Safety of anti-TNFα therapy in children with juvenile idiopathic arthritis

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Received on December 11, 2003; accepted in revised form on February 13, 2004.

Clin Exp Rheumatol 2004; 22: 252-258.

Key words: TNFα, juvenile idiopathic arthritis, adverse effects, infections, tuberculosis.

ABSTRACT

Anti-TNFα agents are frequently used in the treatment of severe JIA. Etanercept, a fully human soluble recombinant tumour necrosis factor p75 receptor Fc fusion protein, has been registered for the treatment of polyarticular course JIA patients who fail to respond or do not tolerate methotrexate (MTX). Infliximab, a chimeric human-mouse monoclonal antibody to TNFα, is expected to be registered soon for JIA and Crohn's disease (CD) in children. As in adults, both agents are effective in controlling inflammation and inhibiting the progression of joint destruction. Despite this good clinical efficacy, the physician must remain alert for potential side effects, especially after prolonged use. This review gives an overview of the reported adverse events.

Introduction

Tumour Necrosis Factor alpha (TNFα) is a proinflammatory cytokine that plays a key role in the immune response, in the defence against micro-organisms and in initiating inflammatory processes. In mice models TNFα induces maintenance of the latency of tuberculosis. Blocking TNFα in cases of active infection with *Mycobacterium tuberculosis* results in failure to form tight granuloma's in mice and thereby dissemination can easily occur (1). Besides its effect on synovial fibroblasts, endothelial cells, and inflammatory cells, TNF-α also causes systemic symptoms like fever and cachexia. Elevated levels are found in the blood and synovial fluid of rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) patients (2).

Since their introduction in 1998, anti-TNFα agents have been frequently used in the treatment of severe JIA. Two drugs are registered for children. Etanercept (Enbrel®) is a fully human soluble recombinant tumour necrosis factor p75 receptor Fc fusion protein (2, 3). It has been registered for the treatment of polyarticular course JIA patients who fail to respond or do not tolerate methotrexate (MTX). Infliximab (Remicade®) is a chimeric human-mouse monoclonal antibody to TNFα that has been registered for the treatment of rheumatoid arthritis (RA) and Crohn's disease (CD) in adults (4). Formal approval for JIA and CD in children is expected soon, depending on the results of ongoing phase III trials. Molecular and pharmacologic differences between etanercept and infliximab are described in Table I.

Both agents are effective in controlling inflammation and inhibiting the progression of joint destruction, even when the response to one or more other disease modifying antirheumatic drugs has proved insufficient (3, 4). Adverse effects of TNF-α blockade include infectious, autoimmune and allergic events. Since the frequency of these adverse events was rather low in the initial clinical trials in RA and JIA, infliximab and etanercept therapy were considered to be relatively safe (5-7)

To date, more cases of serious side effects induced by anti-TNFα agents have been reported. They raise the question as to what the long-term effect of inhibition of the TNFα-pathway will be. Children with JIA who face the prospect of long-term anti-TNF therapy constitute an important group in this regard. This review article provides an overview of the adverse events in children reported after the use of etanercept or infliximab, with a focus on infectious and autoimmune complications and the possible association with malignancies. Because of the differing aspects that must be highlighted the two therapies are discussed separately.

Table I. Molecular and pharmacologic differences between infliximab and etanercept

	Infliximab	Etanercept
Description	Human-mouse chimeric IgG1k monoclonal antibody against TNFα	2 soluble human p75 TNF receptors conjugated to the Fc part of a human IgG1 antibody
Molecular weight (43)	149,100 kD	150,000 kD
Route of administration (3,4)	IV	SC
Target for binding (3,4)	Monomeric and trimeric forms of soluble and membrane bound TNFα	Monomeric forms of soluble and membrane bound TNFα, lymphotoxin-α
Affinity of binding (43, 44)	High affinity, slow dissociation	High affinity, rapid dissociation
Possible effect on cells (43)	Cell lysis, cell apoptosis by complement activation	No cell lysis
Effect on Tcells (48)	Long-lasting Th1 suppression	No Th1 suppression

IV= intravenous; SC = subcutaneous.

Table II. Patients characteristics of trials done with patients suffering JIAtreated with etanercept.

Trial	**Lovell *et al.* (8, 9)**			**Quartier *et al.*(10)**
	Initial safety study		Extension safety study	
Study design	Prospective, multicenter trial consisting of an open-label phase and a double-blind, placebo-controlled phase		Open-label, multicenter, extended treatment	Open-label, prospective, multicenter
	Open-label phase	Double-blind phase		
Number of patients	69	51	58	61
Patients characteristics				
Mean age (yrs.)	10.5	10.6	10	12.2
Mean duration of JIA(yrs.)	5.9	5.8	5.9	6.6
Co-medication (no. of patients)				
DMARDs	51	35	43	10
Corticosteroids	25	19	22	44
NSAIDs	66	49	56	Unknown

DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal anti-inflammatory drugs.

Infectious complications

Etanercept

Two open-label, prospective and multicenter trials have been carried out to asses the efficacy and safety of etanercept in children (Table II). Lovell *et al.* examined treatment with etanercept in 69 children aged between 4 and 17 years suffering from JIA with a polyarticular course (8). The study design consisted of 2 phases: a 3-month, non-comparative phase and a 4-month, double-blind, placebo-controlled phase. Patients were treated with 0.4 mg/kg etanercept twice per week, with a maximum-dose of 25 mg. The infectious complications that occurred are summarised in Table III. During the initial phase one patient was hospitalised for gastritis-flu syndrome.

In the placebo-controlled phase of the trial 51 patients continued with the therapy. The placebo group consisted of 26 patients, and the treatment group of 25 patients who received etanercept injections. The etanercept group did not experience a significantly higher frequency of adverse effects in the double blind phase than during the first phase of the trial and no significant differences compared to the placebo-treated patients were found.

The trial was followed by a non-blind extension study in which 58 patients continued etanercept therapy for 12 months (9). During the trial 9 children (16%) were hospitalised for a serious adverse event. Six of them presented with a serious infection (Table III).

The most serious event during the extension study with etanercept was septic shock in a 10-year-old girl. After arterial occlusion of the left leg was diagnosed, bloodcultures were positive for group A β haemolitic streptococci. She took etanercept for ~ 2 years in the present trial and was on low-dose prednisone (~5 mg/day for >2 years) and methotrexate (0.8 mg/kg/week). The patient recovered, but amputation of her left foot was necessary because of ischemic gangrene (9).

During the extension study with etanercept, 3 children (2 boys and 1 girl) were admitted to hospital due to varicella zoster virus (VZV) infection. None of them had received a varicella vaccination upon exposure to etanercept. One of the boys had a cervical subluxation and developed aseptic meningitis after the varicella infection (9). A case of VZV infection with a fatal course was reported 2 years after bone marrow

Table III. Infectious events during the Lovell trial (8, 9)*.

	Open-label phase	Double blind phase Etanercept (n = 25) (6.8 patient-years)	Placebo (n = 26) (3.7 patient-years)	Extension trial Etanercept (n = 58) (52.6 patient-years)
Infectious events	43 (62%)			
URTI	35%	1.92	1.68	1.31
Pharyngitis	14%	0.48	0	0.21
Gastrointestinal infection	12%	Unknown	Unknown	Unknown
Skin infection	Unknown	0.48	0	0.19
Flu syndrome	Unknown	0.24	0.6	0.17
Otitis	Unknown	0.12	0.6	0.13
Conjunctivitis	Unknown	0	0	0.10

Serious infectious event	No. of pts. who developed a serious infection during the extension trial
Peritonitis / appendicitis	1
Varicella infection	2
Infection with varicella zoster virus, complicated by aseptic meningitis and cervival subluxation	1
Sepsis	1
Post-operative wound infection / soft tissue infection	1

URTI = upper respiratory tract infection.
*Values are the number of events per patient-year (event-rate). Patients may have had more than one event of the same type. All occurrences of each event were counted for each patient. After the first 12 months of the extension study, only significant adverse events were recorded. Events are listed by decreasing rate for the extension trial (9).

transplantation during etanercept therapy (10).

The second trial was conducted by Quartier *et al.* in 61 patients who were followed up for a median of 13 months to assess the efficacy and safety of etanercept in patients with JIA (11). The number of infectious adverse events in this study is not exactly known. However, a high percentage of the patients (20%) experienced a severe side effect, including infections.

Post-marketing surveillance reported additional cases of infection, which underline the risk of infection during etanercept treatment. Among these post-marketing reports are abscess with bacteraemia and urinary tract infection (12). One case of tuberculous arthritis in a JIA patient has been described, although an increased risk for developing tuberculosis (TB) during etanercept therapy not has been proven thus far (13). It should be noticed, however, that 52% of the tuberculosis cases reported during etanercept treatment in adult patients were extra-pulmonary, in contrast to the normal distribution of 15-25% (14).

Infliximab

Because infliximab was introduced later than etanercept in JIA, only a few reports on the long term side effects of infliximab in JIA have been published. The adverse reactions reported so far have been limited to upper respiratory and urinary tract infections (15-17).

More is known about the use of infliximab in paediatric patients suffering from Crohn's disease. Over one hundred paediatric patients with CD receiving infliximab have been reported (18-20). In two studies that examined the efficacy and safety of infliximab in a total of 34 paediatric patients with Crohn's disease, no serious infections occurred (18, 19). However, the follow-up in these trials only lasted for 12 weeks and the populations studied were small (15 and 19 patients, respectively). This period seems to be too short to allow us to judge the long-term safety and the risk for infection during infliximab treatment.

A retrospective study focused on 82 patients for 26 months who were treated with infliximab for Crohn's disease. The mean follow-up per patient was not given. During this trial 3 patients developed herpes zoster and one patient developed *Listeria monocyto - genes* meningitis (20). Furthermore, 2 of the children suffering from Crohn's disease were diagnosed with histoplasmosis after treatment with this antibody (21). One boy experienced reactivation of an intramyocardial inflammatory process (*Staphylococcus aure - us*) after infliximab therapy (22).

Overall, according to the trials discussed above the risk of infection during treatment with infliximab in paediatric patients with Crohn's disease seems small. However, the infections that do occur can be serious, involving unusual species and an atypical presentation. Again, little is known about the potentially increasing risks following long-term treatment. Furthermore, adult patients with Crohn's disease who receive infliximab clearly incur an increased risk of developing severe infections, including tuberculosis, aspergillosis and histoplasmosis (1, 21, 23-25).

Multiple reports of tuberculosis among adult patients treated with TNF antagonists for RA or Crohn's disease have raised concerns about the safety of long-term anti-TNF blockade (1, 23, 26-30). Keane *et al*. reported 70 cases of tuberculosis in 147,000 adult patients treated with infliximab for RAor Crohn's disease, in which 56% were extrapulmonary. Disseminated tuberculosis was diagnosed in 24% of the patients. The infection occurred after treatment for a median of 12 weeks (26). At the end of November 2001, after infliximab was licensed for 3 years, the Food and Drug Administration (FDA) had registered reports of a total of 117 cases of infliximab-associated tuberculosis, some of them being fatal (31). In March 2003 this number was 242 (32). Not only is the incidence of tuberculosis infection alarmingly high after short treatment; the presentation is different as well. As demonstrated by Keane *et al*. and Hamilton *et al*., more than 50% of the cases present with extrapulmonary or disseminated disease, compared with the usual distribution of 15%-25% (26, 32).

So far one paediatric patient who developed a tuberculosis infection after the use of infliximab has been reported (35). A 9-year-old girl with systemic juvenile idiopathic arthritis was treated for 4 years with methotrexate, cyclosporin, and recurrent (methyl)prednisone at different doses, and finally etanercept. Because of continuing disease activity she was treated with high dose infliximab (20 mg/kg/month) for 4 months (36). The arthritis persisted and infliximab therapy was stopped. Three months later she developed a cystic subcutaneous swelling at the left wrist. PCR on the aspirated fluid was positive for *Mycobacterium tuberculosis* and tuberculostatic therapy was started. One month later the girl developed respiratory and circulatory insufficiency during a minor surgical procedure and died within a few hours. Microscopy showed a massive lipid pneumonia involving fulminant alveolar damage with an infiltrate of neutrophils and macrophages that was highly suggestive for an opportunistic infection. Hardly any normal lung tissue was seen. A diagnosis of pulmonary tuberculosis could not be confirmed. Bacterial cultures revealed *E. coli* and Enterobacter species (35).

Autoimmune events

Demyelination of the central nervous system (CNS) is a serious adverse event which has been reported after the use of TNF antagonists in adult patients. Contrary to tuberculosis infections, more cases have been reported after etanercept therapy (37). No cases of demyelinisation in JIApatients have been described during etanercept or infliximab treatment. The youngest person to be diagnosed with demyelination and later with multiple sclerosis (MS) after etanercept injections was a 21-year-old woman with juvenile idiopathic arthritis (38). Post-marketing surveillance describes cases of optic neuritis (12). For the present, the risk for children to develop these symptoms is unknown.

During the extension trial and post-marketing surveillance, two cases of manifest diabetes mellitus type 1 in children were reported after the use of etanercept injections for JIA (12, 39). There have been no cases of the onset of this disease after anti-TNFα therapy in adult patients.

Cases of drug-induced systemic lupus erythematosus (SLE) were reported after the use of both infliximab and etanercept in adult patients (40-42). In most patients, symptoms resolved after the discontinuation of therapy. The cases of SLE were associated with a higher rate of antinuclear antibodies and anti-dsDNA antibodies, developing after the start of infliximab or etanercept treatment. In most cases symptoms are limited to increased titers of anti-ds DNA antibodies, generally without the full clinical spectrum of SLE symptoms There have been no cases of drug-induced SLE in children.

Lymphoproliferative disorders

Since the introduction of anti-TNF therapy, concerns have been raised as to whether these new agents increase the risk of malignancies (2). It is known that patients who suffer from RA run an increased risk of developing a lymphoproliferative disorder, both Hodgkin's disease and non-Hodgkin's lymphoma. This increased risk for lymphoma may partly be a result of the deregulated immune function, which is of course one of the characteristics of this disease. Another risk factor is treatment with immunosuppressive drugs. The use of azathioprine, cyclophosphamide and methotrexate may contribute to the increased risk of developing lymphoma in patients with RA. This hypothesis is supported by the clinical observation that some of the lymphomas that developed during treatment regressed without anti-lymphoma treatment after discontinuation of therapy.

Between May 1999 and December 2000, twenty-six cases of lymphoproliferative disorders were reported to the FDAafter the use of anti-TNF therapy. Eighteen cases were reported after etanercept (incidence of 19 cases per 100,000 patients), and 8 following infliximab treatment (6.6 per 100,000 patients). All patients were aged above 25 years. No cases of lymphoma after the use of an anti-TNF agent were reported in paediatric patients (43).

Otheradverse events

Etanercept

During the first phase of the safety trial carried out by Lovell *et al*. the most common adverse events besides infection were injection side reactions (39%), headache (20%), abdominal pain (16%), vomiting (14%), nausea (12%), and rash (10%). No significant differences in adverse effects occurred between the two study groups during the first and second phases of the trial. Three patients in the etanercept group experienced serious adverse effects. One patient withdrew because of urticaria. Two patients were hospitalised, one for depression and a personality disorder, the other for gastritis-flu syndrome (8). In the following extension study, prolonged exposure to etanercept did not lead to a higher frequency of general adverse events (9).

The study conducted by Quartier *et al*. reported a higher percentage of severe side effects than the extension study by Lovell *et al*. Two patients developed severe psychiatric disorders and 2 pa-

tients had pancytopenia. Furthermore retrobulbar optic neuropathy, headaches and marked dysthesia, uveitis flare, vasculitic skin rash with systemic symptoms, major weight gain (6-20 kg) and appendicular abcess occurred (11). The risk of developing uveitis or vasculitis during etanercept treatment is not clear at the moment. Post-marketing surveillance reported additional cases of severe side effects. Besides the infections and autoimmune events mentioned above, there have been cases of pancytopenia, seizures, cutaneous vasculitis, coagulopathy and elevation of transaminase levels (12).

Infliximab

As noted above, little has been reported concerning the use of infliximab in paediatric patients with JIA.

According to trials that examined children with Crohn's disease treated with infliximab, there are few side effects (18-20). Those mentioned were self-limited and mainly restricted to injection side reactions. One cause for concern is the development of antibodies against infliximab which are associated with an increased risk of infusion reactions and a reduction in the response to treatment (44). Severe systemic reactions have been described in adults, but not in children (45).

Discussion

Treatment with anti-TNFα agents has become an important cornerstone in the treatment of severe, non-remitting forms of JIA. However, discontinuation of the treatment often leads to a relapse of disease activity. Therefore, long-term treatment with anti-TNF is an important issue with regard to severe infections, autoimmune disorders and possible malignancies.

The initial trials with etanercept showed few side effects. However, this lack of side effects may be due to the relatively short period of immune suppression studied. Further trials revealed serious infections, including three varicella zoster virus infections. For the prevention and treatment of VZV infections during TNF blockade the following guidelines are recommended. Unvaccinated children receiving etanercept who are exposed to varicella, but do not have a history of varicella infection should be treated with varicella-zoster immunoglobulin as soon as possible after exposure. Acyclovir should be given at the first sign of infection (9).

Tuberculosis is another serious infection following anti-TNF treatment that primarily develops in adult patients after the use of infliximab. The risk in children is not known. However, as the use of anti-TNFα therapy in paediatric patients with JIA or CD increases, it can be expected that the risk of developing tuberculosis infection will be present in children as well. Although the possibility of a latent infection is lower compared to adults, *de novo* infections can easily occur. Ten percent of the normal population who become infected develop active TB. The percentage is not known in subjects undergoing anti-TNFα treatment although it would be expected to be much higher. The diagnosis of (latent) tuberculosis in immunocompromised patients presents a problem. The incidence of extra-pulmonary, miliary and disseminated tuberculosis after infliximab therapy has been reported to be high and delayed the diagnosis (30,35). Furthermore, skin tests are often negative due to an anergic immune system and symptoms can mimic the underlying disease. Finally, in the absence of granuloma, due to TNFα blockade the histopathology and X-ray are generally negative.

Cultures and PCR on body fluids are recommended to confirm the diagnosis of a tuberculosis infection. An algorithm has been suggested by Hamilton *et al*. in cases of alarming symptoms during infliximab therapy. Different guidelines have been published regarding how to make risk assessments and in which cases one should consider pre-emptive therapy (32). Before starting treatment with anti-TNFα (especially infliximab) in children and adults, screening for (latent) tuberculosis is highly recommended.

The reason that almost all cases of tuberculosis infection were reported after treatment with infliximab, and not following etanercept, may lie in an intrinsic difference in the mechanism of action between the two agents (Table I). The induction of long-lasting T cell suppression after infliximab, but not etanercept therapy in large part explains the difference in the number of patients who subsequently develop tuberculosis, as the Th1 response is crucial in the defence against these intracellular mycobacteria (48). Long-term follow-up studies, preferably on larger populations, of paediatric JIA patients treated with anti-TNFα medication, is needed to make a reliable risk assessment for the development of serious infections including VZV and tuberculosis in this group. Meanwhile the close monitoring of patients being treated with anti-TNFα medication for the occurrence of side effects and infections is essential. Special attention should be paid to those patients with a history of recurring infection or with underlying conditions which may predispose him or her to infection.

Although reports of autoimmune events such as diabetes mellitus, demyelination and SLE after anti-TNF treatment in the paediatric population have been limited, caution is warranted. Animal models have shown that TNF suppression plays an important role in the progression of diabetes manifestations. This could represent a possible trigger for diabetes during anti-TNF therapy. However, the reported patients may have been genetically predisposed to diabetes mellitus and the manifestation of the condition at this time could have been coincidental. Bloom *et al*. suggest that TNF inhibition may lead to more rapid development of diabetes mellitus in a predisposed host (39).

Furthermore at least two patients aged 21 years old with a history of JIA, developed symptoms of CNS demyelination (37,38). The precise role of TNFα in demyelination is not clear. In studies with infliximab and lenercept, another TNF antagonist consisting of a TNFα receptor connected to a human IgG heavy chain, treated patients experienced a significantly higher number of exacerbations than placebo-treated patients (49,50). Although the relationship remains unclear, as with infections physicians should remain alert to the

possibility of the development of a new autoimmune disease such as diabetes mellitus, SLE or CNS demyelination during TNF suppression.

Apart from the beneficial effects of anti-TNFα therapy on the progression of JIA, treatment with an TNFα antagonist remains a non-curative treatment; it does not cure the disease and is associated with adverse events which may constitute a risk for (predisposed) patients. Attempts should be made to lower the risks of this therapy, for instance by drug targeting. Metselaar *et al*. have reported on a very effective, liposomal formulation of the glucocorticosteroid prednisolone in a rat model for RA. By means of this targeted delivery, the systemic effects of the drug are highly reduced and its effectiveness is increased. In the future, it may be possible to target anti-TNF agents directly at the inflamed joint, thereby preventing systemic effects and reducing the risk of serious adverse events caused by these powerful agents (51).

In general, more research on a larger scale will be necessary to determine the long-term effects of the suppression of TNFα. This is especially important for children who face the prospect of lifelong anti-TNF therapy.

Conclusion

Although short-term relief has been documented, anti-TNFα treatment appears to be a less promising therapy than was expected when it was introduced. While in children long-term treatment with anti-TNFα medication seems to be necessary, an increasing number of serious side effects must be expected with regard to infections, autoimmune events and lymphoma. Children on anti-TNF therapy should be monitored carefully and efforts should be made to develop other medical regimens.

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