



# TNF $\alpha$ Blocker

## Therapy Monitoring through the Detection of Antibodies against TNF $\alpha$ Blocker

Tumour Necrosis Factor alpha (TNF $\alpha$ ) belongs to the pro-inflammatory cytokines that encourage and uphold infection reactions. Cytokines, produced by macrophages and t-cells, play a central role in both acute and chronic infections.

The TNF $\alpha$  concentration is raised in the affected joints in many rheumatic diseases (rheumatoid arthritis, chronic polyarthritis, ankylosing spondylitis i.e. M. Bechterew disease) and plays a significant role in the joint destruction and in the courses of other diseases. Even in Crohn's disease, an overproduction of TNF $\alpha$  can be observed that obviously affects the course of the disease.

In the 1990's, pharmaceutical companies developed biotechnologically produced medications that aimed at hindering TNF $\alpha$  ("TNF $\alpha$  blockers") and therewith produced a positive affect on the various disease symptoms (Feldmann et al. 2001).

### Use of TNF $\alpha$ Blockers

In 1998, the first TNF $\alpha$  blockers were approved for use in the therapy of rheumatoid arthritis, since then two other TNF $\alpha$ -blockers have been marketed:

- Infliximab (Remicade®),
- Etanercept (Enbrel®) and
- Adalimumab (Humira®).

All three are comparable in the aspect of their effectiveness in facilitating improvement in clinical symptoms (Herold 2004) but in Crohn's disease, Infliximab has proved itself to be the most effective TNF $\alpha$  blocker. TNF $\alpha$  blockers are used when the treatment of rheumatoid arthritis and psoriasis arthritis with basic therapeutic medications fail.

Even though the TNF $\alpha$  blockers differ in respect to their chemical structures and methods of operation, the pharmacological effects are the same in all three substances. All three medications can help improve the disease activity and discomforts as well as effectively hindering the progression of joint destruction (Herold 2004).

### Etanercept (TNF receptor)

Etanercept is a genetically produced variant of TNF receptors. The physiological effect mechanism of TNF $\alpha$  occurs through their binding to the body's own TNF $\alpha$  receptors. The artificial TNF receptor Etanercept bonds to TNF $\alpha$  (and also TNF $\beta$ ) and competes with the physiological TNF $\alpha$  receptors. Therefore TNF $\alpha$  molecules can no longer be effective and the infection reaction is inhibited. Etanercept is administered subcutaneously. In connection to Crohn's disease, Etanercept is inactive.

### Infliximab (TNF $\alpha$ antibody)

Infliximab is a chimeric, monoclonal antibody to TNF $\alpha$ . That means that it is an antibody that is made up of components from two different species of living beings. In this case, one part is derived from humans and the other from mice. It is genetically engineered from a very specific cell-line, a cell clone, and is therefore denoted as monoclonal. The antibody Infliximab creates, together with TNF $\alpha$  as antigen, stable antigen-antibody complexes and so hinders the binding of TNF $\alpha$  to the TNF $\alpha$  receptor. Infliximab is administered as an infusion.

### Adalimumab (TNF $\alpha$ antibody)

Adalimumab is a fully humanistic antibody. Adalimumab differs from Infliximab in that it no longer contains any components from mice, but instead is composed entirely of human material. Therefore, it is hoped that allergic reactions to therapy occur more seldom. In addition, with Adalimumab there is no possibility of the development of so-called human anti-chimeric antibodies (HACA's= antibodies that the body develop e.g. against the non-human, chimeral mouse components in Infliximab, and in the worst case scenario, weaken or even fully neutralise the effectiveness of the TNF $\alpha$  blockers). Adalimumab is not administered as an infusion but rather as a subcutaneous injection.

### Indications

All three TNF $\alpha$  blockers are approved for the treatment of rheumatoid arthritis. Infliximab and Etanercept are also approved for the treatment of ankylosing spondylitis, psoriasis and psoriatic arthritis. Infliximab is furthermore approved for the treatment of Crohn's disease.

### Side-effects of TNF $\alpha$ Blockers

Generally, it should be noted that substances that inhibit TNF $\alpha$  also weaken the body's defence against infection and cancer cells. Therefore, a higher incidence of infection and cancerous disease is possible.

The following side-effects were of significance to patients that were administered TNF $\alpha$  antibodies as a therapy (Antoni 2002):

1. Infections, including sepsis and tuberculosis (reactivation of a latent tuberculosis)
2. Cancerous disease (e.g. lymphoma)
3. Other haematological disturbances (e.g. anaemia, pancytopenia)
4. Demyelination disturbances / neuropathology

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5. Worsening of a heart insufficiency
6. Development of auto-antibodies and an auto-immunity
7. Sensitivity reactions to infusions and injections

The most common side-effect of **Etanercept**, especially at the beginning of therapy, is a slight, local reaction of the skin at the injection site. This presents itself as reddening, itching, pain or swelling. Other common side-effects of Etanercept are infection of the upper respiratory organs, for instance colds or sinus infections. Apart from these, during the treatment with Etanercept other, more serious or even life-threatening infections could develop. This especially applies to patients with other, accompanying diseases to the rheumatoid arthritis, which render them more susceptible to infection. During a treatment with Etanercept, various auto-antibodies, that is antibodies against the body's own antigens (e.g. anti-dsDNA antibodies) may develop. Whether long-term auto-immune diseases may be triggered through treatment with Etanercept is not known at this point of time. About 1% of patients develop antibodies against Etanercept, these however, do not impair the effectiveness of the substance.

With the treatment with **Infliximab**, acute, infusion related reactions may occur during, or up to two hours after the infusion, such as: fever, ague, urticaria, chest pain, heightened or lowered blood pressure and dyspnoea. The symptoms of dyspnoea and urticaria are the prime reasons for the termination of therapy with Infliximab. Patients often complain of headaches, tiredness and chest or abdominal pain. Other side-effects which are also thought to be triggered by Infliximab involve mostly the upper-respiratory system, skin, hair and nails. It is also possible that collagen disturbances, psychiatric disturbances, disturbances of the nervous system, blood formation and eyes occur. Furthermore, disturbances of the circulatory system, the intestinal tract, the liver and gall tracts, the musculatory and skeletal systems, the kidneys and urinal tracts and the reproductive system may occur.

Delayed hypersensitivity reactions often occur in patients who have renewed treatment with Infliximab after a break of two to four years. The risk of these delayed hypersensitivity reactions increases after a therapy pause of over 15 weeks. Some patients develop antibodies against Infliximab, so-called human anti-chimera antibodies. These reduce the effectiveness of Infliximab on one hand and on the other hand can lead to serious allergic reactions (Cohan et al. 2000; Hanauer et al. 2002). An accompanying therapy with immuno-suppressants can reduce the degree of antibody development (Baert et al. 2003). In some patients, moreover, an auto-antibody may develop, that is antibodies against the body's own antigens. The eventual risk of auto-immunological disease therewith increases.

The primary side-effects of **Adalimumab** are skin reactions around the injection site, infection of the organs of the upper-respiratory system, headaches and skin rashes (as per specialist information from the manufacturer Abbott). Further common side-effects such as infections were stated e.g. urinary tract infections also dizziness, nausea, diarrhoea, sore throat, itchiness, flu-like symptoms and abdominal pain. Other serious infections, sepsis and opportunistic infections – partly leading to death - occurred with the use of Adalimumab. Allergic and anaphylactic reactions were also triggered by Adalimumab.

### The Development of Antibodies against Therapeutic Antibodies (Infliximab, Adalimumab) or against TNF Receptors (Etanercept)

Problems in the therapy with TNF $\alpha$  antibodies occur when the human organism develops antibodies against the therapeutic antibody i.e. against the TNF $\alpha$ -blocker (among others). In a cohort study **61% of M. Crohn patients treated with Infliximab reacted with the development of antibodies against Infliximab** (Baert et al. 2003). The presence of antibodies in 7-19% of patients could be associated with infusion reactions. Allergic reactions, and also therapy failure, could be attributed to the development of such antibodies. Through the parallel administration of immuno-suppressants (mostly Methotrexat) a reduction of antibody development could, at least, be achieved (Colombel et al. 2004)

### ELISA Tests to Detect Antibodies against TNF $\alpha$ Antibodies (Therapeutic Antibodies)/ TNF Receptors

Our ELISA's make it possible to detect the human antibody against therapeutic antibodies/TNF receptors. A co-determination of rheumatic factors and irregular antibodies can be excluded.

More information is available on inquiry.

#### Literature

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