

Basel, 6 November 2006

Autoimmune Diseases and Rheumatoid Arthritis

Early diagnosis and effective new treatment options for patients

- More than 60 different autoimmune diseases currently affect millions of people world wide.
- Rheumatoid arthritis (RA) is one of the commonest autoimmune diseases, affecting over 21 million people worldwide.
- 30-40% of RA patients do not have adequate control with or are intolerant to current biologic therapies. 60-80% of RA patients do not achieve control over major signs and symptoms.
- The Roche Group has invested in a broad autoimmune disease portfolio and pipeline containing clinically differentiated compounds.
- Two first-in-class molecules (MabThera/Rituxan, already on the market; Actemra, in phase III) with a novel mechanism of action provide benefits to patients who do not respond adequately to current therapeutic options, or for whom these therapies may be a best first choice in the future.
- MabThera/Rituxan is the first and only selective B cell therapy for RA and provides lasting treatment success.
- Actemra has demonstrated superiority over conventional disease-modifying anti rheumatic drugs (DMARDs) and has significantly improved pain and other symptoms in Japanese monotherapy trials.

Autoimmune diseases – more common than you think

When the immune system targets the body's own tissues instead of foreign invaders, such as bacteria or viruses, the result is an autoimmune disease. Five to eight percent of the population is affected by autoimmune diseases and there are more than 60 different types. Among them are Wegener's granulomatosis, multiple sclerosis (MS), type 1 diabetes mellitus, systemic lupus erythematosus (SLE), juvenile idiopathic arthritis (JIA) and rheumatoid arthritis (RA). Autoimmune diseases can present across a wide spectrum of disease severity, affect any organ system and ultimately lead to death. Most autoimmune diseases affect women more often than men and can manifest themselves at any age. Many autoimmune diseases share similar pathophysiologic mechanisms, but the primary cause is still unknown and there is no cure.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is one of the most common forms of autoimmune disease, affecting over 21 million people worldwide. It is characterised by inflammation of the membrane lining in joints, leading to loss of joint cartilage and bone destruction, the clinical symptomatology of which is joint malalignment, pain, heat, redness, stiffness and swelling. Over the course of the disease this can ultimately result in irreversible joint destruction and disability.

People with RA begin to suffer progressive, permanent joint damage early on in the disease, and this is often associated with multiple joints becoming swollen, warm and tender. Within the first two years of diagnosis, radiographic evidence of joint damage can be found in up to 70% of patients, and within 10 years 50-80% experience increasing difficulty working and performing everyday tasks.

Diagnosing RA

Diagnosing RA presents a challenge because the disease may begin gradually with subtle symptoms. According to the American College of Rheumatology Classification (revised ACR criteria 1987), the symptoms include morning stiffness, arthritis of more than 3 defined joints, arthritis of hand and finger joints, symmetrical arthritis, rheumatoid nodules, rheumatoid factor and radiographic changes. RA is ultimately diagnosed when at least 4 of the 7 criteria are fulfilled over a time period of 6 weeks. In addition to the clinical symptoms, a number of clinical tests are also available to help piece together a diagnosis of RA, as well as to monitor the course of the disease. These laboratory tests include:

- C-reactive protein (CRP), a general marker of inflammation in the body and
- rheumatoid factor (RF)

The role of biomarkers

Detecting the disease as early as possible – even before clinical symptoms occur – could help physicians to intervene at an earlier stage and prevent damage and disabilities. New diagnostic markers could therefore improve existing methods of diagnosing RA.

Researchers at Roche Centralized Diagnostics in Penzberg, Germany, assessed 54 biomarkers using blood samples collected from 6 European centres. As a result, antibodies against cyclic citrullinated peptides (anti-CCPs) were identified as a superior biomarker for the earliest possible detection of RA, exhibiting outstanding performance characteristics such as sensitivity in excess of 75% and specificity in excess of 95%. Anti-CCPs were licensed-in by Roche and are currently in development for a diagnostic test based on the existing and established Elecsys platform used in laboratories worldwide.

Treating RA

A number of treatments are currently available to help people with RA. Some address the symptoms and others modify the course of the disease. They include:

- Nonsteroidal anti-inflammatory drugs (NSAIDs), which reduce pain, swelling, and some inflammation
- Glucocorticoids (corticosteroids), which have an anti-inflammatory effect
- Disease-modifying anti rheumatic drugs (DMARDs), which relieve symptoms, suppress inflammation and help control RA by delaying disease progression
- Biologics, which are genetically engineered drugs that target specific mediators in the immune system called cytokines or specific cells involved in inflammation and the autoimmune process. Like the traditional DMARDs, these agents are often more effective at controlling RA and delaying disease progression, used alone or in combination with methotrexate, than most of the other DMARDs.

The role of the B cell in RA

Lymphocytes are one of the key cell types controlling our bodies' immune responses. They normally recognise “foreign” material and distinguish it from the body’s own components. In RA, however, the immune system responds abnormally, provoking an attack on normal healthy tissues.

There are two main types of lymphocytes:

B cells' key functions are:

- to produce antibodies (immunoglobulins)
- to turn into plasma cells which produce large numbers of antibodies
- to produce cytokines
- to present antigens to T cells

T cells' key functions are:

- to help B cells produce antibodies
- to recognise and destroy virus-infected cells
- to activate other immune system cells by producing cytokines
- to control the level and quality of the immune response

For the last 20 years treatment of RA has focused on T cells and a group of their specific products, the cytokines. New evidence has demonstrated that B cells and their products play several key roles in RA that may need to be addressed in the course of the development of successful therapeutic interventions. B cells play a key role in the chain of inflammatory events that ultimately leads to the damage of bone and joint cartilage that is characteristic of RA.

Targeting B cells: MabThera/Rituxan

MabThera/Rituxan, a monoclonal antibody, is the first and only RA treatment to target B cells. By specifically binding to CD20 antigen, a molecule on the surface of B cells, it breaks the inflammation cascade that causes the disease symptoms.

The B cells that are bound by MabThera/Rituxan recruit the body's natural defences to eliminate the B cells. Once the B cells have been removed, they can no longer produce antibodies that attack the body's own tissues or facilitate inflammation.

As neither stem cells (the precursor cells of B cells) nor plasma cells (a further differentiated B cell capable of producing large amounts of the same antibody) are affected by MabThera/Rituxan, the B cell population is eventually restored from the stem cells, and normal levels of protective antibodies (immunoglobulins) are preserved. Thus the immune system remains intact.

The selective targeting of B cells provides an effective treatment alternative for patients who have not responded adequately or are intolerant to TNF inhibitor therapy.

Targeting a mediator of inflammation: Actemra

Actemra is a humanised monoclonal antibody that blocks the Interleukin-6 (IL-6) receptors and so prevents Interleukin-6 from binding to its receptors. In so doing, Actemra inhibits an important mediator involved in the inflammation processes associated with RA. This compound is being globally co-developed with Chugai, a member of the Roche Group. Phase III studies conducted by Chugai in Japan using Actemra monotherapy have shown Actemra to be superior to conventional disease-modifying anti-rheumatic drugs (DMARDs) in reducing the signs and symptoms of RA and capable of significantly reducing the extent of joint destruction. A large-scale Phase III study of Actemra in rheumatoid arthritis is currently in progress in territories outside Japan. This study is expected to enrol more than 4000 patients in 41 countries. Actemra is a first-in-class IL-6 receptor antibody whose novel mechanism of action may provide a new and effective treatment for RA.

Additional products create a rich pipeline

Roche has a number of new compounds in early-stage (phase I and phase II) clinical trials. These compounds further extend the Roche pipeline of new drugs for this important disease area.

Ocrelizumab R1594

R1594 is a humanised anti-CD20 monoclonal antibody that also targets B cells but is characterised by less immunogenicity and potentially higher tolerability. This compound will move into phase III for the treatment of RA in early 2007. In addition, ocrelizumab also offers a potential treatment for other debilitating autoimmune diseases, such as systemic lupus erythematosus (SLE) and multiple sclerosis (MS).

R1503

This compound is currently in Phase II. It selectively inhibits a protein called p38 MAP kinase which regulates the production of cytokines such as tumour necrosis factor (TNF), Interleukin 1 (IL-1) and IL-6. Inhibition of p38 MAP kinase reduces the production of these cytokines, which are key mediators of the inflammatory process.

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