variables and progression of joint destruction [6,7]. Fourth, even though RA is presumably an incurable disorder and traditional disease-modifying antirheumatic drugs, which slow the progression of RA, usually have limited efficacy in established disease [8], these agents appear to be highly effective in very early RA, suggesting that there exists a window of opportunity during which disease can be controlled in many patients [9]. Finally, RA has been a major area for investigations into the efficacy and safety of innovative therapies that target particular cell surface, cell secreted and intracellular molecules [10]. This has not only permitted new treatment options to be realized in clinical practice but it has also yielded insights into the enormously complex pathogenesis of the disease.

Treatment of RA has undergone dramatic changes with the widespread application of sufficiently high doses of methotrexate [11,12] and with the remarkable efficacy of a

biological agent targeting tumour necrosis factor (TNF) [1,13]. Long-term prognosis in RA depends on interference with the destructive process, because over time increasing damage will result in greater functional loss [14]. In this respect the TNF blockers appear to have even greater efficacy in retarding the process of erosion than their effect on clinical abnormalities reflecting synovitis [15,16]. The initial findings on the efficacy of TNF inhibition not only have encouraged the development of additional TNF blockers for use in RA, but they have also stimulated studies in other chronic inflammatory disorders, many of which yielded highly positive results.

TNF blockade represents an important advance but it is not the ultimate solution to RA therapy, which has stimulated further research into other potential molecules involved in RA pathogenesis and clinical trials targeting such molecules. Evidently, other proinflammatory cytokines, such as IL-1 and IL-6, are such targets. An IL-1 antagonist, anakinra, is already approved, although its efficacy appears to be less than that of TNF blockade [17]; other IL-1 blockers are currently being tested. Phase II trials of an IL-6 blocker, tocilizumab, have also been conducted [18]. Given the autoimmune basis of RA, which is manifested by the production of rheumatoid factor and other autoantibodies and by their association with disease severity, B cells also represent a potential target; in fact, rituximab (anti-CD20) has also proven to be efficacious in phase II trials [19].

A novel therapeutic principle is discussed in this supplement to *Arthritis Research & Therapy*, namely modulation of co-stimulation. Co-stimulation, as detailed in the three reviews in the supplement, is an essential step in the induction of the adaptive immune response, which centres around T cell activation. T cells have long been regarded as essential in the initial phases of RA. However, despite evidence of lymphokine production, even in established disease [20], failure of some T-cell directed therapies to improve long-standing RA [21], as well as the profound efficacy of agents targeting proinflammatory cytokines mostly produced by non-T-cells

such as TNF, suggested that T cells play no or only a minor role in perpetuating the disease. Skapenko and coworkers (pp S4-S14) revisit the importance and various aspects of the role played by T cells in RA.

The apparent efficacy of interference with co-stimulation using CTLA4-Ig (cytotoxic T lymphocyte-associated antigen 4-immunoglobulin; abatacept) [22] has restored T cells to a central position in RA, even late RA. The detailed consequences of blocking the interaction between CD80/86 and CD28 in RA still require study, in particular because co-stimulatory pathways other than CD28-mediated ones remain unaffected. The effects of modulating co-stimulation might involve reduction in the intercellular crosstalk that is needed for the activation of macrophages and other cell populations [23] as well as reduction in B-cell activating capacity, directly by interfering with T cell help or via induction of regulatory T cells, which appear to be deficient in RA [24]. Malmström and coworkers (pp S15-S20) discuss the importance of co-stimulation and the possible consequences of its modification.

As Ruderman and Pope review (pp S21-S25), clinical responses to abatacept in phase II and phase III trials were similar to those with other biological agents such as the TNF blockers, rituximab and tocilizumab. Trials with these agents found a large number of American College of Rheumatology (ACR) 20 responders, a fair number of ACR 50 responders and relatively few true remissions. Because the biologics target different molecules (various proinflammatory cytokines, a B-cell surface molecule [CD20] and a co-stimulatory molecule expressed on T cells), these are interesting results. Does this mean that many targets are of equal importance? Does it mean that we can eliminate one element of the 'inflammatory house of cards' [10], consistently having some effect but rarely with full collapse of the inflammatory process? What does this tell us about the pathobiology of RA?

Another interesting observation is the importance of combining biological agents with methotrexate; for most biologics such combination therapy is superior to either agent alone. What is the role played by methotrexate in this context? Does it merely change the pharmacokinetics of biological compounds or does it have a synergistic effect? Despite the enhancement in effect yielded by combination with methotrexate, even better responses would be welcome; could a combination of two biological agents (with or without methotrexate) more frequently result in remission or even cure? Could abatacept – which, as Ruderman and Pope reveal, is also efficacious in patients who fail to respond to TNF blockers – represent a major component of such combination therapy? These are questions that must be addressed in future trials.

It is generally gratifying to witness the emergence of new treatment principles from theoretical indications to reality –

from the realm of basic sciences to successful clinical trials showing efficacy and safety, and subsequently to clinical practice and long-term use. This has been especially so for RA, a disease with frequently devastating and long-term consequences for those affected, whose fate has already improved significantly over recent years and will hopefully improve further. However, this is also true for many other immuno-inflammatory disorders, in which innovative therapies were pioneered by advances made in our field.

Competing interests

JSS is on the Advisory Boards of Centocor/Schering-Plough, Abbott, Wyeth, Bristol-Myers Squibb, Roche and UBS.

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