Growth and body mass index in a cohort of patients with juvenile idiopathic arthritis: effects of second line treatments

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Abstract

Objective

Juvenile idiopathic arthritis (JIA) may affect natural growth. The aim of the study has been to assess auxological parameters of JIA patients, receiving different anti-rheumatic treatments.

Methods

This is a retrospective study; JIA patients were recruited from the Rheumatology Unit of Anna Meyer Children's University Hospital of Florence, Italy from March 1996 to June 2016.

Results

Two hundred and thirty-two patients were included in the current study. The best result in terms of catch-up growth occurred in systemic JIA patients. All JIA categories showed standard deviation score (SDS) gain for height except those belonging to enthesitis related arthritis category. Patients treated with disease-modifying anti-rheumatic drugs (DMARDs) only maintained constant growth during study follow-up. Patients who needed biologic therapy showed an impaired growth during pre-DMARDs treatment and an increased growth velocity mostly during biologic therapy. Body mass index (BMI) decreased in almost all JIA categories. The best BMI reduction was observed among patient receiving biologic drugs.

Conclusion

Patients with JIA followed in our centre had a gain of height SDS and lost BMI SDS in 5 years of follow-up. We observed a stable and good pattern of growth in patients treated with DMARDs and an increased growth velocity during biologic treatment.

Key words

biologic therapies, body mass index, growth, height, juvenile idiopathic arthritis

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood. The improved physiopathological knowledge and the availability of new therapies acting on specific targets have led to an important improvement of outcome in the past two decades (1).

JIA may affect natural growth causing several degrees of growth retardations (2). Disease characteristics, cytokine profile, functional limitation and nutrition have been associated with growth impairment in patients with JIA (3). The role of TNF-α, IL-1 and IL-6 in the pathogenesis of JIA is well known. TNF-α and IL-1β have a local action on growth plate of long bones by inhibiting the expression of genes encoding chondrocyte-specific matrix molecules (4). Whereas IL-6 may influence growth through inhibition of committed stem cells of growth plate and may inhibit liver growth hormone (GH) signalling by inducing suppressor of cytokine signaling proteins 3 (SOCS3) (5). Significantly short stature (final height SDS <-2) has been shown in 41% of patients affected by systemic JIA and 11% of patients affected by polyarticular disease (4). Furthermore also oligoarticular JIA patients experienced abnormal growth (6). JIA therapy may influence growth and in some cases restore it (5, 7-8). So far, limited data on this subject are available (9-11). Hence we reported the trend of auxological parameters of JIA patients followed in our unit, with particular regard to treatment received. The aim of the study has been to assess auxological parameters of a group of pre-pubertal and pubertal patients affected by JIA, receiving different anti-rheumatic treatments, in order (a) to evaluate growth patterns of patients affected by JIA in our clinic, and eventually highlight the best response in terms of catch-up growth and (b) to assess body mass index (BMI) trend during the natural history of disease.

Materials and methods

This is a retrospective study; patients were recruited from the Rheumatology Unit of Anna Meyer Children's University Hospital of Florence, Italy, from March 1996 to June 2016.

Inclusion criteria

Patients were required to fulfill the International League of Association for Rheumatology (ILAR) criteria for JIA (12), to be followed in our unit for at least 1 year and to have all follow-up data available.

Exclusion criteria

The presence of another chronic disease (including coeliac disease) or joint abnormalities making height measurement difficult. Patients without sufficient auxological measures (at least 3 measures 4–6 months apart) were also excluded and those, in the presence of growth failure and/or pubertal delay, who did not undergo endocrinologic evaluations and appropriate laboratory tests in order to rule out other possible causes, were also excluded.

All the information recorded from medical charts was collected in a customised database, including demographic and clinical data.

At each clinic visit height was measured by using a wall-mounted stadiometer, and weight was measured to the nearest 0.1 kg. Age-related reference values of height and BMI (kg/m^2) were obtained from a wide sample of Italian children (13). Height and BMI were normalised for chronologic age by conversion to standard deviation scores (SDSs). Growth velocity was defined as the change in height SDS during the follow-up. A positive value indicated increase in growth velocity and a negative value impaired growth. Pubertal staging was carried out according to the Tanner and Whitehouse criteria (14), and testicular volume was determined with the Prader orchidometer.

Statistical analysis

Height and BMI differences for exposure to treatment administration and other factors (*e.g.* age, JIA category) were evaluated with t test for paired samples and, when appropriate with *t*-test for unpaired samples. The significance of the difference between the mean values was fixed at the value of p=0.05. All analyses were conducted using STATA v. 11.0.

Table I. Height trends in whole study group and pre-pubertal and pubertal ages. Distribution for JIA category, age at disease onset, treatment received.

Variable		Total		Prepubertal		Pubertal	
		ΔH SDS (95% CI)	*p*-value	ΔH SDS (95% CI)	*p*-value	ΔH SDS (95% CI)	*p*-value
JIA category	Oligo	0.13 (0.02; 0.24)	0.01*	0.15 (0.03; 0.26)	0.00*	-0.07 (-0.17; 0.04)	0.10
	Poly	0.02 (-0.15; 0.19)	0.4	0.17 (-0.03; 0.37)	0.05	-0.13 (0.30; 0.04)	0.07
	Systemic	0.68 (0.24;1.13)	0.00*	0.57 (0.03; 1.10)	0.02*	0.41 (-0.24; 1.05)	0.09
	Psoriatic	0.24 (-0.19; 0.66)	0.12	0.06 (-0.27; 0.39)	0.34	0.07 (-0.38; 0.51)	0.37
	ERA	-0.11 (-0.43; 0.21)	0.24	-0.11 (-0.82; 0.61)	0.33	-0.04 (-0.35; 0.27)	0.4
Age at onset	< 5 y	0.23 (0.11; 0.35)	0.00*	0.23 (0.12; 0.34)	0.00*	-0,03 (-0.17; 0.11)	0.35
	5-10 y	0.03 (-0.12;0.18)	0.36	0.01 (-0.16; 0.16)	0.47	-0.05 (-0.19; 0.09)	0.24
	>10 y	-0.09 (-0.24; 0.06)	0.11	No observations		-0.08 (-0.23; 0.07)	0.14
Treatment	NSAIDs/IAS	0.07 (-0.07; 0.21)	0.15	0.06 (-0.09; 0.20)	0.22	-0.07 (-0.21; 0.08)	0.18
	DMARDs	0.18 (0.04; 0.31)	0.00*	0.26 (0.14; 0.39)	0.00*	0.03 (-0.11; 0.18)	0.33
	BIOLOGICS	0.13 (-0.04; 0.29)	0.06	0.20 (0.01; 0.39)	0.02*	-0.10 (-0.25; 0.05)	0.09
All patients		0.12 (0.39; 0.21)	0.00*	0.17 (0.08; 0.26)	0.00*	-0.05 (-0.13; 0.03)	0.12

*$p<0.05$. ΔH: difference between height at last visit – height first visit; Oligo: oligoarticular JIA; Poly: polyarticular JIA; ERA: enthesitis related arthritis. NSAIDs: non-steroidal anti-inflammatory drugs; IAS: intra-articular steroid injections; DMARDs: disease-modifying anti-rheumatic drugs; BIOLOGICS: biological drugs; SDS: standard deviation score.

Results

Two hundred and thirty-two patients were included in the current study (172 females, 60 males; mean age at JIA onset 5.3±3.8 years). All patients except 4 (1 South American, 3 Asian) were Caucasians. One hundred and thirty-five (58%) had oligoarticular JIA; 56 (24%) had polyarticular rheumatoid factor–negative JIA; 14 (6%) had systemic JIA (SoJIA); 11 (5%) had psoriatic arthritis and 16 (7%) had enthesistis-related arthritis (ERA). The mean follow-up time was 5.3 years ±3.8.

The cohort was divided into 3 groups according to the treatment received: patients treated with non-steroidal anti-inflammatory drugs (NSAID) or intraarticular steroid injections (IAS), patients treated only with disease-modifying anti-rheumatic drugs (DMARDs) and patients treated with biologic agents with or without concomitant DMARDs. Eighty-six (37%) patients received biological therapy: all of them received anti-TNF-α treatment except 4 patients with SoJIA; 21 patients received >1 biologic (2 biologics in 15 patients, 3 biologics in 4 patients and 4 biologics in 2 patients). Thirteen patients received CTLA-4 Ig; one patient received anti-IL6; anti-IL 1 was used in 5 patients (all with SoJIA).

The whole population studied had an average height of -0.19 SDS at disease onset and of -0.06 SDS at last follow-up visit, with an overall gain of 0.12 SDS ($p<0.05$). Only 3 patients had a significantly short stature (height SDS <-2) at the end of follow-up (2 oligoarticular JIA and 1 polyarticular JIA). The height trend distributed by JIA category, age at disease onset and treatment received is shown in Table I.

In each type of category, the best result in terms of catch-up growth occurred in SoJIA patients (Δ H 0.68 SDS, $p<0.05$) as expected, while among the other JIA categories the better gain of H SDS was observed in psoriatic JIA patients (Δ H 0.24 SDS, p=NS). All JIA categories showed SDS gain for height except ERA patients who exhibited a reduction of H SDS (Δ H -0.11 SDS, p=NS). According to time of disease onset, earlier onset (<5 years of age) was associated to the best gain of H SDS (Δ H 0.23 SDS, $p<0.05$), while patients >10 years old at disease onset had no height SDS gain at all (Δ H -0.09, p=NS).

Patients on DMARDs only had better H SDS gain than other treatment subgroups during the overall follow-up (Δ H 0.18 SDS, $p<0.05$).

We also studied height pattern considering the pubertal stage and we found that the gain of H SDS was reached mostly during pre-pubertal age (Δ H 0.17 SDS, $p<0.05$).

Furthermore, we compared growth velocity of patients treated with DMARDs only (60 subjects on methotrexate and 7 on sulfasalazine) and patients who added biologic drugs (75 subjects) after DMARDs treatment failure (Fig. 1) at each phase of treatment. Patients treated with DMARDs only maintained constant growth along study follow-up and had a little increase of growth velocity on DMARDs treatment. Patients who needed biologic therapy showed an impaired growth during pre-DMARDs treatment and an increased growth velocity mostly during biologic therapy. Indeed, the major H SDS gain was observed during biologic treatment, with significant increase of growth velocity when compared to growth velocity pre-DMARDs.

No correlation between growth and inflammatory markers (CRP and ESR) was found.

We also analysed the BMI modifications over time. Considering all patients together, BMI showed a slight reduction with a BMI of -0.09 SDS (Δ BMI -0.09 SDS, p=0.06). Interestingly, looking at BMI trend during pre-pubertal age we observed a significantly reduction of BMI SDS (Δ BMI -0.17 SDS, $p<0.05$) whereas the opposite happened during pubertal age (Δ BMI 0.07 SDS, p=0.054).

Our results showed a BMI reduction in almost all JIA categories especially in

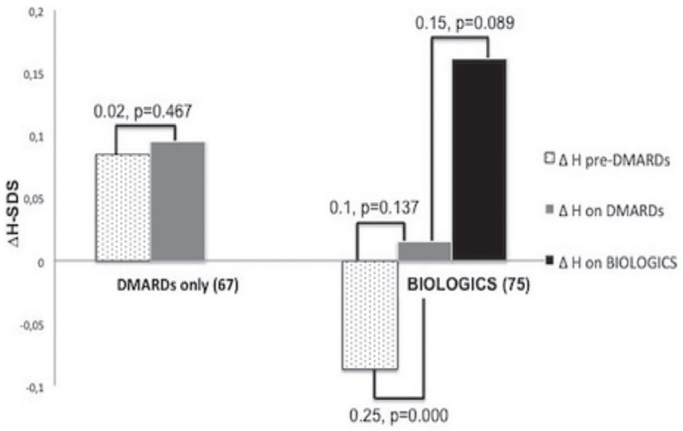

Fig. 1. Growth velocity of patients treated with DMARDs only and patients who added biologic drugs after DMARDs treatment failure at each phase of treatment.

polyarticular JIA (Δ BMI -0.25 SDS, $p<0.05$). Once again ERA patients had an opposite trend with a significant gain in BMI SDS (Δ BMI 0.37 SDS, $p<0.05$).

Younger patients at disease onset (<5 years old) reduced their BMI SDS significantly over follow-up time (Δ BMI -0.26 SDS, $p<0.05$), whereas older patients at disease onset (>10 years old) increased it (Δ BMI 0.17 SDS, $p<0.05$). According to the treatment received the best BMI reduction was observed among patient receiving biologic drugs (Δ BMI -0.73 SDS, p=NS).

Discussion

Impaired physical growth in JIA patients has been already documented. Given the availability of newer therapies making the use of corticosteroid less frequent and just for brief periods of time, JIA patients now are less affected by iatrogenic growth impairment. In our cohort only 3 patients (1.3%) had significantly short stature at the end of study follow-up (2 with oligoarticular JIA and 1 with polyarticular JIA), interestingly none belonging to SoJIA category probably because the earlier introduction of biologic agents.

Our cohort showed a growth pattern consisting of an increase of H SDS and a slight decrease of BMI SDS (Δ H 0.12 SDS, $p<0.05$; Δ BMI -0.09 SDS, p=NS). This pattern was particularly evident in prepubertal age (Δ H 0.17 SDS, $p<0.05$; Δ BMI -0.17 SDS, $p<0.05$).

Only ERA patients showed an inversed trend, with a decrease of H SDS and an increase of BMI SDS. A possible explication is that patients belonging to this category were older at disease onset than subjects of the other JIA categories (11.67 years of ERA patients *vs.* 4.06 for oligoarticular, 3.86 for polyarticular, 4.7 for systemic and 5.75 years for psoriatic patients) while the gain of H SDS and the loss of BMI SDS happened almost totally in the pre-pubertal age.

In agreement with these findings, we noted that younger patients at disease onset had the best H SDS gain and the older did not increase their H SDS whereas the opposite happened to BMI SDS.

Observations from the literature show that stunted growth in JIA is more frequent in patients with severe SoJIA. This is confirmed in our cohort; indeed, SoJIA patients had the worst H SDS at disease onset (-0.78 SDS) but also the better results in catch-up growth (Δ H 0.68 SDS, $p<0.05$). De Benedetti *et al.* (5) studied a homogeneous patients population with severe SoJIA treated with an IL-6 inhibitor and observed marked catch-up growth during treatment with tocilizumab, with significant increase of H SDS during anti-IL6 treatment.

With regard to the treatment received we noticed that patients on DMARDs treatment without biologics showed the best H SDS gain over the overall study time (Δ H 0.18 SDS, $p<0.05$). Comparing growth velocity of patients treated with DMARDs only and patients non responding to DMARDs that needed biologic therapy, our data pointed out that although patients on DMARDs had a stable growth, patients who did not respond to DMARDs had a better growth velocity, with an important gain of H SDS just once biologic agents was added.

Giannini *et al.* (9) reported the effects of etanercept on growth in 598 patients belonging to polyarticular and SoJIA categories. This study documented a significant gain of height and BMI percentiles after 3 years of treatment for children treated with etanercept with or without MTX, but not in patients treated only with MTX.

Another retrospective study of 100 JIA patients treated with biologic agents demonstrated improved growth, although when the growth retardation developed before biologic introduction it persisted at last follow-up visit despite the treatment received. That population was composed by a high percentage of SoJIA patients (29%) and difficult to treat patients referred to a tertiary centre (10). Tynjala *et al.* had different results, with a restoration of normal growth after introduction of anti-TNF-α in a cohort of patients with polyarticular course of disease, as we observed in our study (11).

Previously published data are difficult to compare because of the heterogeneity of the patient groups, the variable treatment received and the measuring systems adopted (absolute values, percentiles, standard deviation scores).

To our knowledge this is the first study that analysed auxological parameters pattern in a large cohort of JIA patients, belonging to all JIA categories and receiving several different treatments.

Our study showed that patients with JIA followed in our centre had a gain of height SDS and lost BMI SDS in 5 years of follow-up, particularly in the SoJIA category and not in ERA patients. With regard to the treatment received, we observed stable and good pattern of growth in patients treated with DMARDs and an increased growth velocity during biologic treatment confirming that cytokine targeted therapy may also play a key role in restoring the growth abnormalities in children and adolescents with JIA. Nevertheless further studies are required to completely characterise the ability to prevent the impaired systemic and local growth alterations.

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