Original paper

Reumatologia 2015; 53, 1: 14–20
DOI: 10.5114/reum.2015.50552

Influence of biologic therapy on growth in children with chronic inflammatory connective tissue diseases

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Abstract

Objectives: Connective tissue diseases (CTD) are a heterogeneous group of chronic inflammatory conditions. One of their complications in children is the inhibition of growth velocity. Due to direct inflammation within the musculoskeletal system as well as glucocorticoid therapy, this feature is the most essential and is mainly expressed in the course of juvenile spondyloarthropathies and juvenile idiopathic arthritis (JIA). Duration of the disease, but predominantly the activity of the inflammatory process, seems to have a significant impact on the abnormal growth profile in children. Effective biological therapy leads to improvement of the patient's clinical condition and also, through the extinction of disease activity and reduction of daily doses of glucocorticosteroids (GCS), it gradually accelerates and normalizes the growth rate in children with CTD. Our objective was to evaluate the impact of biological therapy on growth in children with chronic inflammatory CTD.

Material and methods: Data from 24 patients with CTD treated with tumor necrosis factor-α-blockers (etanercept, adalimumab, golimumab) and an interleukin-6 receptor blocker (tocilizumab) were reviewed at the time of disease onset, biological treatment initiation and at least 12 up to 24 months onwards. The rate of growth was correlated with the daily doses of GCS, and the type and duration of biological therapy.

Results: Patient median height, measured as the change in height standard deviation score, was 0.36 ±1.07 at disease onset and –0.13 ±1.02 at biologic therapy initiation. The growth velocity accelerated in 17 patients (70.1%) during the biological treatment. Mean height-SDS improvement between biological treatment initiation up to two years was 0.51 ±0.58. In 47% of patients daily doses of GCS were reduced to 0 mg/kg/day.

Conclusions: In the treatment of CTD, biological agents restore growth velocity not only by inflammation inhibition, but also through limiting GCS daily doses.

Key words: biologic treatment, connective tissue diseases, growth impairment, chronic glucocorticosteroid therapy.

Introduction

Connective tissue diseases (CTD) in children are a heterogeneous group of chronic inflammatory conditions mostly including juvenile idiopathic arthritis (JIA), autoimmune vasculitis, dermatomyositis, and systemic lupus erythematosus. One of their complications is the inhibition of growth velocity [1]. Due to direct inflammation within the musculoskeletal system, this feature is the most essential and is mainly expressed in the course of juvenile spondyloarthropathies and JIA [2]. Duration of the disease, but predominantly the activity of the inflammatory process, seems to have a significant impact on the abnormal growth profile in children [3]. Excessive stimulation of

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Submitted: 28.10.2014, **Accepted:** 10.02.2015

pro-inflammatory cytokines, especially interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α), causes abnormal secretion of hormones, including growth hormone (GH) and insulin-like growth factor (IGF) [4]. It also causes fluctuations of cortisol concentration in serum. These disorders are significantly worsened by steroids, which are used as a first-line therapy in children with systemic inflammatory CTD [5]. By inhibiting the ongoing inflammatory process, glucocorticosteroids (GCS) improve the general condition of the patient, but used chronically they significantly affect the growth rate through an adverse effect on the hypothalamic-pituitary-adrenal axis (HPAX) [6, 7]. A group of drugs successfully used in the treatment of chronic inflammatory CTD are biological agents [8, 9]. Their mechanisms of action involve inhibition of the activity of pro-inflammatory cytokines: TNF-α (etanercept, adalimumab, golimumab) and IL-6 (tocilizumab). Biological therapy causes rapid remission of the inflammatory process and enables faster reduction of daily doses of GCS. According to reports of recent studies, effective biological therapy not only brings improvement of the patient's clinical condition, but through the extinction of disease activity and reduction of GCS doses it gradually accelerates and normalizes the growth rate in children with chronic inflammatory CTD [10].

Material and methods

Patients

The profile of 24 patients (15 girls, 9 boys) aged 7–21 with chronic inflammatory CTD (polyarteritis nodosa, dermatomyositis, juvenile idiopathic arthritis – polyarticular, oligoarticular and systemic) was retrospectively analyzed. The mean disease duration was 6.5 years (3–17 years). Patients were initially treated with GCS (prednisone at a dose of 0–0.9 mg/kg/day) and selected disease-modifying anti-rheumatic drugs (DMARDs) (methotrexate at a dose of 10–20 mg/m^2 body surface area/week; sulfasalazine at a dose of 20 mg/kg/day, hydroxychloroquine at a dose of 200 mg/day, cyclosporine at a dose of 3 mg/kg/day, azathioprine at a dose of 2 mg/kg/day) (Table I). Due to the severe course of disease, refractory to standard treatment, biological therapy was implemented – etanercept subcutaneously at a dose of 0.8 mg/kg per week (12 patients), adalimumab subcutaneously at a dose of 40 mg per two weeks (9 patients, 4 of them after ineffective etanercept treatment), golimumab subcutaneously at a dose of 30 mg/m^2 body surface per month (2 patients) and tocilizumab intravenously at a dose of 8 or 12 mg/kg per two weeks or 10 mg/kg per month (5 patients). Duration of biological therapy was 12–96 months (mean 43.2 months). All patients have never received growth hormone treatment.

All patients were treated with biological agents according to the guidelines of the National Health Fund Therapeutic program. Golimumab was administered under the program of a clinical trial, after obtaining approval from the local bioethics committee.

Growth assessment

Growth profile was evaluated using standardized Polish growth charts developed by the Institute of Mother and Child in Warsaw (2007). A pediatrician or a registered nurse made the measurements. The height standard deviation score (height SDS; *z* score), was defined as the observed height minus mean height for age divided by SD, where SD was the standard deviation for the normal population of the same chronological age and gender. Growth rate was evaluated at the time of the disease onset, during the initiation of biological therapy and after at least 12 months up to 2 years of its duration. The rate of growth was correlated with the daily doses of GCS, and the type and duration of biological therapy.

Results

Median height, expressed as the SD score (SDS), was 0.36 ±1.07 at disease onset, and 0.13 ±1.02 at the time of biological treatment induction. Acceleration of growth velocity was observed in 17 patients (70.1%) with chronic inflammatory CTD two years after biological therapy initiation. Mean height SDS improvement between biological treatment initiation up to two years of its duration was 0.51 ±0.58 (Fig. 1).

In the group where improvement of the growth profile was seen, 1 patient was treated for system-

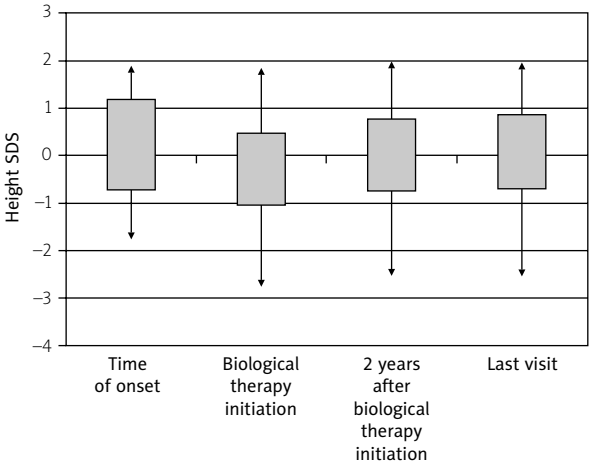


Fig. 1. Height-SDS variations in children with connective tissue diseases treated with biological agents.

Table I. Patients' characteristics

Patient No.	Type of connective tissue disease	Age of onset	Disease duration (years)	Initial therapy	Age of biological therapy initiation	Type of biological agent	Current concomitant therapy	Duration of biological therapy (months)
1	systemic JIA	3	4	GCS 0.5 mg/kg/day, MTX	5	tocillizumab	MTX	24
2	systemic JIA	4	10	GCS 0.6 mg/kg/day, MTX	6	etanercept, adalimumab	GCS 0.06 mg/kg/day, MTX	96
3	systemic JIA	6	7	GCS 0.4 mg/kg/day, MTX	10	tocillizumab	MTX	39
4	polyarticular JIA	14	5	GCS 0.5 mg/kg/day, MTX	17	tocillizumab	MTX	12
5	polyarticular JIA	8	10	GCS 0.3 mg/kg/day, MTX	14	etanercept, adalimumab	GCS 0.05 mg/kg/day, MTX	56
6	polyarticular JIA	4	12	GCS 0.6 mg/kg/day, MTX	12	adalimumab	GCS 0.15 mg/kg/day, MTX	39
7	polyarticular JIA	12	4	GCS 0.65 mg/kg/day, MTX	13	etanercept	MTX	31
8	polyarticular JIA	10	7	GCS 0.5 mg/kg/day, MTX	14	etanercept, adalimumab	GCS 0.05 mg/kg/day, MTX	36
9	polyarticular JIA	13	3	sulfasalazine	13	adalimumab	sulfasalazine	39
10	polyarticular JIA	5	5	MTX	8	golimumab	MTX	37
11	polyarticular JIA	5	6	GCS 0.5 mg/kg/day, MTX	9	tocillizumab	MTX	30
12	polyarticular JIA	7	4	GCS 0.2 mg/kg/day, MTX	5	golimumab	MTX	33
13	polyarticular JIA	15	3	sulfasalazine	15	tocillizumab	GCS 0.05 mg/kg/day, sulfasalazine	34
14	oligoarticular JIA	3	9	GCS 0.5 mg/kg/day, hydroxychloroquinecyclosporine	5	etanercept	GCS 0.25 mg/kg/day, sulfasalazine, MTX	70
15	oligoarticular JIA	12	6	GCS 0.16 mg/kg/day, MTX	15	etanercept	MTX	30
16	oligoarticular JIA	13	3	GCS 0.5 mg/kg/day, MTX, hydroxychloroquine	14	etanercept	MTX, hydroxychloroquine	19

Table I. Cont.

Patient No.	Type of connective tissue disease	Age of onset	Disease duration (years)	Initial therapy	Age of biological therapy initiation	Type of biological agent	Current concomitant therapy	Duration of biological therapy (months)
17	oligoarticular JIA	14	4	GCS 0.5 mg/kg/day, MTX	15	etanercept, adalimumab	GCS 0.03 mg/kg/day	43
18	oligoarticular JIA	3	4	GCS 0.75 mg/kg/day, MTX	4	etanercept	GCS 0.15 mg/kg/day, MTX	36
19	oligoarticular JIA	11	3	GCS 0.4 mg/kg/day, MTX, cyclosporine	12	etanercept	MTX	32
20	oligoarticular JIA	7	4	GCS 0.5 mg/kg/day, MTX	8	adalimumab	MTX	43
21	oligoarticular JIA	10	3	GCS 0.6 mg/kg/day, MTX	10	adalimumab	MTX	30
22	polyarteritis nodosa	8	13	GCS 0.3 mg/kg/day, azathioprine	14	etanercept	GCS 0.125 mg/kg/day, azathioprine	84
23	polyarteritis nodosa	9	12	GCS 0.3 mg/kg/day, MTX	13	etanercept	GCS 0.05 mg/kg/day	84
24	dermatomyositis	3	17	GCS 0.875 mg/kg/day, azathioprine	15	adalimumab	GCS 0.15 mg/kg/day, azathioprine	60

GCS – glucocorticosteroids, MTX – methotrexate

ic JIA (33.3%), 5 patients for oligoarticular JIA (62.5%), 9 patients for polyarticular JIA (90%) and 2 patients for polyarteritis nodosa (100%). The height SDS changes in children with particular diagnoses are shown in Figures 2, 3, 4 and 5.

Four children (23.5%) were treated with tocilizumab, 2 children (11.7%) with golimumab, 5 children (29.4%) with etanercept, 4 children (23.5%) with adalimumab, and 2 children (11.7%) firstly with etanercept and secondly with adalimumab. In 47% of patients (8 out of 17 with an improved growth rate) daily doses of GCS were reduced to 0 mg/kg/day. In 2 patients (11.7%) doses of steroids were minimized to less than 0.05 mg/kg/day. Unfortunately, in 4 children the GCS therapy was continued at a dose of more than 0.05 mg/kg/day. Three patients (17.6%) had never received steroids. At the latest follow-up, the mean height SDS was –0.03 ±1.09.

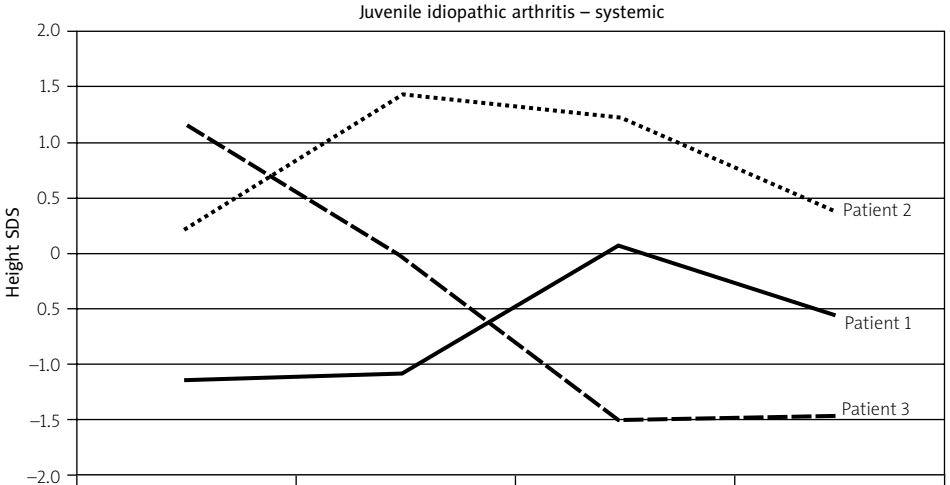
In 7 children (29.2%), despite biological agent administration, the growth velocity did not improve. In that group, 2 patients were treated for systemic JIA (28.5%), 3 patients for oligoarticular JIA (42.8%), 1 patients for polyarticular JIA (14.3%) and 1 patient for dermatomyositis (14.3%). Three patients were treated with etanercept (42.8%), 2 patients with etanercept and secondly with adalimumab (28.6%), 1 patient with tocilizumab (14.3%), and 1 patient with adalimumab (14.3%).

In 3 patients the daily dose of GCS was reduced to 0 mg/kg/day. Four patients were treated with GCS at a mean dose of 0.1 mg/kg/day (0.003–0.25 mg/kg/day).

Between the time of disease onset up to biological therapy initiation 6 children (25%) had significant growth inhibition (more than 1 height-SDS). All but one patient received GCS at a dose of 0.5 mg/kg/day or more during that time. After biological treatment induction only 2 of them had only a slight growth rate increase. Significant growth delay was observed in 2 patients (8%) before the diagnosis of CTD.

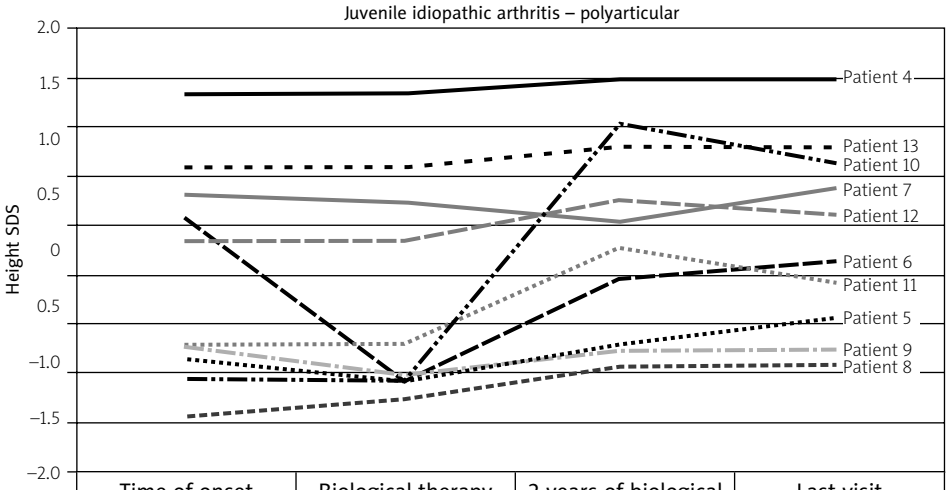
Discussion

There are various factors that may contribute to growth retardation in patients suffering from chronic inflammatory CTD. Disease type and duration, functional joint involvement, age of puberty and severity of the inflammatory process appear to be risk factors for growth impairment



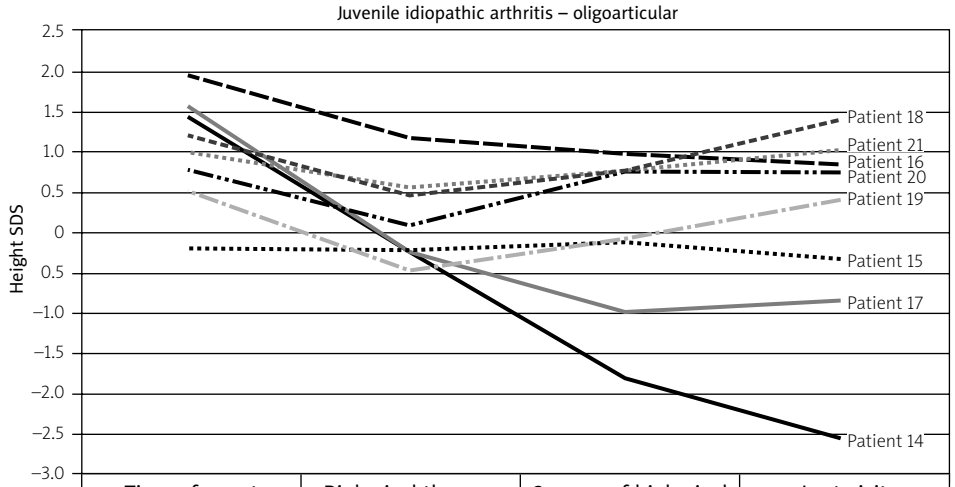
	Time of onset	Biological therapy initiation	2 years of biological treatment	Last visit
Patient 1	–1.14	–1.07	0.07	–0.55
Patient 2	0.22	1.43	1.23	0.38
Patient 3	1.17	–0.02	–1.50	–1.47

Fig. 2. Height-SDS changes in children with systemic JIA after biological treatment initiation.



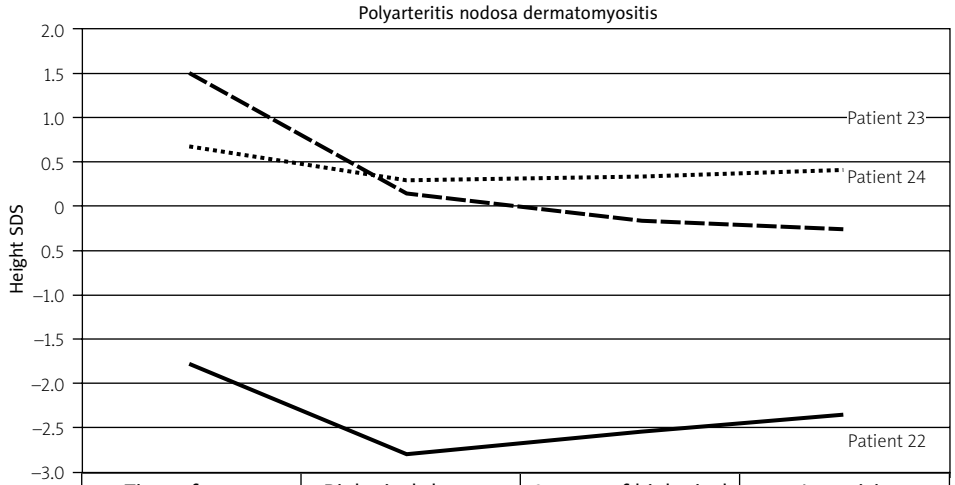
	Time of onset	Biological therapy initiation	2 years of biological treatment	Last visit
Patient 4	1.83	1.85	1.98	1.98
Patient 5	–0.85	–1.09	–0.71	–0.45
Patient 6	0.58	–1.06	–0.05	0.15
Patient 7	0.83	0.73	0.56	0.88
Patient 8	–1.44	–1.28	–0.93	–0.91
Patient 9	–0.73	–1.01	–0.77	–0.75
Patient 10	–1.07	–1.07	1.52	1.13
Patient 11	–0.70	–0.70	0.28	–0.08
Patient 12	0.34	0.34	0.76	0.61
Patient 13	1.10	1.10	1.30	1.30

Fig. 3. Height-SDS changes in children with polyarticular JIA after biological treatment initiation.



	Time of onset	Biological therapy initiation	2 years of biological treatment	Last visit
Patient 14	1.42	–0.22	–1.79	–2.55
Patient 15	–0.20	–0.22	–0.12	–0.32
Patient 16	1.93	1.17	0.98	0.84
Patient 17	1.55	–0.22	–0.98	–0.85
Patient 18	1.20	0.45	0.76	1.39
Patient 19	0.51	–0.47	–0.07	0.41
Patient 20	0.76	0.09	0.75	0.75
Patient 21	0.99	0.57	0.78	1.04

Fig. 4. Height-SDS changes in children with oligoarticular JIA after biological treatment initiation.



	Time of onset	Biological therapy initiation	2 years of biological treatment	Last visit
Patient 22	–1.76	–2.78	–2.56	–2.36
Patient 23	0.68	0.29	0.34	0.42
Patient 24	1.51	0.14	–0.16	–0.26

Fig. 5. Height-SDS changes in children with polyarteritis nodosa and dermatomyositis after biological treatment initiation.

[11]. Glucocorticosteroids, being a first-line therapy, are a frequent cause of deteriorating linear growth in children even if they are administered at low doses [12].

Biological therapy might be effective for both inhibiting the inflammatory process and reducing the daily doses of GCS [13]. By achieving this goal the acceleration of growth velocity might be expected. There are only a few recent studies on the influence of antiTNFα treatment on growth in children with JIA. Giannini et al. [14] reported that even without DMARD therapy, a significant increase in height, weight and BMI in children was observed during long-term etanercept therapy. Moreover, the improvement in growth velocity is the best in patients with the greatest growth retardation. On the other hand, Uettwiller et al. [15] recently found that biologic therapy may be insufficient to restore normal growth velocity. Tynjälä et al. and Schmeling et al. [16] reported that the variation of inflammation activity remains a significant predictor of growth velocity. It simply means that the improvement in growth velocity may be observed due to inflammation inhibition and not by a direct effect of biological agents on growth. It is also proven that there is a significant relation between the variations in GCS doses and the change in growth velocity. The results from our study showed the significant acceleration of growth velocity in children with CTD treated with various biological agents. There were no significant differences between the particular therapies. In around half of the children with growth rate improvement the daily dose of GCS could be reduced to 0 mg/kg/day or less than 0.05 mg/kg/day.

Conclusions

In conclusion, to our best knowledge, this is the first study reporting the impact of biological therapy on growth velocity and GCS consumption not only in JIA, but also in other CTD in children. We have shown that biological drug treatment allows one to control the inflammatory process and also to reduce or withdraw the daily doses of GCS. Normal growth is one of the most important goals in CTD treatment, and biological agents might play a crucial role in achieving it.

The authors declare no conflict of interest.

Financing of the work – the statutory program of the Medical University of Lodz (503/8-000-01/503-01).

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