EXTENDED REPORT

Adalimumab in the therapy of uveitis in childhood

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Br J Ophthalmol 2007;**91**:319–324. doi: 10.1136/bjo.2006.103721

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Accepted 4 October 2006
Published Online First 11 October 2006

Purpose: Chronic anterior uveitis in children often takes a serious course. Despite various immunosuppressive drugs some children do not respond sufficiently and there is a high risk of them becoming seriously disabled. Anti-TNF alpha therapy has been shown by our group and others to be mostly ineffective (Etanercept) or partly effective (Infliximab) with the risk of anaphylactic reactions. Here we report on 18 young patients treated with Adalimumab (Humira®), a complete humanised anti-TNF alpha antibody.

Methods: We retrospectively analysed 18 patients, who were treated with Adalimumab (20–40 mg, every 2 weeks, when ineffective every week); 17 had juvenile idiopathic arthritis, one was without detectable underlying disease. The age at onset of arthritis varied from 0.5–15 years and for uveitis from 2–19 years. Patients were included when the previous anti-inflammatory therapy had been ineffective. It consisted of systemic steroids (n = 18), Cyclosporin A (n = 18), Methotrexate (n = 18), Azathioprine (n = 12), Mycophenolate mofetil (n = 4), Cyclophosphamide (n = 2), Leflunomide (n = 3), Etanercept (n = 8) and Infliximab (n = 5). The grading for uveitis was: (a) effective: no relapse or more than two relapses less than before treatment, (b) mild: one relapse less than before treatment, (c) no response: no change in relapse rate and (d) worsening: more relapses under treatment than before. The grading for arthritis (depending on the clinical findings), using three out of six parameters of the ACR PED Criteria, was: effective, mild, no response, worsening.

Results: For arthritis (n = 16) the response to Adalimumab was effective in 10 of 16 patients, mild in three patients, three did not respond. For uveitis (n = 18) Adalimumab was effective in 16, mild in one child, and one patient did not show any effect. After a very good response initially a shorter application time had to be used to maintain the good anti-inflammatory effect in one child. Additional immunosuppressive treatment was used in seven of the effectively treated children. Due to elevation of liver enzymes in one patient, who also took MTX, Adalimumab had to be discontinued. No anaphylactic reactions or increased frequency of infections since start of Adalimumab treatment was reported.

Conclusions: For our group of children with long lasting disease our results show that Adalimumab was effective or mildly effective against the arthritis in 81%, but in uveitis in 88%. While these results regarding arthritis are comparable with other TNF-alpha blocking drugs (Etanercept), Adalimumab seems to be much more effective against uveitis than Etanercept. Anaphylactic reactions, found in a previous study from our group after Infliximab treatment, were not seen with Adalimumab. The necessary dosage and the treatment period, which probably have to be defined individually for each patient, remain unclear.

Uveitis in children remains one of the most challenging problems in intraocular inflammation. Especially chronic anterior uveitis, associated with juvenile idiopathic arthritis (with or without antinuclear antibodies) and intermediate uveitis may cause long lasting, recurrent disease, and especially chronic anterior uveitis needs early and aggressive treatment, for good visual acuity results. Because periocular and periarticular steroid therapy is difficult to apply in children, oral corticosteroids remain the first line of treatment. Side effects like Cushing Syndrome and growth retardation are serious and not tolerable for a longer time in children. Therefore a variety of other immunosuppressive agents are in use. Besides the very toxic Cyclophosphamide, there are Methotrexate, Cyclosporin A, Azathioprine, and recently also Mycophenolate mofetil.[1] None of these drugs have been demonstrated to be effective in controlled studies. Conduction of such trials is complicated for a variety of reasons including funding issues, but also because only few uveitis centres have sufficient numbers of patients with severe, complicated disease courses, suitable for enrolement in such investigations. The goal for immunosuppressive treatment of uveitis in children is to prevent complications like cataract (corticosteroid sparing effect), to reduce the rate of recurrences, and to be as non-toxic as possible.

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. The management of JIA has improved in recent decades, and morbidity due to the disease has significantly decreased as a result of the use of more effective drugs and their combinations. In particular, anti-TNF agents seem most effective.

In the model of experimental autoimmuneuveitis (EAU) it has been demonstrated that tumor necrosis factor-alpha (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 aqueous humor and serum is detectable.[2] Intravitreal TNF-α injection in mice[3] and rats[4] results in acute uveitis after infiltration of polymorphonuclear granulocytes. Lacombe et al[5] analysed TNF-α levels of uveitis patients in aqueous humor and serum, concluding, that an elevated level of TNF-α in serum, but not in aqueous humor, seems to be associated with a recurrent pattern, e.g. chronic uveitis. So, blocking TNF-α seems to be a promising approach in the therapy of uveitis.

Today, there are three drugs commercially available to influence TNF-α:

Etanercept (Enbrel®), a recombinant fusion protein, combining two extracellular human p75 TNF receptors with the Fc domain of a human IgG1, neutralizing TNF-α before binding to its receptor;

Infliximab (Remicade®), a mouse-human chimeric IgG1 monoclonal antibody to TNF-α, neutralizes both the soluble and the membrane-bound form of TNF-α;

Adalimumab (Humira®), a recombinant human IgG1 monoclonal antibody to TNF-α, also effecting TNF-α bound to receptors like Infliximab.

TNF inhibitors have been shown to be effective and safe for the treatment of various diseases, like rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, Crohn's Disease, sarcoidosis,[6] and also uveitis.

So far only a limited number of controlled studies have shown such an effect, especially investigating etanercept and infliximab, but it seems that not all three are equally effective in these disorders. For adult rheumatoid arthritis, all three TNF inhibitors seem to be very effective.[7 8] Etanercept has been investigated in three monotherapy and two MTX-added studies,[9–12] while Infliximab was proven to be effective in one large study (ATTRACT).[13–15] Finally for RA, also Adalimumab as monotherapy[16 17] and in combination with MTX[17–20] or standard treatment of rheumatoid arthritis[21] has been shown effective. Recently there has been a report of a successful treatment of juvenile-onset HLA-B27-associated severe and refractory heel thesitis (one patient)[22] and of orbital myositis (two patients) with Adalimumab.[23] For JIA, etanercept is the only one licensed, but phase III trials for Infliximab and Adalimumab are now complete, but not yet published.

TNF inhibitory drugs have also shown to be effective in preventing experimental uveitis by Avunduk et al who used Etanercept in the Endotoxin-induced model (EIU).[24] Koizumi et al [25] have demonstrated that Etanercept significantly reduces leukocyte rolling and adhesion in the EIU model.

The first results in adult uveitis demonstrated the effectiveness of these drugs. Various studies have investigated Infliximab in Behçet's Disease and other intraocular inflammations,[26–43] Etanercept has also been studied.[28 44] Only one recently published article reports the use of Adalimumab in Behçet's Disease.[45] Meanwhile, first experience also is available for Etanercept in the treatment of juvenile uveitis,[46–51] and also for Infliximab,[52] but not for Adalimumab.

The aim of this prospective study was to investigate the efficacy of Adalimumab, the side effects and the steroid-sparing effect on juvenile uveitis and, when associated, on juvenile arthritis.

PATIENTS AND METHODS

In a retrospective analysis, we included 18 children or young adults with juvenile uveitis and/or arthritis. The age at the beginning of arthritis varied from 0.5–15 years and of uveitis from 2–19 years.

All patients were seen at the Dept. of Ophthalmology and Dept. of Paediatrics, University of Tuebingen, and/or at the Rheumatic Children's Hospital, Garmisch-Partenkirchen. All children with arthritis had also been controlled by their pediatric rheumatologist. Inclusion criterion was that previous therapy was ineffective for the control of uveitis, consisting of at least one additional immunosuppressive drug besides steroids. Table 1 summarizes the age and gender of the children, onset of arthritis and/or uveitis, the diagnosis regarding uveitis and rheumatologic disorder (as far as detectable), and also the previous treatment.

Seventeen of these children had juvenile idiopathic arthritis, one child had no detectable underlying disorder. The previous therapy consisted of systemic steroids (n = 18), Cyclosporine A (n = 18), Methotrexate (n = 18), Azathioprine (n = 12), Mycophenolate mofetil (n = 4), Cyclophosphamide (n = 2), Leflunomide (n = 3), Etanercept (n = 8) and Infliximab (n = 5). In three of the seven Etanercept-treated children, a first episode of uveitis started under this treatment. One child (no. 18) developed a severe recurrence of her uveitis after a recurrence free period of years. Discontinuation of Etanercept stopped uveitis directly. Infliximab had to be stopped in two children due to anaphylactoid reactions.

The primary outcome parameter was the recurrence rate of uveitis or arthritis. A ''relapse'' of uveitis was defined as increase of the cells in the anterior chamber of 2+ or more (or from 3+ to 4+), according to the SUN-criteria.[53] Baseline for a changing recurrence frequency was an observation period of at least 2 years before initiation of Adalimumab and at least 6 months after begin of treatment. A ''relapse'' of arthritis was defined as increase of clinical (reduction of motility) or laboratory inflammation parameters (ESA, CRP).

The grading of uveitis and arthritis is detailed in table 2. The secondary study parameter was the time of improvement after starting Adalimumab. ''Improvement'' for uveitis was defined as a reduction of at least 2+ cells in the anterior cells. ''Improvement'' for the arthritis was defined according to the ACR PED Criteria. So the number of active joints, the number of joints with limited range of motion, ESR and additionally CRP had been determined before and during Adalimumab. Since this is a retrospective study, it was not possible to determine the remaining ACR PED Criteria as well (VAS scales, CHAQ).[54] In addition, the individual joints were classified as ''improved'' or ''not improved''. All estimations of the arthritis have been done exclusively by pediatric rheumatologists. Improvement was only marked in patients when Adalimumab was initiated in active stage of disease, what was not the case in all patients.

Adalimumab was started at a dosage of 20–40 mg every two weeks depending on body weight. This frequency was chosen due to a half-life of 15–19 days.[55] If ineffective, as happened in one child, the treatment interval was reduced to 1 week (patient no. 12), in one child treatment interval was every 3 weeks (no.5). The previous treatment was stopped (in case of other TNF-α-blocking substances) or slowly tapered. The median observation period for children in which this strategy was effective for arthritis and uveitis (n = 13), was 16.8 months (at least 5 months).

RESULTS

For arthritis (n = 16) Adalimumab was effective in 10 patients, mildly effective in three patients, three children did not show any response. For uveitis (n = 18) Adalimumab was effective in 16 children, mildly effective in one child, and one child did not show any effect. The rapid onset of response for uveitis was possible to state in 11 children. Response was found after 2–16 weeks (medium 6 weeks). For arthritis response was stated for 8 children after 2–4 weeks (medium 3 weeks). After very good response in child no. 12 the application time had to be shortened from every 2 weeks to weekly, to continue the good anti-inflammatory effect. Additional immunosuppressive treatment was used in seven of the effectively treated children (MMF 2, Aza 2, CsA 2, MTX 1). Due to elevation of liver enzymes in one patient (no. 6), who also was under treatment with MTX, Adalimumab and MTX had been stopped. After a few weeks the treatment was started with Etanercept, and the inflammation of joint and the eye remained controlled. There were no anaphylactoid reactions or a higher incidence of infections since beginning of the Adalimumab treatment in any patient of the group. In 15 children systemic steroids were stopped, in the remaining 3 children a reduction to low dose was possible.

Table 1 Underlying diagnosis, pre-treatment, duration and effect of treatment

Patient No.	Gender	Begin of disease (years) Uveitis/ Arthritis	Diagnosis	Previous history (besides steroids)	Duration of Adalimumab treatment and add. therapy (month)	Side effects	Effects on: Arthritis	Effects on: Uveitis	Consequence
1 KK	f	3/4	Uveitis with JIA/ category psoriasis arthritis, HLA-B27 pos	CsA, MTX, Etanercept	4, then stopped	Injection painful	non-effective	noneffective	Infliximab: effective
2 FW	m	11/non	chronic anterior uveitis of unknown origin	CsA, MTX, Etanercept, Aza, Immunoglobulines, Infiximab	3, then stopped, low dose steroids	no	–	mild	MMF, Steroids: partially effecttive
3 CT	f	5/5	Uveitis with JIA/ category oligoarthritis	Aza, CsA, MTX, Infliximab, MMF	27, MMF low dose	mild local reaction	effective	effective	–
4 KT	f	2/3	Uveitis with JIA/ category oligoarthritis	CsA, MTX, Aza, Cyclosposphamid, MMF, Infliximab	26, low dose steroids, MMF	–	effective	effective	–
5 KD	f	6/4	Uveitis with JIA/ category oligoarthritis, with secondary glaucoma	CsA, MTX, Cyclosposphamid, Procarbazine	37, begin: all 6 weeks: mild later: all 3 weeks: effective	HSV Keratitis	effective	effective	–
6 KJ	f	$2^{10}/_{12}/2^{6}/_{12}$	Uveitis with JIA/ category oligoarthritis	MTX Aza, CsA	4, stopped due to side effects	liver enzymes elevated, stopped	effective	effective	Etanercept: effecttive
7 TA	m	$5^{5}/_{12}/4^{1}/_{12}$	Uveitis with JIA/ category polyarthritis, RF neg, HLA-B27 pos	Etanercept (first uveitis induced), CsA, MTX	2, stopped due to ineffectivity for the arthritis	–	non-effective	effective	CsA, Steroids: effective
8 RM	m	$4^{6}/_{12}/4^{9}/_{12}$	Uveitis with JIA/ category oligoarthritis	MTX, Aza, CsA, Leflunomide, MMF	15, Aza and steroids low dose	–	effective	effective	–
9 DA	f	$8^{3}/_{12}/15^{1}/_{12}$	Uveitis with JIA/ catgory oligoarthritis	CsA, Etanercept (first uveitis induced), MTX, Aza, Leflunomide	25	–	effective	cells effective, IOP: +++	–
10 MM	f	4/0	Uveitis with JIA/ category oligoarthritis ANA pos	CsA, MMF, Etanercept, Cyclophosphamid, Aza, MTX	20, CsA	–	–	effective	–
11 WJ	m	5/5	Uveitis with JIA/ category persistent oligoarthritis HLA-B27 pos	MTX, Aza, CsA, Infliximab	20		mild	effective	–
12 WD	f	$3^{8}/_{12}/^{1}/_{2}$	Uveitis with JIA/ category oligoarthritis	MTX, CsA, Etanercept	25, every week	Injection painful	effective	effective	–
13 ES	f	$19/1^{3}/_{4}$	Uveitis with JIA/ category polyarthritis, begin with oligoarthritis, ANA pos	Etanercept (first uveitis induced), Aza, CsA, MTX	19	Burning sensations	mild	effective	–
14 KL	f	6/6	Uveitis with JIA/ category extended oligoarthritis, ANA pos, HLA-B27 neg	MTX, MMF, Infliximab, CsA, Aza	7		non-effective	effective	–
15 KC	f	2/2	Uveitis with JIA/ category extended oligoarthritis,	MTX, CsA	8, MTX	Burning sensations	effective	effective	–
16 DS	f	$5^{1}/_{2}/15$	Uveitis with JIA/ category extended oligoarthritis, ANA pos, HLA-B27 neg, RF neg.	CsA, MTX	8, CsA	Burning sensations	effective	effective	–
17 SAS	f	$2^{3}/_{4}$-/$3^{1}/_{12}$	Uveitis with JIA/ category extended oligoarthritis, ANA pos, HLA- B27 neg. RF neg.	MTX, CsA, Aza,	7, Aza		effective	effective	–
18 BT	f	$2^{1}/_{2}/3^{7}/_{12}$	Uveitis with JIA/ category extended oligoarthritis ANA pos, HLA-B27 neg	Aza, MTX, CsA, Leflunomide, Etanercept	25	Mild local reaction	mild	effective	–

ANA, antinuclear antibodies; Aza, Azathioprine; CsA, Cyclosporin A; HSV, herpes simplex virus; JIA, juvenile idiopathic arthritis; MMF, Mycophenolate mofetil; MTX, Methotrexate; neg, negative; pos, positive; RF, rheumatoid factor

In one patient (no. 5) a basal cell carcinoma had developed under the previous treatment (CsA, MTX, cyclophosphamide). After beginning of treatment with Adalimumab this tumour had not changed in size, but, being aware of it, some weeks later was removed.

Seven patients reported about problems with the injection, reaching from mild local reaction (one child), burning sensations (three children) to pain around the injection site (two children). Cooling the injection site before injection strongly reduced the burning sensations.

Table 2 Grading system for arthritis and uveitis

Grading	Arthritis	Uveitis
+	Effective: complete response without any sign of arthritis	Effective: no relapse or more than 2 relapses less than before treatment
(+)	Mild: improvement of arthritis with remaining signs	Mild: one relapse less than before treatment
0	No response: no clinical change in arthritis	No response: no change in relapse rate
–	Worsening: progress of sign of arthritis	Worsening: more relapses under treatment than before

DISCUSSION

Here we report, for the first time, the use of Adalimumab in juvenile uveitis. For our group of children with severe uveitis, mostly associated to juvenile idiopathic arthritis, treatment with Adalimumab was effective in 83%, and for the associated arthritis in 63%. Regarding the effect on arthritis these results are comparable with other TNF-alpha blocking substances like Etanercept[46 47 56] and Infliximab, but Adalimumab seems to be much more effective than Etanercept for uveitis.

The effect of anti-TNF-α treatment in uveitis may, at least in part, be explained by increasing the fraction of peripheral CD4+ T cells expressing IL-10 with a recovery of visual function. Because the level of interferon-gamma decreased, these findings suggest that blocking TNF-α causes deviation of the immune response toward the Th2 type. This has been demonstrated in patients who were treated with a recombinant protein generated by fusing the p55 TNF-α receptor with human IgG1 correlates[57] but also in EAU[58]

Also, down regulation of macrophages has been shown to be an important mechanism for TNFα-blocking drugs.[59–61]

Our group of patients also included seven children who previously had not responded to Etanercept, and three of these seven children had experienced a first episode of uveitis under Etanercept. This has been also reported in other studies.[28 46 51 62 63] At the moment it remains unclear if this reflects the clinical outbreak of a previous subclinical uveitis, or if Etanercept can induce uveitis.[62] We have seen one adult patient with rheumatoid arthritis (a disease which is not known to be associated with any form of uveitis) who developed anterior uveitis under the treatment with Etanercept. This could indicate that Etanercept by itself can induce uveitis. On the other side, in patient no. 6 Adalimumab treatment had been stopped due to elevation of liver enzymes (probably due to the additional MTX-treatment), when she was in complete remission for arthritis and uveitis. She was later treated with Etanercept, and the anti-inflammatory effect continued like under Adalimumab.

In 2468 rheumatoid arthritis patients treated in clinical trials with Adalimumab (median of 24 months), 48 malignancies of various types were observed, including 10 patients with lymphoma. The Standardized Incidence Ratio (ratio of observed rate to age-adjusted expected frequency in the general population) for malignancies was 1.0 (95% CI, 0.7, 1.3) and for lymphomas 5.4 (95% CI, 2.6, 10.0) (Product Information for Humira). Recently Chakravarty *et al*.[64] analysed a cohort of 15 789 patients with RA, and they found that non-melanoma skin cancer was associated with an hazard ratio of 1.19 ($p = 0.042$), but 1.28 ($p = 0.014$) with the use of prednisone, 1.24 ($p = 0.89$) with the use of TNF-inhibitors alone, and in combination with Methotrexat 1.97 ($p = 0.001$). One of the children in our study had developed basal cell carcinoma, which we were not aware of, before treatment with Adalimumab. She had not seen any progression, and few weeks after starting Adalimumab the tumour was excised.

Recently, additional side effects for Adalimumab have been published, like drug-induced lupus erythematodes in one patient[65] and endophthalmitis by Propionibacterium acnes in another patient, who additionally was under treatment with leflunomide.[66]

While all three TNF-inhibitors seem to be similarly effective in treating rheumatoid arthritis, the first reports for Etanercept in juvenile idiopathic arthritis[67 68] were much more enthusiastic than for Infliximab, where Gerloni et al [69] reported having to stop the therapy in seven of 24 patients due to adverse events during the infusions. More favourable results are reported in the meantime for Infliximab[70] for this group of children. We also found Infliximab effective against uveitis and arthritis in our children, but two children soon developed anaphylactoid reactions. This side effect has been described in adults in app. 10% of patients under treatment with Infliximab. It may be possible that children are more susceptible to this dangerous side effect. No anaphylactoid reactions have been seen in the Adalimumab treated patients, including the two children who previously had developed anaphylactoid reaction under Infliximab (No. 3 and 4). Some of the children complained about painful injection sites, an effect which seems very individual.

Besides patient No. 5, who has developed HSV-keratitis, no severe infections were detected in our group. But it has been shown for Adalimumab, and also for Infliximab, that pre-existing tuberculosis can exacerbate under treatment.[71]

Further studies have to show that differences do exist between etanercept on the one side and Infliximab or Adalimumab on the other side, regarding their effect to uveitis. Both groups differ in their binding characteristics, because Infliximab and Adalimumab bind to both soluble and membrane-bound TNF, while Etanercept only binds to soluble TNF.[72] Different effects on complement activation and apoptosis may result. So, Infliximab may lyse in vitro TNF-producing cells via activation of complement,[73] and seems to induce apoptosis of immunocompetent cells and monocytes.[74] Also the different pharmacokinetic behaviours of these three TNF-inhibitors may influence the effect on uveitis, probably less on arthritis. Especially the frequency of drug administration could be a very crucial point for the treatment of these children (see patient No. 8 and 12).

Delaunay et al [75] and others[76] have demonstrated that a switch from one TNF-inhibitor to the other in RA, spondylarthropathies and psoriatic arthritis can be useful. Our study confirms these results for uveitis disclosing favourable results in all directions: good results for Adalimumab, when Infliximab or Etanercept were not effective or not tolerated, but also effects for etanercept or Infliximab in case of no response to Adalimumab. Whether Adalimumab is more effective than Infliximab is unclear at the moment. Interestingly, Mushtaq et al [45] recently described three patients with Behcet's disease who were uncontrolled under Infliximab but were free of recurrences after switching to Adalimumab. So, the group of TNF-inhibitors has extensively enlarged our repertoire of effective treatment modalities, in addition to immunosuppressive drugs.

Our group recently published the positive effects of Mycophenolate mofetil in uveitis in childen.[1] The group which showed less effect in this study was the JIA associated group, and this study also had four patients who had developed

recurrences despite Mycophenolate mofetil treatment before Adalimumab treatment started. This drug could be an alternative for MTX in patients who need additional immunosuppressive treatment under Adalimumab, as in patients no. 3 and 4.

In conclusion, the results for our group of children with most severe uveitis mostly associated with JIA, show that Adalimumab seems to be a highly effective treatment, controlling inflammation of the eye and the joint, with acceptable mild side effects. The dosage and the duration of treatment have still to be investigated in a larger study.

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