Effectiveness of Adalimumab in the Therapy of Paediatric Uveitis

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Abstract

In recent years, no drugs have been received with such enthusiasm as the tumour necrosis factor-α (TNF-α)-blocking agents etanercept (Enbrel®), infliximab (Remicade®) and adalimumab (Humira®). This article summarises our knowledge of these drugs in the treatment of juvenile idiopathic arthritis (JIA)-associated uveitis. These agents offer a very effective treatment method when the disease is refractory to second-line immunosuppressive therapy. Of the three drugs available, infliximab and adalimumab seem to have a better effect in terms of reducing ocular inflammatory activity. Etanercept may also be effective, but can reactivate the disease and probably also result in new onset of uveitis, which has been described only rarely with infliximab and adalimumab. Important side effects of these drugs include reactivation of tuberculosis and induction and reactivation of demyelinating diseases. Because of its administration by subcutaneous injection and its better side-effect profile, at present adalimumab may be the most favourable TNF-α-blocking agent.

Keywords

Juvenile idiopathic arthritis, juvenile uveitis, children, tumour necrosis factor-α (TNF-α), anti-TNF-α

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In recent years, no other drugs have been received with such enthusiasm as the group of tumour necrosis factor-α (TNF-α)-blocking agents. Why are these drugs so interesting for uveitis patients, and is it possible to see superiority of one of the drugs in this group over the others?

Juvenile Idiopathic Arthritis-associated Uveitis

When specialists in ocular inflammatory disorders are asked about the worst types of ocular inflammation, almost all of them will mention serpiginous chorioiditis, Behcet's disease and chronic anterior uveitis (CAU) in paediatric patients, which is often associated with juvenile idiopathic arthritis (JIA) and antinuclear antibodies.[1] While the first two intraocular inflammations are rarely found in young life, CAU is a real problem for paediatric patients, parents and ophthalmologists, and carries all the disadvantages of a chronic disease:

- Children with CAU almost never show signs of inflammation of the external eye (in contrast to the HLA-B27-associated type); this means parents can easily be unaware that their child has an ocular inflammation, and subsequently fail to take their child to an ophthalmologist.
- Once it has been detected, the intraocular inflammation may react slowly to topical treatment, but often needs extended dosages of topical steroids. The natural fluctuation of cell counts in the anterior chamber makes it difficult to control the actual amount of inflammation induced by this chronic inflammation.
- The ocular structures involved in uveitic complications (lens and macula) are more vulnerable in children than in adults due to inflammation or steroid-induced effects.
- If the ocular inflammation is not associated with severe arthritis, children may receive topical or even systemic corticosteroid treatment for much too long. There are no studies available about the long-term effect of corticosteroids given to such children for controlling the course of the inflammation.
- When the stage of immunosuppressive treatment is reached, the situation is even worse: there is no drug approved for the treatment of CAU in children when the arthritis is minimal because there has never been a controlled study in paediatric CAU patients.

Because of all of the problems listed above (unclear activity of the inflammation due to natural fluctuation, unclear timing of control visits, non-existing therapy guidelines regarding a change from corticosteroids to immunosuppressives), until a few years ago children with CAU had a poor prognosis, often culminating in cataract, secondary glaucoma and, finally, phtisis bulbi.

The Role of Tumour Necrosis Factor-α in General Inflammation and Uveitis

TNF-α is a cytokine that is produced in a soluble and membrane-bound form by different cells of the immune system, including macrophages, T cells and natural killer cells. It acts by binding to two receptors: p55 TNFr and p75 TNFr. Its pleiotropic action in the

immune system includes activation of T cells and recruitment of inflammatory cells such as macrophages into the sites of inflammation. In the model of experimental autoimmune uveitis (EAU), it has been demonstrated that TNF-α may play a key role in uveitis. In the model of endotoxin-induced uveitis (EIU) in rats, an early rise of TNF-α in the aqueous humour and serum is detectable. Injection of TNF-α into the vitreous of rats[2] and mice[3] results in acute uveitis with infiltration of polymorphonuclear granulocytes. In patients with chronic uveitis, TNF-α levels have been shown to be elevated in serum, but less so in the aqueous humour.[4] Mice that are deficient in p55 TNFr and p75 TNFr have attenuated ocular inflammation compared with controls, using an immune complex model for uveitis.[5] A TNF-α receptor–immunoglobulin G (IgG) fusion protein has been shown to decrease the intensity and prolong the onset of uveitis.[6] Therefore, there seems to be a clear rationale for the use of TNF-α-blocking agents in uveitis.

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Available Tumour Necrosis Factor-α-blocking Drugs

Currently, there are three TNF-α-blocking drugs in clinical use: etanercept, infliximab and adalimumab. Etanercept (Enbrel®) is a soluble fusion protein of the extracellular ligand-binding portion of human TNF receptor p75 and the Fc portion of human IgG_1. In particular, it inhibits the trimer form of TNF-α – inhibiting TNF-β to a lesser extent – without affecting production or serum levels of TNF. It is injected subcutaneously at a dose of 0.8mg/kg once or twice a week in children and adolescents. The half-life of etanercept is 4.25 days. Infliximab (Remicade®) is a chimaeric IgG_1 monoclonal antibody composed of a human constant and a murine variable region. It inhibits the monomer and trimer forms of TNF, blocking soluble and transmembrane TNF-α. It is administered intravenously at a dose of 3–10mg/kg over at least two hours every two to eight weeks. The half-life of infliximab is eight to 9.5 days. Adalimumab (Humira®) is a recombinant human IgG_1 human monoclonal antibody that binds specifically to TNF-α, blocking soluble and transmembrane TNF-α. It is administered subcutaneously every other week at a dose of 40mg/kg. As for infliximab, the half-life of adalimumab is eight to 9.5 days. All three drugs are approved for the treatment of various rheumatic disorders in adults. Etanercept is also approved for the treatment of ankylosing spondylitis, psoriasis and JIA. The spectrum of side effects is becoming clearer after years of use.

Side Effects

Injection-site Reactions

After injection of etanercept or adalimumab, reddening with swelling at the injection site may occur. Although this is harmless, it may lead to reduced compliance among patients. Cooling the skin before injection may help to control this side effect.

Autoantibody Production

Experimental reduction of TNF-α activity may lead to reduced control of autoantibody formation and increased risk of infection. Clinically, antinuclear autoantibodies are found in up to 75% of patients. Fortunately, this leads to clinical lupus erythematosus only in rare cases. Due to its chimaeric character, infliximab can also induce antichimaeric antibodies:[7] it can lead to anaphylactic reaction[8] and formation of neutralising antibodies, as well as anti-DNA antibodies, which is why it is normally administered with methotrexate (MTX). The extent to which similar effects are seen with adalimumab is unclear at the moment.

Infection

It seems that all TNF-α-blocking agents can induce infections. In particular, they can reactivate tuberculosis, which may result in sepsis. Recently, uveitis due to tuberculosis under etanercept has also been described.[9] Therefore, before using TNF-α blockers, tuberculosis must be excluded.

Induction and Reactivation of Uveitis

Reactivation is a particular problem with etanercept,[10–12] but this drug can probably also induce uveitis for the first time, as has been shown in patients with HLA-B27-associated arthritis and JIA, and also in those with rheumatoid arthritis, a disorder that is not normally associated with uveitis. In some patients, a rechallenge has shown the definite role of etanercept in this process. Induction of uveitis has only rarely been described with infliximab and adalimumab. The anti-TNF-α antibodies bind the transmembrane-bound TNF of T cells, inducing apoptosis of activated lymphocytes. Guignard et al.[13] suggest that this apoptosis effect, which is not found in etanercept, may be a reason for the different effects of the three drugs.

Induction and Reactivation of Demyelinating Diseases

There are multiple reports about induction of retrobulbar optic neuropathy, optic neuritis and multiple sclerosis.[14,15] This seems to be a side effect of this group of drugs, as suggested in case reports for all three drugs.

Tumour Necrosis Factor-α-blocking Agents and Paediatric Uveitis

TNF-α blockers have become third-line drugs in the treatment of JIA-associated uveitis, the only investigated form of paediatric uveitis. However, recent reports and studies suggest that these three drugs have different effects in terms of managing the uveitic inflammation.

Etanercept

Smith et al.[16] showed in a very small randomised, placebo-controlled, double-masked study in children with mild uveitis that the effect of etanercept (seven patients treated) on anterior segment inflammation was not different from that of placebo (five patients treated). Our group reported a retrospective study of 19 patients with uveitis[17] with JIA as underlying disease treated with etanercept. There was mild improvement of the uveitis in seven patients and no response in nine patients, and three patients worsened. However, in all patients the arthritis responded well to treatment with etanercept.[17] In a prospective study with 10 patients receiving etanercept and 10 receiving placebo, etanercept did not show an effect in terms of preventing relapses of uveitis compared with placebo.[18]

Infliximab

In a prospective study, Saurenmann et al.[19] reported on the different responses to etanercept and infliximab in JIA-associated uveitis. Overall, there was a better response to infliximab than to etanercept in reducing uveitis. The good response of uveitis to infliximab is supported by several other reports.[20–23] Tynjälä et al. were the first to report an exacerbation of uveitis while treating with infliximab. In their retrospective study with 24 patients taking etanercept and 21 patients taking infliximab, inflammatory activity improved more frequently in the infliximab-treated group.[24] Similar results have been published by Galor et al.,[25] who compared etanercept and infliximab in 22 patients. All of the etanercept-treated patients had to change medication to achieve control of ocular inflammation compared with only one patient in the infliximab group.

Adalimumab

While the experience with adalimumab is limited in adults, there is evidence for its effect in JIA-associated uveitis, substantiated by three studies that published data on its effect in groups of 14–20 patients. Unfortunately, for paediatric uveitis there are no official criteria to define the efficiency of the drug, which was the major difference between these three studies. Our group recently reported a retrospective trial of 18 patients with anterior uveitis, 17 of whom had JIA-associated anterior uveitis.[26] All of the patients had been treated previously with at least two other immunosuppressive drugs (MTX and cyclosporine A) in addition to oral corticosteroids, with no effect. Adalimumab was effective – defined by no relapse or at least two fewer relapses compared with the pre-treatment period – in 16 patients, mildly effective in one patient and not effective in one patient. The median time to response was three weeks (range two to four weeks).

Vazquez-Cobien et al. reported on 14 patients, of whom 13 showed a decrease in ocular inflammation on adalimumab,[27] defined as "sustained decrease in anterior chamber cell count over two visits three months apart". The median time to response was six weeks (range two to 12 weeks). All children had previously received at least one immunosuppressive drug that had been ineffective in treating uveitis. This study used weekly dosing instead of the standard treatment of every other week.

Recently, Tynjälä et al.[28] reported on 20 children, 18 of whom had been treated with at least one other immunosuppressive and 95% of whom had previously been on infliximab. The mean duration of adalimumab therapy was 18.7 months. Of the 20 patients, seven (35%) showed improved activity and one (5%) showed worsening activity, and in 12 patients (60%) no change was observed in the activity of uveitis. Those with improved activity were younger and had shorter disease duration. Inactive disease in this study was defined as 0 cells in the anterior chamber.

These reports, all resulting from highly selected, previously adequately treated patients from tertiary care centres, show very promising results for the use of adalimumab, since the side effects – such as injection-site reactions and the formation of neutralising antibodies – tend to be less frequent. The difference in the improvement rate seems to be dependent on the different outcome measurements. In our study we used the reduction of recurrences, defined as continuing increase of cells in the anterior chamber for some days. We strongly believe that a cell count of 0.5 – and probably even 1+ – in CAU children is still a very good situation; this is in contrast to some other types of uveitis, which were the basis of the Standardization of Uveitis Nomenclature (SUN) criteria.[29] In this regard the SUN criteria need some revision: response criteria for CAU should be defined depending on the underlying uveitis.

Summary and Conclusions

In the 'steroid' era, there was general agreement among experts that achieving 0 cells in the anterior chamber of CAU children was generally too difficult and that the prognosis in terms of the visual outcome might not be better. In the current era, new studies are needed regarding the response criteria and the final end-point of an effective treatment. Because of the half-lives of the TNF-α-blocking drugs, we strongly recommend controlling children at different time-points in the interval of application: the most reliable day for estimating the number of cells in the anterior chamber is just before re-administration of the drug.

Further studies are needed to confirm that differences do exist between etanercept on the one hand and infliximab or adalimumab on the other hand in terms of their effect on uveitis. Both groups differ in terms of their binding characteristics, because infliximab and adalimumab bind to both soluble and membrane-bound TNF, while etanercept binds to soluble TNF only. Different effects on complement activation and apoptosis may result: infliximab may lyse *in vitro* TNF-producing cells via activation of complement, and seems to induce apoptosis of immunocompetent cells and monocytes. In addition, the different pharmacokinetic behaviours of these three TNF inhibitors may influence their effect on uveitis, and probably less so on arthritis. In particular, the frequency of drug administration could be a very crucial point for the treatment of these children.

In conclusion, TNF-α blockers offer a very effective method of treating JIA-associated uveitis that is refractory to second-line immunosuppressive therapy. Of the three drugs available, infliximab and adalimumab seem to have a better effect on reducing ocular inflammatory activity. Because of its administration by subcutaneous injection and its better side-effect profile, adalimumab may be the most favourable TNF-α-blocking agent, but prospective, randomised trials are required to confirm this hypothesis. Unfortunately, signals from industry indicate that there is only very limited interest in such trials. Fortunately, adalimumab is now approved in the US for children with JIA, and approval in the European Medicines Agency (EMEA) countries is expected within the next few months.

Regarding treatment with TNF-α-blocking agents, some important open questions remain:

- What is the risk of infection besides tuberculosis, and what is the risk of malignancies?
- For how long do the drugs have to be used?
- What is the result of combining these drugs with immunosuppressive drugs in terms of increasing effectiveness and reducing antibody production?
- How should ineffective treatment be handled: changing regimen, reducing the treatment interval or adding other immunosuppressives?
- Why do some children with chronic uveitis respond very well to etanercept while others do not?
- Why do TNF-α blockers become ineffective after a certain period of time (without autoantibody production), and why is it effective

to change to another TNF-α blocker, even when the second drug may previously have become ineffective too?

We have to be aware that nowadays the development of drugs, especially biologicals, is so rapid that some of these important questions may not be answered before the 'new drug' has become an 'old drug' and been substituted by a more recent agent. However, these open questions should lead to extremely careful use of TNF-α blockers in all patients with uveitis, but especially in children. All of the published data demonstrate very good effects in children in whom the previous therapy was not effective, showing that these drugs can help even in situations that seem to be hopeless. The first five- or even 10-year observations will hopefully tell us that TNF-α-blocking drugs have enormously changed the prognosis of paediatric uveitis, a previously often blinding disease. ■

Manfred Zierhut is an Associate Professor of Ophthalmology at the University Eye Hospital in Tübingen. His scientific interests include clinical and experimental immunology, especially in uveitis, conjunctivitis and keratitis, eye diseases caused by systemic disorders, immunological mechanisms leading to uveitis, therapy of Behçet's disease, allergies of the eye and dry-eye syndromes. Dr Zierhut is a member of the Intermedial Uveitis Study Group, the Inflammation Society and the Tear Film and Ocular Surface Society (TFOS). He has 105 original publications in journals, 62 chapters in books and 190 posters/proceedings of meetings and abstracts, is the editor of 24 books, has given more than 600 lectures and has been the chief organiser of 32 workshops or meetings. Dr Zierhut is Editor in Chief of *Ocular Immunology and Inflammation*. He also heads the German and European Uveitis Patient Interest Groups. He completed his residency at the Universities of Hannover and Tübingen and a fellowship at Massachusetts Eye and Ear Infirmary at Harvard Medical School.

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Editor's Recommendation

Adalimumab in Juvenile Idiopathic Arthritis-associated Chronic Anterior Uveitis

Tynjälä P, et al., *Rheumatology (Oxford)*, 2008;47:339–44.

The aim of this study was to evaluate the efficacy of adalimumab in juvenile idiopathic arthritis (JIA)-associated uveitis. This entailed a retrospective observational study of 20 patients with JIA and chronic uveitis on adalimumab treatment. The ocular inflammation and improvement was assessed according to the Standardization of Uveitis Nomenclature (SUN) criteria. Results showed at the initiation of adalimumab the mean age of patients was 13.4 years and the mean duration of uveitis was 8.7 years. Seventeen patients (85%) had polyarticular JIA and 19 (95%) had previously been on anti-tumour necrosis factor (TNF) treatment. The mean duration of adalimumab therapy was 18.7 months. Of the 20 patients, seven (35%) showed improved activity, one (5%) showed worsening activity and in 12 (60%) no change was observed in the activity of uveitis. Those with improved activity were younger and had shorter disease duration. The mean number of flares/year decreased from 1.9 to 1.4. Serious adverse events or side effects were not observed. Seven patients discontinued adalimumab during the follow-up: six because of inefficacy and one because of inactive uveitis. The study concluded that adalimumab is a potential treatment option in JIA-associated uveitis, even in patients non-responsive to previous other anti-TNF therapy. ■