Growth reconstitution in juvenile idiopathic arthritis treated with etanercept

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Abstract

Objective

Growth failure is a leading problem in uncontrolled juvenile idiopathic arthritis. It also affects 10% of patients who are not treated with corticosteroids. The influence of proinflammatory cytokines like interleukin-1β, interleukin-6 and tumour necrosis factor on the neuroendocrine axis as well as on the production of insulin-like growth factors (IGFs) has been postulated. The objective of the current study was to evaluate effects of highly active antirheumatic treatment with tumour necrosis factor antagonist on growth retardation. Seven out of 18 patients with refractory juvenile idiopathic arthritis treated with etanercept demonstrated growth retardation leading to short stature.

Methods

Antropometric measurements and disease activity parameters – including the number of swollen and tender joints, morning stiffness, ESR and CRP levels – were monitored monthly during the first year of treatment and every 3 months thereafter. Serum levels of IGF-1 and IGF-BP were measured as well.

Results

Upon treatment with etanercept, growth velocity increased from 3.7 ± 1.2 cm before the beginning of the therapy to 7.6 ± 1.2 cm in the first year of treatment (p < 0.001). The average length-standard-deviation-score (SDS) increased from –2.4 ± 1.0 to -1.9 ± 0.9 after one year and to –1.1 ± 0.9 after two years (p = 0.05) indicating catch-up growth. Prior to the therapy, serum levels of insulin-like growth factor-1 and of insulin-like growth factor binding protein-3 were within the normal range but increased significantly upon treatment (p < 0.001). An inverse correlation of the IGF-1 serum level to CRP was found.

Conclusions

An intensified anti-inflammatory treatment using etanercept has a beneficial effect on growth in children with a so far uncontrolled inflammatory disease. This effect might be related to the cessation of the inhibitory effect of proinflammatory cytokines on the synthesis of IGF-1 and IGF-BP-3 in the liver. Growth failure should be included in the evaluation of antirheumatic treatment.

Key words

Juvenile idiopathic arthritis, growth hormone, etanercept, insulin-like growth factor.
Introduction
Juvenile idiopathic arthritis (JIA) is the most common systemic autoimmune disease occurring in childhood with an incidence of 10-20 per 100,000 children below the age of 16 years (1). According to the International League Against Rheumatism (ILAR) classification, patients can be subclassified depending on the number of affected joints during onset and course of the disease and the presence of extraarticular manifestations which include fever, pericarditis, liver and spleen enlargement, lymphadenopathy and skin involvement (2). Pharmacomedical treatment consists of a combination of nonsteroidal antirheumatics, corticosteroids and so called “disease modifying antirheumatic drugs” (DMARD). Despite treatment, a number of children – especially those with the polyarticular and the systemic onset subtypes – still have a poor prognosis (3, 4).
Growth failure without growth hormone (GH) deficiency is an additional problem in uncontrolled JIA (5). The precise etiology of growth retardation is unknown. High disease activity as well as treatment with glucocorticoids are of significant importance. However, corticosteroids are often necessary to control the disease. Growth retardation also affects 10% of patients who are not treated with corticosteroids (6, 7). The influence of proinflammatory cytokines like interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor (TNF) on the neuroendocrine axis as well as on the production of insulin-like growth factors (IGFs) has been postulated (8). Low concentrations of IGF-1 and IGFBP-3 have been documented in JIA (9). Numerous investigations of GH concentration and secretion have been performed in patients with JIA, also during long term corticosteroid therapy, with quite controversial results. There are several studies showing an increased growth rate resulting from exogenous GH treatment in children with JIA on the short term. However, there still are not enough studies revealing an increased final height induced by GH treatment (10, 11). The recognition of growth impairment is important because a reduced final height is one of the permanent consequences of the disease.

Patients, materials and methods
Patients
The patient cohort with growth delay consisted of seven girls out of 18 patients treated with etanercept in a single pediatrics rheumatology center who demonstrated short stature (length-standard-deviation-score (SDS) <-2) or a growth rate of SDS <-1 (12). The patient characteristics are outlined in table 1. All seven children revealed an active, non-remittent disease refractory to multiple treatment regimens for 5 to 15 years. Concomitant therapy consisted of non-steroidal antirheumatic drugs at the recommended dosage, methotrexate given orally at a dosage of 10-15 mg/m2 body surface weekly and a low dose of oral glucocorticoids as outlined in Table I.

Methods
Etanercept was given twice weekly at a dosage of 0.4 mg/kg bw subcutaneously as indicated in the study from Lovell et al. (13). Dose response studies in JIA have not been performed so far. One girl (patient 7) presented at the age of 17 was treated with both etanercept and growth hormone (GH) after GH deficiency had been excluded. Anthropometric measurements taken by using a mounted stadiometer, and the number of swollen and tender joints and the duration of morning stiffness were recorded monthly during the first year of treatment and every 3 months after that. Laboratory parameters, including the erythrocyte sedimentation rate (ESR), serum levels of C reactive protein (CRP) and interleukin-6 (IL-6, enzyme linked immunosorbent assay (ELISA), Immulite, Biermann, Bad Nauheim, Germany) were monitored at the same time. Serum levels of IGF-1 and IGFBP-3 were measured at the same time. Serum levels of IGF-1 and IGFBP-3 were measured before, after 12 months on treatment in 2 patients and after 24 months in the other 5 patients. IGF-1 and IGFBP-3 were measured using an immunoradiometric assay (DSL-2800 ACTIVETM Non-Extraction IGF-1 IRMA, DSL-6600 ACTIVETM IGFBP-3 IRMA,
To define the improvement, the core set criteria of Gianinni were used, including the physician’s global assessment of the severity of the disease (10 cm visual analogue scale), the global assessment of overall well-being (10 cm visual analogue scale), the number of active joints (defined as joints with swelling or joints with limitation of motion and pain, tenderness or both), the number of joints with limitation of motion, functional score (Childhood Health Assessment Questionnaire, CHAQ) and the ESR. Improvement is defined by a decrease of at least 30% in at least three of six criteria with worsening of no more than one of the six response criteria of more than 30% (14).

Documentation and collection of data were performed after written informed consent has been obtained. This has been approved by ethical committee of the Medical Faculty of the Martin-Luther University Halle-Wittenberg.
Statistical analysis

Values were compared before and during treatment by using the non-parametric Mann-Whitney U test and the Student t-test.

Results

In all 7 children with growth delay, morning stiffness and tender joints disappeared completely, and the number of swollen joints was reduced significantly. After one month of treatment with etanercept all patients reached a response level of 30%, and a 50% response level after 3 months of treatment according to the Gianinni criteria. At 6 months of treatment all but one patient reached a response level of 70%. This regression of active disease allowed a discontinuation of concomitant treatment with oral corticosteroids in all 7 children (after 6 months in patients 1 and 4; 9 months in patient 2; 11 months in patient 3; 12 months in patients 5, 6 and 7). Apart from injection site reactions, no side effects were noted.

Before treatment the patients had a growth delay resulting in a length-SDS of –1.0 to -3.9. The growth rate of all patients increased significantly as shown in Figure 1. This effect was most pronounced in the first year of treatment with etanercept. The average growth velocity of all patients increased significantly from 3.7 ±1.2 cm/year (mean ± standard deviation) to 7.6 ± 1.2 cm/year (prior to versus after the first year of treatment, p < 0.001, t-test), to 6.2 ± 1.4 cm/year in the second year (p < 0.01, t-test) and to 6.0 ± 1.7 cm/year in the third year (p < 0.05, t-test). This led to an increase in the length-SDS from –2.4 ± 1.0 (mean ± standard deviation) to -1.9 ± 0.9 after 1 year and to –1.1 ± 0.9 after 2 years (both p = 0.05, U-test) (Fig. 2).

Because of her extremely short stature at presentation, one girl was treated with both etanercept and GH. At the start of the therapy, this 17-year old girl was at a puberty stage 3 according to the Tanner scores for the breasts, and a puberty stage 2 for pubic hair development. Menarche had not occurred so far. The bone age was delayed to an age of 13.5 years. Growth hormone deficiency was excluded by a normal response to arginine infusion. Upon treatment, growth velocity increased from 1.7 cm/year to 6.9 cm during the first year and to 3.7 cm during the second year.

Prior to the use of etanercept, levels of ESR, CRP and IL-6 were elevated in all children. Upon therapy, all parameters rapidly reached normal levels in all cases already during the first four weeks of treatment and remained persistently normal in all 7 children while controlled monthly during the first year and every 3 months thereafter.

Pre-treatment levels of IGF-I and IGFBP-3 were low, but within the normal range in all patients. The average IGF-I serum level increased significantly from 177 ± 62 ng/ml prior to therapy to 432 ± 193 ng/ml during the therapy (p < 0.001, U-test). The average IGFBP-3 serum level rose from 5.2 ± 0.6 mg/ml before the therapy to 5.9 ± 0.5 mg/ml during the therapy (p < 0.001, U-test) (Fig. 3).
Interestingly there was an inverse correlation of IGF-1 serum levels to CRP demonstrated ($r = -0.537$, $p < 0.05$, figure not shown).

**Discussion**

There are multiple factors which contribute to growth retardation in patients suffering from juvenile idiopathic arthritis. Both the chronic inflammatory state and the anti-inflammatory treatment with glucocorticosteroids may deteriorate linear growth (15). Disease duration, degree of functional joint involvement, and the age of puberty appear to be risk factors for growth impairment, especially in systemic and polyarticular JIA.

JIA is more common in girls. Despite immunological abnormalities also neuroendocrine mechanisms have been suggested in the pathogenesis of JIA. Normal to low levels of cortisol have been observed in children with active JIA despite high serum levels of IL-6, IL-1β, and TNF-α, which activate the hypothalamic-pituitary-adrenal axis. JIA patients demonstrate low levels of insulin-like growth factor 1, which mainly mediates the effects of GH (16, 17). It appears that stimulated and spontaneous GH secretion is normal in children with active JIA, but the response to endogenous and exogenous GH with regard to IGF-1 and IGFBP-3 production is impaired, indicating a degree of GH insensitivity in such children. In addition, there is also evidence of target insensitivity to IGF-1. The pathomechanism of this is not known so far (18, 19).

Linear growth is suppressed either by disease activity or glucocorticosteroids, even if administered at low doses as was the case in the cohort of JIA patients reported on here (20, 21). The most obvious decrease in growth velocity was seen in children with polyarthritis and growth velocity was affected slightly more in children with moderate than with mild disease. The cumulative total dose of glucocorticosteroids did not have statistically significant influence on growth. It has been suspected that the activity of the inflammatory process was the most important growth-impairing factor and glucocorticosteroids aggravated only this effect. This reflected the growth promoting effect when the inflammatory process is being controlled. While treatment with supraphysiologic doses of growth hormone only led to an increase of growth velocity without catch-up growth and without a positive influence on the active of the rheumatic disease, highly active immunotherapy with TNF-antagonists which control disease activity led to an increase growth rate with catch-up growth.

In JIA patients corticosteroids are necessary only in cases of highly active uncontrolled disease. Reducing the amount of corticosteroids is therefore a major goal in combination anti-rheumatic therapy. Treatment with etanercept allowed for corticosteroids to be discontinued completely in all patients after the first year of treatment. The growth rate was increased to normal during the first year of etanercept therapy, although the initial dosage of corticosteroids remained unchanged. In addition, most of the patients demon-
strated a higher increase in growth velocity with catch-up growth in the first year of therapy than in the second year. We therefore conclude that the increase of growth rate was not primarily due to a decrease corticosteroids intake. One girl who had been treated with the combination of both growth hormone and etanercept did grow in the same extend as the other children who only have been treated with etanercept.

In conclusion, the activity of the inflammatory process was the most important growth-impairing factor and glucocorticosteroids aggravated only this effect. Therapy with etanercept allows to control the inflammatory process and therefore also to spare corticosteroids. In JIA patients with growth delay highly active antirheumatic therapy should be instituted before growth hormone substitution is considered and growth failure should be included in the evaluation of antirheumatic treatment.

References
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