Immunological therapies for rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic inflammatory arthritis of the synovial joints that causes loss of function and a shortened life expectancy. In the last 10 years there have been major advances in the treatment of RA, including more aggressive use of disease-modifying anti-rheumatic drugs and the development of immune therapies targeted to molecules and cells important in the immunopathogenesis of RA. Molecular messengers that travel between cells (cytokines) have been found to be of major importance. Blocking the cytokine tumour necrosis factor α (TNF-α) produces significant improvement in RA, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn’s disease. The use of cytokine blockers has shown the extent to which immune and inflammatory pathways are shared in a number of inflammatory diseases. There has also been an important proof of principle that blocking single cytokines can produce profound effects in inflammatory diseases.

Advances in the treatment of rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis of the synovial joints that causes loss of function, disability, a shortened life expectancy and considerable health care costs1–3. RA is present in ~1% of the adult population of the UK, and is more common in women.4

In the last 10 years there have been major advances in the treatment of RA. This has included more aggressive use of disease-modifying anti-rheumatic drugs (DMARDs) and the development of immune therapies specifically targeted to molecules and cells important in the immunopathogenesis of RA. A realization that RA is particularly destructive to synovial joints in the first few years of disease has led to an increased use of DMARDs at an early stage.5 These drugs have also been used more frequently in combination with other DMARDs. This more aggressive approach to therapy is reflected in the guidelines for the treatment of RA from the American College of Rheumatology.6 Most DMARDs have been discovered serendipitously rather than by design. They are associated with problems due to lack of efficacy and side effects. In particular,
~10% of RA patients fail to show any response to traditional DMARDs. Consequently, rheumatologists have been searching for new therapies.

The therapeutic targeting of specific aspects of the immune response in RA followed a decade or more of laboratory work that had identified key signals and molecules involved in the immunopathogenesis of RA. Molecular messengers that travel between cells (cytokines) have been found to be of major importance. In particular, the cytokine tumour necrosis factor-α (TNF-α) has been shown to be a key factor in the pathology of RA. The development of targeted biological therapies to block cytokines such as TNF has been one of the major advances in medicine in the last 20 years. In addition, the use of these new therapies has not been restricted to rheumatological diseases and is having a major impact in the treatment of other inflammatory diseases including inflammatory bowel disease and psoriasis. Observations of the effect of immune manipulation in different diseases are providing new insights into their immune pathology.

The problem of uncontrolled rheumatoid arthritis

RA produces both disability through uncontrolled synovial joint damage and a reduced lifespan. The mortality associated with severe RA is similar to that for non-Hodgkin lymphoma and type II diabetes mellitus. Early death is largely a result of increased incidence of ischaemic heart disease, infection and malignancy.

Uncontrolled RA leads to synovial joint damage that results in progressive loss of skeletal function. The joint damage is caused by invasion of inflamed synovial membrane, which lines the synovial joints, through the articular cartilage and subchondral bone. These small areas of damage, described as erosions, accumulate to destroy individual joints. The disability that occurs secondary to joint damage can be measured using tools such as the Health Assessment Questionnaire (HAQ). As disability increases, health care costs spiral upwards. Direct health-care costs for treating the consequences of RA are high, and ~30% of patients are unable to work within 10 years of onset of RA. Individuals living with RA bear the physical and psychological burden of disability and continuous pain. In addition, patients often complain of overwhelming fatigue, a symptom that is rarely considered by clinicians.

The immunopathogenesis of rheumatoid arthritis

Once molecular biologists and immunologists started to identify the key cells and molecules of importance in the pathogenesis of RA, the hunt was on for targets for new therapies. Conventional views of RA pathogenesis assume that an as yet unknown antigen (self or non-self) is presented on an
antigen-presenting cell (monocyte-macrophage, dendritic cell etc) attached to a class II major histocompatibility complex (MHC II) molecule. The antigen in this form is then presented to a T lymphocyte which binds to it through its T-cell receptor (TCR), forming a complex of antigen, MHC II and TCR. Other co-stimulatory molecules, such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), are also involved in the interaction between T lymphocyte and antigen-presenting cell that produces a message within the T lymphocyte. This message activates intercellular signalling molecules and results in activation of the T lymphocyte. The T lymphocyte releases intercellular messages in the form of cytokines that have a number of actions important in the initiation of an inflammatory response. Inflammatory cytokines of importance in RA include TNF-α and interleukins 1 and 6 (IL-1 and IL-6). Some cytokines, called chemokines, attract inflammatory cells which travel to the synovial joint. These include interleukin 8 (IL-8) and RANTES. Other cytokines, such as vascular endothelial growth factor (VEGF), stimulate the formation of new blood vessel growth, or angiogenesis, which allows access of an influx of inflammatory cells and the blood supply to support the expanding volume of inflamed synovial membrane. The influx of inflammatory cells is dependent on cells sticking to intercellular adhesion molecules such as αVβ3. As other inflammatory cells become activated, they produce inflammatory cytokines in turn. Monocyte-macrophages and fibroblasts in the synovial membrane produce TNF-α and IL-1. Both TNF-α and IL-1 produce cartilage destruction in synovial joints. These cytokines also stimulate the production of cartilage-degrading enzymes including the matrix metalloproteinases. A number of anti-inflammatory cytokines, receptor antagonists and soluble cytokine receptors, including interleukin 10 (IL-10), are produced in the synovial joint. However, the anti-inflammatory effect is not strong enough to stop the inflammation and, despite increased amounts of these molecules, inflammatory damage continues. It is still unclear why, once activated, the immune response initiated in RA fails to turn itself off.

RA is strongly associated with the autoantibody rheumatoid factor (RF) produced by B cells. The exact role of B cells in RA is uncertain. However, the recent demonstration that blocking B cells in RA leads to clinical improvement has made the subject fashionable again.

Immunological therapies for rheumatoid arthritis

The first attempts at immunotherapy for RA were targeted at cells rather than molecules. The perceived importance of T lymphocytes in the initiation of RA resulted in attempts to alter the immune response by depleting T lymphocytes. However, this approach was largely unsuccessful. Aiming at T cells had seemed logical as they have a key role in
initiating and directing immune responses. During this period other groups were targeting inflammatory cytokines, with a major effort focused on the inflammatory cytokine TNF-α. These molecules are much further downstream in the immune response but produce many of the symptoms and destructive effects seen in RA.26

**Tumour necrosis factor α blockade from bench to bedside**

The development of targeted immunological therapies for the treatment of RA demonstrates how laboratory advances can lead to treatments over a period of several years. In the early 1980s TNF-α had been identified in the synovial membrane of individuals with RA.27 By the late 1980s specific antibodies had been produced to block TNF-α. The first of these was CA2 (later named infliximab), a chimaeric mouse antibody

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**Table 1** Immunological therapies for rheumatoid arthritis in current use or in late phase II/III development

<table>
<thead>
<tr>
<th>Class of target</th>
<th>Candidate target</th>
<th>Available therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines</td>
<td>TNF</td>
<td>Infliximab, etanercept, adalimumab</td>
</tr>
<tr>
<td></td>
<td>IL-1</td>
<td>Anakinra; others in development</td>
</tr>
<tr>
<td></td>
<td>IL-6</td>
<td>MRA</td>
</tr>
<tr>
<td>Co-stimulatory molecules</td>
<td>CTLA-4</td>
<td>Abatacept (under development)</td>
</tr>
<tr>
<td>Adhesion molecules</td>
<td>αVβ3</td>
<td>Under development</td>
</tr>
<tr>
<td>Cells</td>
<td>T lymphocytes</td>
<td>Campath</td>
</tr>
<tr>
<td></td>
<td>B lymphocytes</td>
<td>Rituximab</td>
</tr>
</tbody>
</table>

**Table 2** Differential effects of TNF blockade in different inflammatory diseases

<table>
<thead>
<tr>
<th>Improvement in disease</th>
<th>Deterioration of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Induction of ANAs and SLE</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td></td>
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</tbody>
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ANAs, antinuclear antibodies; SLE, systemic lupus erythematosus.

**Table 3** Currently available biological therapies for rheumatoid arthritis

<table>
<thead>
<tr>
<th>Class of therapy</th>
<th>Target</th>
<th>Drug</th>
<th>Molecule</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine blocker</td>
<td>TNF-α</td>
<td>Infliximab</td>
<td>Chimeric monoclonal antibody</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>TNF-α</td>
<td>Adalimumab</td>
<td>Human monoclonal antibody</td>
<td>SC</td>
</tr>
<tr>
<td></td>
<td>TNF-α, TNF-β</td>
<td>Etanercept</td>
<td>p75 receptor–Fc fusion protein</td>
<td>SC</td>
</tr>
<tr>
<td></td>
<td>IL-1</td>
<td>Anakinra</td>
<td>IL receptor antagonist</td>
<td>SC</td>
</tr>
<tr>
<td>Cell blocker</td>
<td>CD20 on B cells</td>
<td>Rituximab</td>
<td>Monoclonal antibody</td>
<td>IV</td>
</tr>
</tbody>
</table>
that had been produced to reduce the chance of adverse allergic reactions and tolerance secondary to the production of antibodies to a foreign protein. A mouse–human chimaeric antibody contains the whole of the variable regions of a mouse antibody attached to human constant regions. This produces an antibody that is approximately 25% mouse and 75% human. Initially, CA2 was used as a tool for the further determination of the importance of TNF-α in the pathogenesis of RA. Experiments carried out at the Kennedy Institute of Rheumatology in London suggested that TNF-α had a key role in the inflammation of the synovial joint seen in RA. Many experiments on the importance of cytokines in RA relied on the use of cells from synovial membranes harvested from synovial joints normally discarded during joint replacement surgery. Early experiments had shown that cultures of these synovial membrane cells continued to produce a number of inflammatory molecules, including the cytokines IL-1 and TNF-α, for several days after harvesting. When TNF-α was blocked using antibodies such as CA2 it appeared that it had a unique position in the hierarchy of inflammatory cytokines. Blocking TNF-α also blocked the production of other cytokines, including IL-1. Subsequent experiments demonstrated the efficacy of TNF-α blockade in animal models of RA. This included significant improvements in the collagen-induced arthritis model of RA in DBA1 mice. In the early 1990s, TNF blocking antibodies were first administered intravenously to human subjects with RA in a very successful pilot study.

**Tumour necrosis factor α inhibition**

Initial results of TNF blocking antibodies in an open-label study showed significant improvements in measures of disease activity, which persisted with re-treatment. These included reduction in swelling and tenderness in joints and a reduced acute phase response, with decreased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Visual analogue measures of the general health of patients also improved. This study was followed by a double-blind placebo-controlled trial showed efficacy in individuals with active RA. Subsequently, longer-term studies have also shown a reduction in joint damage as measured by a reduced number of erosions and less joint-space narrowing.

These initial clinical trials demonstrated the efficacy of blocking TNF-α with an intravenously administered monoclonal antibody (infliximab). However, other clinical trials were also demonstrating that TNF could be blocked using soluble TNF receptors. TNF-α acts through two cell-membrane-bound receptors, the p55 and p75 receptors. Binding a p75 TNF receptor to the Fc portion of human IgG1 antibody (IgG1–p75 receptor fusion protein) produced another way of blocking TNF.
the anti-TNF agent etanercept, with trials showing that it was effective in reducing both disease activity scores and joint damage over time.\(^{40,41}\) Subsequently, a further TNF blocking antibody (adalimumab), with similar efficacy to both infliximab and etanercept, has become available.\(^{42,43}\) Adalimumab is a fully human antibody with no rodent components.

During the development of infliximab it became apparent that some individuals receiving this treatment produced antibodies against this agent. The formation of these human anti-chimaeric antibodies (HACA) can result in a gradual reduction of efficacy as the HACA neutralizes the infliximab. The production of these antibodies was not surprising because infliximab consists of a partially mouse-derived chimaeric antibody. The use of the DMARD methotrexate in conjunction with infliximab reduced this antibody production. In addition, it now appears that the concurrent use of methotrexate also increases the efficacy of infliximab.\(^{44,45}\) Further studies have shown that the use of methotrexate with etanercept and adalimumab also increases the efficacy of these treatments.\(^{42,46}\)

The use of TNF blocking therapies has also been associated with some significant side effects.\(^{47}\) These have been rare, but include reactivation of latent *Mycobacterium tuberculosis*, increased risk of other infections, injection/infusion site reactions, induction of autoantibodies and autoimmune diseases, and worsening of severe heart failure. Screening individuals for tuberculosis before they commence TNF blocking therapy largely overcomes the problems with reactivation of *M.tuberculosis*.\(^{48}\) It also appears that this complication is more commonly associated with infliximab than the other TNF blocking agents. Although described, the induction of autoimmunity by TNF blocking agents is rare. TNF blockade can also induce autoantibodies such as antinuclear antibodies (ANAs), less often anti-double-stranded DNA antibodies (dsDNA) and sometimes systemic lupus erythematosus (SLE).\(^{47,49,50}\) Initial concerns that TNF blockade might produce increased numbers of lymphomas and other malignancies do not appear to have been realized. However, more follow-up will be needed before definite conclusions can be drawn.

**Looking for other sites to block**

The blockade of other cytokines and immunological pathways might also produce benefit in RA.\(^{51-53}\) IL-1 was thought to be an ideal candidate for blockade as this cytokine is particularly damaging to cartilage and bone in RA.\(^{54}\) A number of attempts at IL-1 blockade have been tried. The currently available IL-1 blocking therapy is anakinra, an IL-1 receptor antagonist that binds to the cell-bound IL-1 receptor and inhibits the binding of endogenous IL-1.\(^{55}\) There has been some success with this approach, and disease activity scores have been improved. The effect does not appear to
be as strong as for TNF blockade and, despite being licensed in the UK, anakinra is rarely used to treat RA. However, it has been used effectively to treat adult Still’s disease and Muckle–Wells syndrome.\(^{56}\)

A number of other targets are currently being explored for their potential as new immune therapies. They include new TNF-\(\alpha\) blockers of a similar kind to those already available and inhibitors of other cytokines such as IL-6. The IL-6 inhibitor MRA has shown promise in phase II studies and is undergoing further development.\(^{57,58}\) MRA consists of a humanized anti-IL-6 receptor monoclonal antibody that blocks the action of IL-6. It is likely that blocking different cytokines will produce different effects on the RA disease process. This will increase our knowledge of the importance of different inflammatory pathways in RA. Other immunological therapies in development rely on blocking molecules important in the close interactions (co-stimulation) between T lymphocytes and antigen-presenting cells such as CTLA-4.\(^{59-61}\)

In the last few years increasing attention has been paid to targeting B lymphocytes in RA. Rituximab is an antibody directed against the B-lymphocyte cell surface marker CD20 (CD20 is not present on all plasma cells or on very early B cells). Rituximab was developed for the treatment of B-cell lymphomas, but studies of its use in severe RA has demonstrated good efficacy.\(^{24}\)

**Using biological therapies in the clinic: licensed treatments and national guidelines**

The anti-TNF antibodies infliximab and adalimumab, the TNF receptor fusion protein etanercept and the IL-1 inhibitor anakinra are all licensed in the UK for the treatment of RA. The National Institute for Clinical Excellence (NICE) produced guidance for the use of etanercept and infliximab in March 2002 and is due to review this in the near future.\(^{62}\) Present guidance recommends that etanercept and infliximab can be used to treat active RA which has failed to respond to at least two DMARDs. NICE also recommended that the British Society for Rheumatology (BSR) guidelines for prescribing TNF blockers should be followed. These were produced in 2001 and updated in July 2004.\(^{63}\) There is also international consensus on the use of these therapies for the treatment of RA.\(^{64}\)

**Inducing remission**

Remission in RA rarely occurs spontaneously. However, it remains the goal of those treating individuals with RA. The definition of remission is controversial, but it is common to define it on the basis of a disease activity score
(DAS) <2.4.\textsuperscript{65} The DAS is a composite score of a joint count of tender and swollen joints, ESR and a patient visual analogue score (VAS) of perceived health status. The best possible treatment of individuals with tight control of disease activity using DMARDs can produce clinical remission in some individuals.\textsuperscript{66} However, at present TNF blockade is the only therapy which consistently stops continuing joint damage through erosions.

With remission as the ultimate goal of therapy, attempts have been made to increase numbers of individuals achieving remission. Use of TNF blockade in early RA appears to allow induction of remission that may continue for several months or years using conventional DMARDs such as methotrexate as maintenance therapy.\textsuperscript{67–69} Rituximab also appears to produce a prolonged depletion of B lymphocytes, and improvement in disease activity may also last for several months or years.\textsuperscript{70}

**Immune-mediated inflammatory diseases**

The use of TNF blockers is also effective in other inflammatory disease,\textsuperscript{71} including ankylosing spondylitis, psoriatic arthritis and psoriasis, Crohn’s disease and some rarer inflammatory diseases including systemic vasculitis\textsuperscript{72} and Behcet’s disease.\textsuperscript{73,74} This demonstrates that particular cytokines are important in a number of different inflammatory diseases. These cytokines are constituents of ‘public pathways’ of inflammation. In contrast, some cytokines are specific to a particular disease and define a unique part of its pathology and are part of a ‘private pathway’.

TNF blockade is not effective in all inflammatory diseases. Indeed, in some diseases it has led to a worsening of the clinical situation. TNF blockade worsened the clinical course in trials of therapy for multiple sclerosis.\textsuperscript{75} Thus inflammatory diseases can be classified on the basis of their response to TNF and other immunological therapies. This will lead to a greater understanding of the important inflammatory pathways in different diseases.

An understanding of the shared inflammatory networks of many inflammatory diseases has led to the definition of these diseases as immune-mediated inflammatory diseases (IMIDs). This approach does not recognize the conventional boundaries defined by the traditional specialties of internal medicine. Patients with these illnesses may be better cared for by specialists in inflammatory disease, and in some institutions the care of these individuals is being centralized in IMID centres.

**The future**

As experience in using immunological therapies for the treatment of RA is gained, the exact role of these agents will become better defined. There
will also be the opportunity to observe large cohorts of treated individuals and monitor them for unexpected adverse effects. An example of this has come from a large database of 4000 individuals with RA on treatment with anti-TNF agents included in the BSR Biologics Register.76 This has recently identified a small number of individuals with progressive interstitial lung disease while receiving TNF blockers and azathioprine. This observation requires further exploration. The addition of therapies targeted at different immunological mediators and cells will also lead to increased understanding of the immunopathogenesis of RA.

The clinical use of cytokine blockers has shown the extent to which immune and inflammatory pathways are shared in a number of inflammatory diseases. Blocking TNF has shown this cytokine to be of key importance in the pathology of RA, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn’s disease.

The advances in therapy that have occurred in the treatment of RA have been enormous. There has also been an important proof of principle that blocking single cytokines can produce profound effects on inflammatory diseases. However, the greatest effect is on the individuals who suffer with these diseases. Before the availability of TNF blockers, the 10% of individuals with the most aggressive RA were effectively untreatable. The vast majority of these individuals are now treated effectively.

However, these treatments remain expensive, and the use of protein-based biological therapies requires subcutaneous or intravenous administration. The current therapies have proved that blocking immune mediators, including TNF, can have a significant effect on RA and other inflammatory diseases. The challenge for the future is to develop novel cheaper therapies using small-molecule technology that can be given orally.

References


