招待講演 1

Special Lectures on the Pathogenesis and the Pathogenesis-based Treatment of Rheumatoid Arthritis

Insights into the pathogenesis of rheumatoid arthritis from application of anti-TNF therapy

The Kennedy Institute of Rheumatology and Imperial College School of Medicine, London

RN Maini, PC Taylor, E Paleolog, P Charles, S Ballara, FM Brennan, M Feldmann

Cytokines are key regulators of the inflammatory and tissue destructive response in rheumatoid arthritis (RA). Over a decade ago, *in vitro* culture studies from our group on RA synovial tissue suggested that neutralisation of TNF α by specific antibodies reduced the production of IL-1. Since other *in vitro* studies had demonstrated that TNF α and IL-1 exerted pro-inflammatory effects and also degraded cartilage and bone, TNF α was a candidate therapeutic target. Further pre-clinical data supported this concept particularly the arthritogenic potential of a human TNF α transgene and therapeutic efficacy of anti-TNF α antibodies in murine experimental models.

In 1992 our group treated 20 RA patients with infliximab, a chimeric, high affinity and neutralising monoclonal antibody produced by Centocor Inc (PA, USA) and observed remarkable improvement in clinical signs and symptoms. In collaboration with rheumatology centres in Leiden, Erlangen and Vienna, a randomised placebo-controlled trial which conclusively demonstrated, for the first time, the efficacy of an anti-TNF therapeutic agent.

Subsequent Phase II/III clinical trials have shown that infliximab added to methotrexate (MTX), in patients with active disease despite MTX therapy, gave the most promising efficacy and safety data. MTX is currently widely used and is regarded as the drug which offers the most durable and effective therapy for RA. Hence patients who have incomplete responses, or relapse of disease on MTX, provide a targeted population requiring anti-TNF therapy in clinical practice.

A Centocor sponsored Phase III, placebo-controlled multi-centre study (Anti-TNF α Therapy of Rheumatoid Arthritis with Concomitant Therapy, known as the ATTRACT study) involving 428 patients lasting 2 years has recently been completed. It confirms the efficacy of infliximab in combination with MTX in controlling signs and symptoms. In addition, analysis of x-rays of hands and feet at the end of 1 year has demonstrated arrest of progression of joint space narrowing (cartilage loss) and bone erosions in the majority of infliximab treated patients. In comparison, patients treated with placebo alone (with MTX) continued to show progressive cartilage and bone damage.

These remarkable clinical data have prompted us to investigate the mode of action of anti-TNF α therapy and from these studies to unravel some of the complex pathogenic pathways in this disease.

The first notable alteration of the biological response, within a few days following infliximab in RA, was a reduction in C-reactive protein. Measurement of serum IL-6 concentrations in these patients showed a

reduction within hours of the treatment. These data supported the hypothesis that $\text{TNF}\alpha$ was a regulator of the production of other pro-inflammatory cytokines, and we concluded that the regulation of IL-6 contributed to reduction of CRP.

The second observation of interest was the reduction in the cellularity of synovial tissue obtained by arthroscopic biopsy of the knee joint. This was a result of diminution in the number of lymphocytes and macrophages. Infliximab is complement fixing and cytolytic *in vitro* and one possibility we considered was that reduced cellularity was due to cell lysis associated with binding of antibody to $\text{TNF}\alpha$ on the surface of cells. An alternative or additional mechanism was suggested by the observation of a reduction of adhesion molecules E-selectin, ICAM-1 and VCAM-1, and of cytokines IL-8 and MCP-1. These data were consistent with the hypothesis that infliximab deactivates endothelium and reduces chemokine gradients and hence blocks cell recruitment into the synovium. Direct support for this concept was obtained by gamma camera imaging of $^{111}\text{indium}$ -labelled granulocytes. This study showed a reduction in the uptake of labelled cells, reflecting a diminution in granulocyte retention in joints. Since the same adhesion molecules and counter-ligands are present on lymphocytes and macrophages we favour the unifying concept that $\text{TNF}\alpha$ by direct action or via intermediaries regulates cell trafficking into joints.

Further studies with infliximab have shown a reduction in neovascularisation and VEGF, a major endothelial growth factor. $\text{TNF}\alpha$ therefore also appears to regulate the enriched blood supply which feeds the inflammatory response.

Diminished numbers of CD 3 lymphocytes and macrophages in synovium reduces the drive that leads to $\text{TNF}\alpha$ production. This, in turn, diminishes interaction with synoviocytes and chondrocytes that cause cartilage damage. The fall in circulating levels of pro-MMP-1 and pro-MMP-3 following anti-TNF therapy supports this possibility.

$\text{TNF}\alpha$ has been shown to directly activate osteoclasts and increase the production of RANK ligand by stromal cells and osteoclasts which are present in bone pannus. RANK ligand is also expressed on activated CD 3 lymphocytes in joints. Recent work has shown the importance of RANK ligand in the resorption of bone by osteoclasts. We propose that neutralisation of $\text{TNF}\alpha$ should decrease osteoclast formation and activation by cancelling its direct effect and by reducing the recruitment RANK ligand positive CD 3 cells, as well as $\text{TNF}\alpha$ -induced production of RANK-ligand by cells in pannus tissue at the site of bone erosion.

Since anti- $\text{TNF}\alpha$ therapy is efficacious in only 60-70% of patients and rarely leads to complete remission of disease, other cytokines which are not regulated by $\text{TNF}\alpha$, or like IL-1 act in synergy with it, must play a part in the pathogenesis of RA. The relapse of RA following cessation of anti-TNF therapy is also indicative of other mechanisms-most likely immunological-which maintain disease chronicity.

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