

Current and Future Management of Inflammatory Arthritis

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This talk will focus on Rheumatoid Arthritis (RA), which is the most common form of chronic inflammatory arthritis. There is considerable disease heterogeneity in RA, the basis of which is not well understood, but this fact confounds clinical practice and research. RA is a systemic disease and manifestations such as fatigue and anaemia are common. However, synovial joints are usually the most dramatically affected site in RA and bear the brunt of a sustained inflammatory response. This causes chronic joint pain and stiffness and may eventually lead to joint damage and destruction, with associated disability for the patient. RA is also associated with co-morbidities such as osteoporosis, vasculitis, atherosclerosis and lymphoma. More severe RA reduces life expectancy, largely due to accelerated atherosclerosis (1). RA is often associated with depression, family and social dysfunction and work disability. In Australia, it is estimated that direct and indirect costs of RA exceed \$3.2 billion annually.

RA is thought to be an immunologically mediated disease. Genetic analysis shows the major association of RA is with the major histocompatibility (MHC) region. However, to date RA has evaded simple immunological explanation and RA has features suggesting involvement of both the innate and adaptive immune systems. RA is associated with certain MHC Class II alleles, but the antigen(s) presented to CD4+ T cells is unknown. Rheumatoid factor is an autoantibody, but recognises the Fc region of immunoglobulin, rather than a joint specific antigen. Recently, antibodies to peptides containing post-translationally modified amino acids have been found in RA. These modified proteins might be generated at sites of inflammation and therefore be recognised as foreign by the immune system, perhaps providing a link between inflammation and autoimmunity. In contrast to continuing controversies in understanding the role of adaptive immunity in RA, a great deal is now known about the synovial microenvironment in RA. RA is associated with a mixed leucocytic infiltrate into the synovial lining and joint space, widespread cellular activation, tissue damage and tissue remodelling. There is sustained over-production of an array of inflammatory and destructive mediators, including eicosanoids, cytokines, chemokines and metalloproteinases (2,3).

Current pharmacological therapy for RA largely evolved empirically and has typically been evaluated in patients with established disease. Non-steroidal anti-inflammatory drugs provide short term relief from inflammatory symptoms in RA, but do not alter underlying disease activity. The same is probably true for corticosteroids, although some data suggests high dose steroids given early in

disease may help induce remission. Agents such as gold salts, sulphasalazine, hydroxychloroquine and methotrexate do reduce disease activity, as does the more recently introduced agent, leflunomide. Combinations of these drugs are more effective than single agents. Few studies have examined the impact of aggressive treatment in early RA.

The finding that dissociated RA synovial cells produced cytokines including tumour necrosis factor (TNF) without further *in vitro* stimulation, and that inhibition of TNF reduced the production of other cytokines such as interleukin (IL)-1 and IL-6, led to the idea that TNF may orchestrate a cytokine hierarchy in RA. The potential therapeutic effect of TNF inhibition *in vivo* was tested in murine models of RA and soon led to successful clinical trials in patients with RA. The introduction of TNF inhibitors for RA represents the first attempt to treat a chronic human disease through sustained and selective inhibition of a single cytokine (4). To date, there have been remarkably few side effects. This welcome development has brought RA to the forefront of biotechnology, but has also raised wider issues with respect to the cost effectiveness of expensive new therapies.

Unfortunately, only 50-60% patients with RA respond to TNF inhibitors. This is consistent with data from murine models of RA, which show that severe joint inflammation can still develop in mice lacking the TNF gene (5). Synovial tissues from these mice reveal messenger RNA for multiple cytokines, which may compensate for the lack of TNF. These and other data suggest that mediators such as IL-1, IL-6, GM-CSF, complement factor 5 and RANKL are candidate drug targets. There is also great interest in identifying the downstream *intracellular* signaling pathways which may be shared by a number of inflammatory mediators. Candidates include the NF- κ B (6), MAP kinase and JAK-STAT (7-9) pathways. However, inhibition of common intracellular signaling pathways may come at the price of increased toxicity. Induction or restoration of immunological tolerance to the autoantigen(s) which initiate and may drive RA, remains an important goal of research (10-12). B cells and T cell derived cytokines such as IL-17 are other emerging therapeutic targets.

We have entered an exciting new era in RA, but one that will pose many challenges. As we learn more about the pathogenic components of rheumatoid joint disease, even more therapeutic possibilities will emerge. This new therapeutic era coincides with other important developments, including the rise of medical consumerism, the stringencies of evidence-based medicine, the coming impact of genetics and increasing concern about the growing costs of health care. Our challenges will include improving the ability to stratify patients in terms of the risk for severe RA, as early as possible after first presentation; to harness the potential of genetic markers for predicting disease severity, disease complications and responses to treatment; to evaluate new technologies such as joint ultrasound and MRI as end-points in clinical trials and in clinical care. We will also need to develop a much more comprehensive and structured approach

to the management of RA, including serial joint counts and health related quality of life measures, setting education, treatment and rehabilitation goals and specifically preventing and treating disease complications (13). All of this will probably require a different style of clinical practice, with much greater allied health and IT support for Rheumatologists caring for patients with RA.

1. Accelerated atherosclerosis - an extra-articular feature of rheumatoid arthritis?

Van Doornum S, McColl G, Wicks IP.
Arthritis & Rheumatism 2002;46:862-873

2. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N.Engl. J. Med 2001;344:907-16

3. Firestein GS. Evolving concepts of rheumatoid arthritis. Nature 2003;423:356-361.

4. Molecular targets in immune-mediated diseases: the case of tumour necrosis factor and rheumatoid arthritis. Campbell IK, Roberts LJ, Wicks IP. Immunology and Cell Biology 2003;81:354-366.

5. Severe inflammatory arthritis and lymphadenopathy in the absence of TNF.

Campbell IK, O'Donnell K, Lawlor K & Wicks IP.
Journal of Clinical Investigation 2001;107:1519-1527

6. Distinct roles for rel and NF- κ b transcription factors in inflammatory arthritis.

Campbell I, Gerondakis S, O'Donnell K, Wicks IP.
Journal of Clinical Investigation 2000;105:1799-1806

7. SOCS-1 regulates acute inflammatory arthritis and T cell activation. Egan P, Lawlor K, Alexander W & Wicks IP. J Clin Invest 2003;111:915-924

8. Defective gp-130 mediated signal transduction and activator of signal transduction (STAT) signaling results in degenerative joint disease, gastrointestinal ulceration and failure of uterine implantation. Ernst M, Inglese M, Waring P, Campbell I, Bao S, Clay FJ, Alexander WS, Wicks IP, Tarlinton DM, Novak U, Heath JK, Dunn AR.

Journal of Experimental Medicine 2001: 194;189-204.

9. van der Pouw Kraan TC, van Gaalen FA, Kasperkovitz PV, Verbeet NL, Smeets TJ, Kraan MC, Fero M, Tak PP, Huizinga TW, Pieterman E, Breedveld FC, Alizadeh AA, Verweij CL. Rheumatoid arthritis is a heterogeneous disease: evidence for differences in the activation of the STAT-1 pathway between rheumatoid tissues. Arthritis Rheum. 2003 Aug;48(8):2132-45

10. A pilot randomized trial comparing CD34-selected versus unmanipulated hemopoietic stem cell transplantation for severe, refractory rheumatoid arthritis. Moore J, Brooks P, Milliken S, Biggs J, Ma D, Handel M, Cannell P, Will R, Rule S, Joske D, Langlands B, Taylor K, O'Callaghan J, Szer J, Wicks I, McColl G, Passeullo F, Snowden J. *Arthritis Rheum.* 2002 Sep;46(9):2301-9.
11. Steptoe RJ, Ritchie JM, Harrison LC. Transfer of haemopoietic stem cells encoding autoantigen prevents autoimmune diabetes. *J Clin Invest* 2003;111:1357-63.
12. Martin E, O'Sullivan B, Low P, Thomas R. Antigen specific suppression of a primed immune response by dendritic cells mediated by regulatory T cells secreting interleukin -10. *Immunity* 2003;18:155-167.
13. Screening for Atherosclerosis in Rheumatoid Arthritis: Comparison of Two In-Vivo Tests of Vascular Function. Van Doornum S, Jenkins A, McColl G & Wicks IP. *Arthritis & Rheumatism* 2003;48:72-80