

## **TNF-alpha therapy in childhood uveitis**

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### **Introduction**

A chronic endogenous uveitis is one of the most severe ophthalmologic diseases in childhood that can lead to loss of vision despite advances in diagnosis and therapy. Uveitis can be associated with many systemic diseases, whereas the combination with the juvenile idiopathic arthritis is the most common.

The current therapy in uveitis is based on local or systemic treatment with corticosteroids. In severe courses, immunosuppressives are used, for example methotrexate, cyclosporine A, azathioprine, mycophenolat-mofetil or cyclophosphamide. By using this therapy many patients could partly recover. Therapy refractive uveitis, relapses under immunosuppression or adverse reactions are nowadays treated more frequently by using so-called biologicals. These biologicals contain agents, which directly affect the interaction between inflammatory and host cells on the level of cytokine.

### **Tumour necrosis factor (TNF) alpha**

The proinflammatory cytokine tumour necrosis factor (TNF)-alpha is produced by many cells, e.g. by macrophages, T-cells and natural killer cells. It is a co-stimulator for T-cells, B-cells, cytotoxic T-cells and neutrophilic granulocytes. TNF-alpha induces the expression of MHC-class I and II molecules, interleukine (IL)-2 receptors and adhesive molecules. Because of its stimulation of the production of IL-1 and synthesis of prostaglandins, it enhances inflammatory reactions.

### **Pathogenesis of uveitis: the central role of TNF-alpha**

TNF-alpha is of major significance in the pathogenesis of uveitis. In studies based on animal experiments TNF-alpha could be found in early stages of endotoxine induced uveitis (De Vos et al. 1994). TNF-alpha is attached importance also a pathogenetic role in experimental autoimmune uveitis (EAU) (Nakamura et al. 1994). It is

supposed, that TNF-alpha induces the expression of chemokines, adhesive molecules and other cytokines and therefore actually aggravates inflammation. In the animal model of EAU a blockade of TNF-alpha suppresses the T-cell response and activates the infiltrative macrophages. This inhibits the destruction of the tissue (Dick et al 1998; Robertson et al. 2003). In TNF-alpha receptor deficient mice with immunocomplex induced uveitis a reduction of inflammation could be observed (Brito et al. 1999)

Patients with posterior uveitis showed a modulation of T-cells in blood when treated with anti-TNF-alpha (Greiner et al., 2004). High TNF-alpha serum levels correlated with a recurrent course of uveitis (Santos et al. 2001). In the blood of patients with intermediate uveitis the TNF-alpha expression was significantly higher than in healthy control subjects (Murphy et al. 2004). The serum of Behcet-patients with active disease also showed a significantly higher concentration of TNF-alpha (Turan et al. 1997).

As the inhibition of TNF-alpha can lead to a regression of adhesive molecules, pro-inflammatory cytokines and chemokines, this seems to be an attractive immunologic therapy also in the case of uveitis.

### **TNF-alpha inhibitors**

There are three commercially produced agents available that are able to neutralize the activity of TNF-alpha. Etanercept (Enbrel®) is a soluble TNF-receptor-immunoglobulin-fusionprotein. Soluble TNF-receptors can bind and inactivate the soluble TNF. Infliximab is a monoclonal chimeric mouse-human antibody, binding with high affinity soluble and transmembrane forms of TNF-alpha. In vivo Infliximab quickly builds up stable complexes with human TNF-alpha. Adalimumab is a monoclonal human anti-TNF-antibody.

TNF-alpha inhibitors for the treatment of chronic-inflammatory systemic diseases  
The use of biological agents has drastically increased in the treatment of chronic inflammatory diseases. It has been proved that TNF-alpha blocking agents can alleviate symptoms of many inflammatory diseases, e.g. rheumatoid arthritis, Crohn disease, juvenile idiopathic arthritis, psoriasis, arthritis, still syndrome, granulomatosis Wegener, Behcet disease, scleroderma, sarcoidosis and polymyositis/dermatomyositis.

Effectiveness, safety and adverse reactions of Etanercept have been analyzed in children with juvenile idiopathic arthritis (JIA). In multicentric studies could be proved, that with Etanercept a long persistent remission with good therapy tolerance in children with severe chronic Methotrexat-resistant polyarticular JIA could be achieved. Three of four children with JIA, showing no improvement with Methotrexat-monotherapy, responded favourably to the therapy with Etanercept by showing improved articular findings and pain relief (Lovell et al, 2000 Lovell et al., 2003)

### **TNF-alpha inhibitors for treatment of uveitis**

First observations showed that TNF-alpha inhibitors can be effectively applied for the treatment of chronic uveitis. According to observations of Rosenbaum and Smith (2002) these agents are an effective therapy for uveitis in spondylitis ankylosans, Crohn disease or psoriasis arthritis. **All in all**, etanercept seemed to act better on arthritis than on uveitis (Smith et al. 2001)

Reiff et al (2001) reported, that Etanercept can improve the course of chronic uveitis in JIA patients. The authors have examined 10 children with uveitis, six thereof with oligoarticular JIA. Eight were immunosuppressed. The study contained no control group. However, in a newly published placebo-controlled, randomized and double-blind, prospective study no advantage of etanercept against placebo in treatment of JIA associated uveitis could be observed (Smith et al. 2005). In the research 7 patients were treated with etanercept 0.4mg/kg weight, whereas 5 patients were given a placebo. After these six months of therapy, all patients were treated with etanercept for another six months. In 3 of 7 patients of the etanercept-group and in 2 of 5 patients of the placebo-group the treatment was considered to be successful, and in 1 case per group the therapy was unsuccessful. The small number of patients was indeed an essential limitation of this study. The analysis of a nationwide patient-register for the use of etanercept in JIA-patients showed, that etanercept has no influence on recidive-rates or any new occurrence of uveitis (Schmeling and Horneff 2005)

In a prospective study of Foster et al. (2003) the application of Etanercept didn't contribute to reduce the MTX dosis in uveitis patients or to reduce more recidives.

This study contained only one patient with a JIA-associated uveitis. Other authors even observed a temporal connection between the beginning of etanercept therapy because of arthritis spondylosans and the episodes of a HLA-B27 associated anterior uveitis (Kaipiainen-Sepphänen and Leino 2003, Reddy and Backhouse 2005).

In further studies the efficiency of infliximab for the treatment of uveitis was researched. In 8 children with JIA-associated uveitis infliximab was applied in a dosis of 3-5mg/kg weight every 4-6 weeks for six months. After 3 months inflammation had decreased drastically in 5 cases, after six months now just 2 patients (Honkanen et al. 2001). El Shabrawi and Hermann (2002) reported that 6 of 7 patients with HLA B27 associated uveitis under the treatment with infliximab 10mg/kg weight showed a faster regression of the inflammation. Additionally Joseph et al. (2003) reported a fast improvement of vitreous infiltrates, acuity and a remission of uveitis after six months.

Suhler et al (2005) reported of the efficiency and adverse reactions of infliximab from a prospective clinical phase II study in patients with therapy refractive uveitis. The study contained 31 patients. Treatment-success existed in 22 of 28 patients after 10 weeks, in 9 out of 18 patients and in 1 of 5 patients after 1 and respectively 2 years. The authors showed that the good therapy success was accompanied by a high rate of adverse reactions. Markomichelakis et al. (2004) and Wegschneider et al. (2005) reported that under therapy with infliximab a regression of cystoid macular edema is possible.

In a retrospective study with 7 patients with non-infectious eye diseases, being refractive against an immunosuppressive therapy, depending on the clinical course infliximab 200mg was applied in intervals of 4 to 8 weeks (Murphy et al. 2004). In six patients an improvement could be observed. In 5 patients a remission and a reduction of the immunosuppressive therapy could be achieved. In the cohort there was only one patient with JIA-associated uveitis, in whom also a remission occurred.

Lindstedt et al (2005) reported in another paper about their experiences with infliximab in 13 patients with acuity-endangering uveitis. Six of them suffered from Behcet-disease, 5 from idiopathic posterior uveitis, one patient of sarcoidosis and one of birdshot-retinochoroiditis. Infliximab led to a regression of inflammation and to

an improvement in acuity in all patients. Also in another patient with seronegative JIA, whose uveitis didn't come to healing up with other immunosuppressive agents, infliximab led to an improvement (Mangge et al. 2003)

### **Adverse Reactions in the treatment with TNF-alpha inhibitors**

Hypersensitivity reactions and severe infusion reactions specially when using infliximab can occur. In the patients treated with TNF-alpha inhibitors a higher rate of tuberculosis could be observed. Under therapy with infliximab in 70 out of 121,000 patients newly developed tuberculosis was reported. Until 2001 13 cases of tuberculosis out of 117,000 patients treated with etanercept were reported (Keane et al. 2001; Wallis 2001, Reimold 2003) Under treatment autoantibodies, specially antinuclear antibodies or antibodies against ds-DNA, but also a lupus-like syndrome appeared. In 17 patients, treated with etanercept, and in 2 patients treated with infliximab, demyelination disease could be observed (Mohan 2001) Infliximab led to the aggravation of moderately or severe heart insufficiency. The FDA Arthritis Drug Advisory Committee reported about 16 infliximab patients and 19 etanercept patients with lymphomas. The follow-up period is yet too short, to assess the long-run-risk of TNF-alpha inhibitors with a certain accuracy.

### **Register „Infliximab for treatment of childhood uveitis“**

TNF-alpha inhibitors have an increasingly higher significance in the treatment of severe refractory chronic uveitis. So far, the observation of the small published case-series, particularly in childhood uveitis, indicate that they occasionally are superior to other immunosuppressive therapies and that they have a more rapid effect. Infliximab seems to be better in the treatment of uveitis than etanercept. Hardly any research with infliximab has been carried out with children. (Dekker et al. 2004, Yazici et al. 2003)

TNF-alpha inhibitors have not been authorised for the treatment of uveitis and can therefore only be applied „off label“. TNF-alpha inhibitors are only indicated in case of a therapy refractory disease, which whose course couldn't be influenced with any of the authorised drugs or none of the immunosuppressives.

Therefore studies and registers are desirable to gather data promptly in order to assess the significance of infliximab in therapy of uveitis more precisely. As for that purpose a long-term observation of a great number of patients is necessary, the uveitis section of the German Ophthalmologic Association DOG together with the Working Group of Children and Youth Rheumatologists and the Rheumatology Research Centre in Berlin established a register, which records the long-term effect and possibly adverse reactions of preferably all children treated with infliximab in Germany.

It is reasonable that comparable documentation centres will be initiated also in China.

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