
TNF- α antagonists for the treatment of juvenile-onset spondyloarthritis

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ABSTRACT

Juvenile-onset spondyloarthritis (SpA) is a term for a group of HLA-B27 related disorders. The hallmark signs and symptoms of this group of disorders include peripheral arthritis and enthesitis while sacroiliitis and spondylitis develop in some cases later on and extrarticular manifestations such as anterior uveitis occurs occasionally. Conventional medical therapy in children consists of non-steroidal anti-inflammatory drugs and corticosteroids that are administered intraarticular, even in the sacroiliac joints. Sulfasalazine and methotrexate are given in cases of chronic synovitis or enthesitis. Unfortunately, these forms of therapy have limited efficacy in many cases and disease activity and damage may lead to various degrees of functional impairment. Recently, experience with TNF α -antagonists in adults has opened new perspectives for treating patients with refractory SpA, particularly ankylosing spondylitis (AS). So far there is only little experience in the treatment of juvenile-onset SpA, consisting of case reports and case series where etanercept or infliximab have been given to children suffering from refractory juvenile-onset AS and psoriatic arthritis. From these observations there is evidence that treatment seems to be as effective as in adults. Risks are likely to be the same as in patients suffering from other forms of juvenile idiopathic arthritis. However, without further studies no recommendations can be provided for indication for treatment, dosing, intervals and duration of treatment.

Introduction

The term juvenile-onset spondylarthritis is applied to children suffering from a group of rheumatic disorders involving the peripheral and axial joints and entheses before the age of 16 years. Acute anterior uveitis as well as

other extraarticular manifestations including inflammatory bowel disease (IBD), psoriasis and various skin changes complete the clinical features that characterise this group. Various clinical conditions, including syndromes and diseases constitute the group: juvenile-onset AS, reactive arthritis (ReA) and Reiter's syndrome, a subgroup of juvenile psoriatic arthritis (PsA), and arthritis with IBD (1). Adult criteria are used for classification of juvenile-onset AS (2), while separate criteria have been proposed for juvenile psoriatic arthritis (3). The International Associations for Rheumatology (ILAR) classification for juvenile idiopathic [chronic] arthritis (JIA) is an attempt to put together clinically homogeneous groups according to their clinical features at presentation (Tables I and II) (4). Although JIA includes a subgroup of enthesitis related arthritis, which could be equivalent to juvenile-onset SpA, three clinical forms – juvenile psoriatic arthritis (PsA), reactive arthritis (ReA) and IBD (which is only a descriptor) – are excluded from the group (5). Alternatively, the European Spondyloarthropathy Study Group (ESSG) classification criteria developed for adult onset SpA (6) should be considered.

Pharmacotherapy in children consists of non-steroidal anti-inflammatory drugs (NSAIDs) as well as the application of intraarticular corticosteroids. Sulfasalazine and methotrexate are given in cases of chronic synovitis or enthesopathy. One controlled study of sulfasalazine have only reported a marginal benefit over placebo (7). Therapeutic potential of the various SpA has been very limited and with respect to axial involvement there is no evidence that disease progression may be halted by any of these drugs. Upcoming therapeutic options include two tumor necrosis factor (TNF) α -antagonists: infliximab, a monoclonal chimeric anti-

Table I. Classification of juvenile idiopathic arthritis (JIA) according to (43)

Subtype	Extraarticular manifestation
1 Systemic arthritis	Fever, evanescent skin rash, hepatomegaly, splenomegaly, pericarditis, pleuritis, lymphadenopathy, vasculitis, growth failure, dystrophy
2 Seronegative polyarthritis*	Low grade fever, tenosynovitis, uveitis, vasculitis
3 Seropositive polyarthritis *	Low grade fever, tenosynovitis, uveitis, vasculitis, rheumatoid nodules
4a Early onset oligoarthritis§	Chronic uveitis
4b Extended oligoarthritis§	
5 Enthesitis related arthritis	Enthesitis, acute uveitis
6 Psoriasis and arthritis	Psoriasis
7 Unclassified arthritis or criteria of more than one category is fulfilled	

* At least 5 joints are inflamed

§ Maximal 4 inflamed joints

\$ Maximal 4 inflamed joints during the first 6 months of the disease followed by at least 5 inflamed joints thereafter

Table II. ILAR proposed classification criteria for enthesitis-related arthritis.

Arthritis and enthesitis or

Arthritis or enthesitis with at least two of the following:

- Sacroiliac joint tenderness and/or inflammatory spinal pain
- Presence of HLA-B27
- Family history in at least one first or second degree relative of medically confirmed HLA-B27 associated disease
- Anterior uveitis that is usually associated with pain, redness, or photophobia
- Onset of arthritis in a boy after the age of 8 years of age

Exclusions

- Psoriasis confirmed by a dermatologist in at least one first or second degree relative
- Presence of systemic arthritis (as defined in the criteria)

TNF α antibody; and etanercept, a dimeric p75 TNF α -receptor-Fc γ -fusion-protein. Experience with both of these new drugs is still very limited, especially in juvenile onset SpA.

Juvenile-onset AS

Juvenile-onset AS is much less recognized in childhood than other forms of JIA, partly because axial involvement occurs 5 to 10 years after onset of peripheral disease. Although juvenile-onset AS differentiation from other arthritides may be difficult, some clinical signs, particularly lower-limb disease, enthesopathy and tarsitis allow the recognition of early onset AS. Except for clinical pattern at onset and some genetic markers, juvenile and adult onset AS have much in common. Nearly 10% of white Caucasians adults with AS and up to 50% of other popu-

lations, i.e. Mexicans, have the onset of their disease before the age of 16 years (1, 8) From these data, the prevalence of JAS has been estimated between 11 and 86 per 100,000 children, which is in the range of the incidence of JIA (9, 10, 11). However, the disease is not that often recognized in paediatric rheumatology surveys, where the ratio of juvenile-onset AS to juvenile rheumatoid or chronic arthritis is predominately 1 to 5. (9, 11).

The early course of juvenile-onset AS is often remitting. The peripheral joints most frequently involved include the knees, the ankles, the tarsus and the hips. Persistent peripheral joint involvement is more frequently seen in patients with juvenile than in adult-onset AS; in particular, coxitis may lead to a bad outcome. Enthesitis is a frequent complain at both onset and

during the course of the disease. Spinal and sacroiliac joint involvement develops most frequently between five and 10 years of disease (12). Treatment of juvenile-onset AS is individualized due to the wide range of symptoms, the variable prognosis and the lack of controlled studies. Conventional medical therapy consists of NSAIDs. Often, intraarticular corticosteroids are administered, even in the sacroiliac joints (13). Sulfasalazine can be administered in cases of chronic synovitis or enthesitis. Methotrexate is used occasionally. Despite treatment a number of patients experiences chronic active and severe disease with structural changes, particularly in the hips, tarsus, and sacroiliac joints and alternative treatment is required.

Meanwhile some open trials using the TNF α -antagonists infliximab and etanercept have been performed in adults (14, 15). In addition, there are positive data of controlled randomised studies for infliximab and etanercept in the treatment of adult AS (16, 17). In open studies, the efficacy of infliximab for treatment of AS in adult patients has been shown at a dosage of 3 or 5 mg/kg bw. given intravenously at intervals of 2 weeks up to 14 weeks (18). Improvement of function, pain, and swollen joint scores was observed in the patients receiving 3-5 mg/kg. However, the higher dose seemed to be more effective (19).

So far, experience in juvenile-onset SpA is very limited. Infliximab has been tried in various of our patients, for example an HLA-B27 positive 17-year-old boy suffering from longstanding juvenile-onset AS beginning with an asymmetric oligoarthritis at the age of 8 years and extending to axial disease with bilateral sacroiliitis. During the course of his disease several therapeutic approaches including NSAIDs, sulfasalazine, methotrexate and repeated intraarticular corticosteroid injections failed to achieve a sustained response. Despite treatment with an appropriate dosage of NSAIDs he was unable to walk without using crutches. Lumbar mobility was markedly diminished and the sacroiliac joint was tender at motion or pressure. Active syn-

ovitis of the right sacroiliac joint was documented by magnetic resonance while destruction was present in the left sacroiliac joint. Infliximab was tried at a single dosage of 3 mg/kg bw and was excellently tolerated. Marked improvement was evident already the day after. He was free of pain and walked without any need of aids. Eight weeks after the infusion, the patient still showed significant improvement: Schobers' increased from 3 cm to 6 cm and the finger-to-floor-distance decreased from 35 cm to 22 cm. The outcome parameters Bath AS Functional Index (BASFI) and the Bath AS Disease Activity Index (BASDAI) decreased from 5.8 to 0.5 and from 2.6 to 0.3, respectively (20, 21). Since the response to a single infusion has continued for 14 weeks up to date, further infusions have not yet been performed. Reiff *et al.* presented a small open study using etanercept for the treatment of juvenile-onset AS (22). Eight patients (7 males), with a mean age of 15.9 years (range 12-25 years) suffering from juvenile-onset AS for a mean of 4.5 years (range 1.2-17.5 years) were included. Six patients were HLA-B27 positive. Treatment was performed with etanercept at an average dosage of 0.4 mg/kg bw which is the dosage recommended for treatment of polyarticular JIA (23). In 3 patients the dosage was increased. At entry all patients showed active disease with an elevated ESR; 4 were treated with methotrexate in parallel. Etanercept resulted in a very dramatic and rapid therapeutic response in all 8 children. Morning stiffness disappeared completely, and the number of active joints decreased by 96%. The mean haemoglobin levels increased by 24% reaching normal levels and the mean ESR decreased by 80%, down to 11.4 mm/h. The therapeutic effects were evident for up to more than 24 months. Patients tolerated etanercept without side effects. The long term effects remain to be awaited, and whether radiological progression and ankylosis can be stopped. The results in Reiff's study (22) were within the range of placebo-controlled studies performed in adult AS patients, of whom 80% achieved an improve-

Table III. Juvenile psoriatic arthritis (Vancouver-criteria) (3).

A	Definite psoriatic arthritis
1	Arthritis with typical rash
2	Arthritis with 3 of the following criteria
	Dactylitis
	Nail pitting or onycholysis
	Psoriasis-like rash
	Family history of psoriasis (first or second degrees)
B	Probable psoriatic arthritis
	Arthritis with 2 of the above mentioned criteria
C	Possible psoriatic arthritis
	Arthritis with 1 additional criterium

Table IV. Juvenile arthritis – core set criteria for improvement (29).

1. Physician's global assessment of the severity of the disease (10 cm visual analogue scale)
2. Global assessment of overall well being be the patient or parent (10 cm visual analogue scale)
3. Number of "active" joints (joints with swelling or joints with limiting of motion and with pain, tenderness or both)
4. Number of joints with limiting of motion
5. Functional score (Childhood Health Assessment Questionnaire, CHAQ)
6. ESR

Improvement is defined by decrease of at least 30% in at least 3 of 6 criteria with worsening of no more than one of the six response criteria of more than 30%.

ment which was evident in all predefined treatment response parameters (16). In conclusion, etanercept seems to be a promising reagent for treatment of active and refractory juvenile-onset AS. Controlled studies and long term observations are warranted.

Juvenile PsA

The diagnosis of juvenile PsA is easy if arthritis occurs in the presence of psoriasis before the age of 16 years. However, as in adults the onset of arthritis and psoriasis may not be simultaneous (24). The 1989 proposed criteria for PsA took this into account differentiating definite from probable juvenile PsA (Table III). The incidence of psoriasis in children before the age of 16 years has been claimed to 0.5 per 100. The incidence of PsA is between 2 and 3 per 100,000 and the prevalence is 10 to 15/100,000 (32). The prognosis for PsA resembles the prognosis for polyarticular JIA rather than oligoarticular JIA. Persistent disease occurs in about 70% of patients and goes along with a risk for erosions and joint damage. Despite the lack of controlled studies, conventional therapeutic options in-

clude NSAIDs as well as intraarticular corticosteroids. Methotrexate is the most common drug used in persistent disease (25). Cyclosporine A may substitute or be used in combination (26, 27) (Table II).

Placebo-controlled randomised studies of etanercept and open trials of infliximab in the treatment of adult psoriatic arthritis have been published (15, 28). The results using TNF- α blocking agents in the treatment of psoriatic arthritis were encouraging in regard to arthritis as well as skin manifestations, but no information on axial disease is given. Experience with TNF α -antagonists for treatment of juvenile PsA, however, is very limited. Since etanercept is licensed for treatment of juvenile (chronic) polyarthritis and since classification of JIA does not exclude juvenile PsA, a number of children with polyarticular juvenile PsA will have been treated with etanercept. Unpublished data of the German registry for treatment of JIA-patients with etanercept demonstrated that 6% of 191 registered patients were classified as PsA. The response rate of these patients was within the rate seen in non-psoriatic

polyarticular JIA: more than 80% of the patients reached a 30% response and 70% reached 50% according to the improvement criteria (29) (Table IV). No information is available with respect to axial involvement and skin manifestations of psoriasis in children.

SpA in IBD

Chronic IBD is accompanied by arthritis in 10% to 20% of childhood cases. It has been estimated that sacroiliitis is at least 30 times more common in adult IBD patients than in the general population (30), but sacroiliitis in children with IBD is rare. The prognosis of the peripheral joint involvement, which strictly does not resemble the peripheral disease seen in other SpA, is almost excellent. Axial skeleton involvement however may progress. Treatment is focused on the gastrointestinal involvement. Joint disease often disappears with the remission of IBD but can be handled with NSAID with caution (31). COX-2 inhibitors, which may be of value are currently unlicensed in children. Corticosteroids and sulfasalazine are frequently used.

Infliximab is approved for the treatment of Crohn's disease in adults. In patients with Crohn's disease and spondylarthritis who were treated with infliximab because of their treatment-resistant gut inflammation a substantial improvement in gastrointestinal symptoms was noted, accompanied by a significant improvement of SpA-related axial and peripheral arthritis (32). This quick and substantial improvement of synovitis prompted to further investigate the therapeutic potential of TNF- α blockers in SpA. However, there are no published data about treatment of juvenile SpA associated with IBD.

Acute anterior uveitis

Acute anterior uveitis has been described in conjunction with juvenile-onset AS, where it occurs in a quarter of patients, in juvenile PsA, IBD, ReA and Reiter's syndrome, but also occurs separately in childhood. It is usually unilateral, remittent and only rarely leaves ocular residua. Anti-inflammatory treatment with topical corticosteroids usually succeeds. In juvenile PsA

chronic uveitis occurs and is as complicating as iridocyclitis in oligoarticular onset of JIA. Attempts to treat acute anterior uveitis with TNF α -antagonists have been performed in adults only. There were two open studies reporting the successful use of infliximab in HLA-B27 (with or without Crohn's disease and/or sacroiliitis) associated acute anterior uveitis (33, 34). The use of etanercept for treatment of acute anterior uveitis has not been reported so far.

The therapeutic efficacy of etanercept for treatment of chronic uveitis has been investigated in only one open trial. A significant drop in cellularity was observed in 10 of 16 affected eyes, and 4 of 18 eyes showed complete remission (35). Worth mentioning is that there were also several children who developed uveitis upon treatment. In these patients, however, treatment was not sufficient to prevent or treat uveitis. Therefore, the value of etanercept for the treatment of chronic uveitis remains to be established.

Infliximab has also been studied in JIA patients suffering from chronic uveitis (36). Five of 8 children initially responded with a decrease in cellularity and corticosteroids could be spared or discontinued. Two patients flared after the interval between the infusions of infliximab was prolonged to 6 weeks. In conclusion, infliximab can be of value for treatment of refractory chronic uveitis.

TNF- α antagonists: Potential indications for the treatment

Juvenile onset SpA may severely affect the functional capacity of children, adolescents, and adults. The consequences of disease activity and structural damage and the short and long-term involvement of the joints and entheses include diverse degrees of pain, stiffness, loss of movement, functional impairment, and harm to quality of life. Because the predominantly lower limb pattern of juvenile-onset SpA, most patients have limitation of activities such as walking, standing, climbing stairs, and running. Nearly 60% of children with SpA have moderate to severe limitations by 10 years of dis-

ease (37,38). Patients with disease activity 5 years or more after onset have significant functional impairment. The probability of remission reaches only 17% after 5 year's disease duration. In comparison to adults, patients with juvenile-onset AS require more hip replacements and more patients are in functional classes III and IV (39, 40, 4).

Although there are no specific histological findings in the synovial membrane of peripheral joints of these patients, there is a prominent expression of TNF α , which correlates with T cell and macrophages infiltrates (42), high levels of CD8 activated cells, TNF β , gamma interferon and interleukins 2, 4 and 6 (42-44). Inflammatory infiltrates at the mid-tarsal entheses are not prominent, but bone proliferation.

Thus, refractory disease activity, for example persistent or disabling arthritis and enthesitis of peripheral and axial sites should be considered a major indication for TNF- α blocker therapy. Extraarticular manifestations such as IBD, and psoriasis could be considered in some cases, but the role of TNF- α in anterior uveitis has yet to be determined. The effect of etanercept and infliximab in preventing structural damage, specifically, hip, sacroiliac and foot changes should be investigated.

Final remarks

TNF- α antagonists open new perspectives for treatment of juvenile-onset SpA since they produce dramatic improvement in patients with severe, so far intractable disease. Furthermore, the onset and magnitude of its effects on clinical activity are remarkable. Current experience using TNF- α blocking agents in childhood is very limited and neither etanercept nor infliximab were studied in controlled trials in children or were licensed for treatment of juvenile SpA. Short and long-term efficacy, tolerability and especially safety have to be studied in children before these agents could be recommended for treatment of children. The therapeutic dilemma, to provide active but unstudied and unlicensed drugs to severely affected childhood patients, is a well-known phenomenon throughout the paediatric

disciplines. Inexperienced or only short-ly studied new drugs should be applied with caution only, especially to children. On the other hand, an active drug cannot be withheld to severely affected patients at risk for lifelong mutilation in a situation without any alternative treatment only because they are children.

Etanercept is the only biological agent approved for treatment of children of at least 4 years with refractory and active polyarticular JIA. Current recommendations for treatment are based not very much on experience but on theoretical considerations (45). Too little experience has been made with common situations in childhood like infections or vaccinations with live attenuated germs, which therefore should not be applied. Poor knowledge exists about combination therapy. If TNF- α blocking agents are considered, all children should carefully be investigated and monitored throughout treatment. Attention should be directed not only to infectious diseases but also to autoimmune diseases including "lupus-like syndrome", demyelisation, diabetes mellitus and uveitis (46-49).

Currently a number of open questions are remaining - for example, to whom this new drugs should be offered, at what stage treatment should be initiated, dosing and intervals of treatment, and last but not least what duration of treatment is necessary and which is the best time or condition for termination of treatment either in non-responders or in patients achieving long term complete remission. The influence on radiological progression has not been evaluated in children so far. Controlled studies and long-term investigations are needed in childhood too.

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