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Predictors and long-term outcome in Greek adults with juvenile idiopathic arthritis: a 17-year continuous follow-up study

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Abstract

Objectives. To describe the disease characteristics, continuous course and long-term outcome and to evaluate predictors of outcome in JIA in Greece.

Methods. We performed a retrospective cohort analysis of 17 years' prospective data on JIA. Outcome assessment included radiographic (modified Sharp–van der Heidje score), articular and extra-articular damage (Juvenile Arthritis Damage Index), functional ability (HAQ Disability Index), and the cumulative percentage time spent in a state of active disease and also in clinical remission off medication (CR) (according to Wallace's criteria).

Results. One hundred and two (72 females) patients under regular follow-up were enrolled. The disease age of onset [mean (SD)] was 7.7 (4) years, the interval from onset to last visit was 17.2 (6.7) years and the patients' current age was 25 (5.9) years. At the last follow-up visit, 53 patients (52%) had disease activity, while 23.5% were in CR. The cumulative percentage time spent in a state of active disease and CR over the disease course was 52.6 and 17.8%, respectively. Polyarticular subtype of onset and longer disease activity during the first 5 years were independent predictors of worse outcome. Additional telephone-based interviews of 205 former JIA patients who had been lost to follow-up as adults were performed to extend the interpretation of our findings to a broader JIA population. Almost half (47.6%) of the total cohort of 307 patients were found to be in CR at the final evaluation and 69.7% had no disability.

Conclusion. The available data indicate that JIA as a whole is a heterogeneous disease with significant variability in course and long-term outcome.

Key words: juvenile idiopathic arthritis, long-term outcome, predictors, transition, JIA prognosis

CLINICAL SCIENCE

Rheumatology key messages

- At the last follow-up, 47.6% of adult JIA patients were in clinical remission off medication.
- Only a small number of JIA patients developed severe disability.
- A significant number of JIA patients develop structural damage and enter adulthood with persistent active disease.

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Introduction

JIA is the most common paediatric rheumatic disease, characterized by prolonged synovitis, progressive joint damage and impaired quality of life. It has a worldwide distribution, with an uneven incidence and prevalence among the various geographical regions [1–6]. Head-to-head comparison among relevant publications is rather difficult due to disease heterogeneity resulting in diverse study designs regarding classification criteria, inclusion of

JIA subtypes, disease assessment tools and outcome measures as well as the length of the follow-up periods.

The primary aim of this study was to assess the long-term outcome and disease course and to highlight any predictors of disease severity in a cohort of Greek adults with JIA. Better characterization of JIA patients would provide evidence-based counselling and treatment options to patients and families.

Methods

Study cohort

According to the current transition policy in our centre, JIA patients followed up in the Paediatric Rheumatology Referral Centre are transferred to an adult rheumatology outpatient clinic [7]. Thus, we performed a retrospective cohort analysis of 17 years' prospective data on JIA by studying consecutive adult patients who had been seen as inpatients or outpatients between January 2008 and December 2011 in the adult Rheumatology Unit and had been previously managed in the Paediatric Rheumatology Centre, in Hippokration University Hospital, Thessaloniki, Greece. There are currently no data on the long-term outcome of Greek JIA patients.

The study recruited patients with established diagnosis of JIA according to ILAR criteria [8]: disease duration >5 years, age $\geqslant 18$ years at the last follow-up visit and continuous follow-up since diagnosis. Patients followed up for >6 months by an external rheumatologist(s) and those for whom clinician's file notes were missing for more than one outpatient follow-up visit were excluded from the study. Such restrictions ensured the continuity of care and the non-stop documentation of sequential visits for each patient's disease course but on the other hand characterized a selective population with possible higher burden of the disease. In order to overcome this limitation and to acquire real-life population data, we performed additional telephone-based interviews of former JIA patients who had been lost to follow-up as adults. All these patients met the previously mentioned inclusion criteria regarding age at the time of the interview, disease diagnosis and duration.

The study was approved by the Bioethics Committee of the School of Medicine of the Aristotle University of Thessaloniki and was carried out in compliance with the Declaration of Helsinki. All patients gave written informed consent to participate in this study.

Chart reviews

The following data were retrieved from medical files: demographics, clinical features/complications regarding joint or eye involvement, and the date and type of any performed surgery associated with the disease. Each patient's disease status (active *vs* inactive disease) was determined in each clinic visit, according to Wallace's criteria [9]. Prescribed medications (start and stop date) were also documented. Each episode of inactive disease was assessed to determine whether it met the criteria for complete remission off medication (CR) (at least 12 months of inactive disease while not receiving any anti-arthritis or anti-uveitis medications). Total duration of CR was the sum of periods of CR. Proportion of disease course spent in CR was calculated as the total duration of CR/total disease duration and expressed as a percentage. Total duration of active disease was the sum of periods of active disease. Proportion of disease course spent in active disease was calculated as the total duration of active disease/total disease duration and expressed as a percentage. All the above data were retrospectively retrieved from patients' medical files and the calculations regarding proportion (%) of disease course spent either in CR or in active disease took place at the last follow-up visit.

Assessment tools

Clinical

At the time of the study visit, the patients underwent clinical examination and documentation of swollen and tender joint counts. Physician's and patient's global assessment of overall disease activity were also measured on a 10-cm visual analogue scale (VAS). Thereafter, disease status was determined according to Wallace's criteria while disease activity was measured by the juvenile arthritis DAS-10 (JADAS-10) index [10]. The JADAS-10 cut-off score for classifying inactive disease is 1, whereas the cut-off for classification of minimal disease activity is 2 for oligoarticular and 3.8 for polyarticular JIA [11]. The Ankylosing Spondylitis Disease Activity Score (ASDAS) [12] was additionally calculated in patients who had axial involvement defined as sacroiliitis documentation in a previous MRI assessment. Four disease activity states are defined by ASDAS: inactive disease, moderate, high and very high disease activity. The three cut-offs to separate these states are 1.3, 2.1 and 3.5 U. Joints were also examined for possible restrictions; articular and extra-articular damage was assessed by the Juvenile Arthritis Damage Index (JADI) [13].

Laboratory work-up/radiographic assessment

Levels of ESR and CRP (reference <3 mg/l) were measured, while assessment of autoantibodies included (i) ANA titres, (ii) IgM RF, and (iii) levels of anti-CCP antibodies. Radiographs of the wrists, hands and feet were examined by two radiologists blinded to patient identification and without access to earlier radiographic, clinical or laboratory data. A radiographic abnormality was defined as the presence of erosions and/or joint space narrowing (JSN) even in a single joint. Radiographic joint damage was assessed for all patients at the time of their inclusion in the study by modified Sharp–van der Heijde score [14–16].

Assessment of functional ability was based on the Disability Index score as derived by the HAQ Disability Index (HAQ-DI) [17].

Outcome measures

These included the following markers: (i) JADI-A, JADI-E; (ii) total modified Sharp–van der Heijde score; (iii) HAQ-DI;

(iv) the percentage of the whole disease course spent in a state of active disease; and (v) the percentage of the whole disease course in CR. The final ocular outcome was 'the best corrected visual acuity' as measured by an ophthalmologist at the last follow-up visit.

In the cohort of patients who had been lost to follow-up as adults and participated by telephone, outcome measures included only functional ability, based on HAQs and the identification of CR state at the time of interview. The standardized telephone interview included five questions aimed to capture last experience regarding joint complaints, systemic features, flare of uveitis or psoriasis, last documented disease activity by a rheumatologist, last hospitalization due to JIA and current administration of anti-rheumatic medications. Absence of disease activity in the last 12 months while not taking any medication was the criterion for being classified as CR.

Statistical analysis

The Kolmogorov–Smirnov test for normality was used to assess the normality assumption for continuous variables. The chi-squared test was used to test for independence between categorical variables. Correlations between continuous variables were quantified with the Pearson correlation coefficient. Comparisons of means were conducted using the independent samples *t* test or one-way analysis of variance (ANOVA) with Tukey's *post hoc* test. Multivariable analysis included linear regression and logistic regression modelling according to the nature of the dependent variable. $P < 0.05$ was considered statistically significant. SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis.

Results

A total of 102 patients were enrolled in the study. The main demographic and clinical characteristics are shown in Table 1. The most prevalent JIA subtype was extended oligoarthritis (n = 22, 21.6%). In 74 patients disease onset was recorded before 2000.

Disease course

Proportion of disease course with active disease

Patients spent a mean (S.D.) of 52.7% (27.7%) of their course with active disease (range 3.6–100%) (Table 1). There were significant differences between JIA categories ($P = 0.006$); pairwise comparison revealed that more patients with polyarthritis RF+ as compared with other categories of JIA had active disease.

Proportion of disease course in remission off medication (CR)

Patients spent a mean (S.D.) of 17.8% (28.7%) of their course in a state of CR (range 0–93.8%) (Table 1). Overall, 37/98 patients (37.8%) achieved CR at least once during their follow-up period (four patients had missing data). The proportion of patients who attained CR, was different among the seven JIA-categories ($P = 0.008$) (Table 1). Additionally, 21.6% had at least a second episode of CR. The initial episode of CR lasted significantly longer than the second one (50.3 *vs* 22.5 months, $P = 0.03$). CR lasted at least 5 years in nearly half (51.4%) of those patients who achieved CR (19.4% of the whole group).

Uveitis

Uveitis developed in 11 (10.8%) of the patients with JIA, predominantly in females (10/11 females, $P = 0.224$). Uveitis was positively associated with ANA positivity (81.8% *vs* 27.3%, $P = 0.001$), was more commonly bilateral (81.8% *vs* 18.2%) and related with earlier arthritis onset (mean 3.1 years) compared with patients without uveitis ($P < 0.001$). Finally, 5/11 patients (45.5%, 4.9% of the whole cohort) developed at least one ophthalmological complication.

Surgery

Eleven patients (10.8%) had undergone at least one major JIA-associated operation (prosthetic arthroplasty 9 patients, mandibular correction 1 patient, arthrodesis of the radiocarpal joint 1 patient, hands or foot small joints correction 4 patients). The requirement of arthroplasty was highest in patients with polyarticular course (RF^+ 27.3%, RF^- 21% and systemic 15.4%).

Outcome assessment at the last follow-up visit

Disease activity status

According to Wallace criteria 53/102 patients (52%) had active disease, 19/102 (18.6%) were in remission on medication and 24/102 (23.5%) in CR. Additionally, six patients (5.9%) had inactive disease but did not meet the criteria for remission (Table 2). Disease activity status according to JADAS-10, was as follows: 43 patients were in remission, 13 had minimal disease activity and 46 were in a moderate or high disease activity status. Six patients found in remission according to Wallace's criteria had minimal disease activity based on JADAS-10. Additionally of the 12 patients with axial involvement, 4 were in remission, 3 had a moderate disease activity, 4 a high one and 1 patient had a very high disease activity, based on ASDAS.

Radiographic damage

The results of radiological evaluations according to the modified Sharp–van der Heijde score are shown in Table 3. Erosion(s) or JSN even in a single joint was present in 86 patients (84.3%), while only 15.6% had an absolutely normal total modified Sharp–van der Heijde (TmSvdH) score.

JADI-A and JADI-E

According to JADI most of the 102 patients (87.2%) had detectable damage in $\geqslant 1$ joint or joint group. The median of JADI-A was 6. Approximately half of the patients (57.8%) had $\geqslant 1$ extra-articular damage (Table 3).

Local growth disturbances

Clinical signs of mandibular dysfunction, such as reduced mouth opening, frontal facial asymmetry or retrognathia,

Table 1 Clinical characteristics of patients in the Greek JIA cohort, according to JIA categories

Characteristics	Total cohort (n = 102)	Systemic arthritis (n = 13)	Oligoarthritis persistent (n = 8)	Oligoarthritis extended (n = 22)	Polyarticular RF negative (n = 19)	Polyarticular RF positive (n = 11)	PsA (n = 9)	Enthesitis-related arthritis (n = 18)	Undifferentiated arthritis (n = 2)
Female–male	72–30	8–5	6–2	22–0	16–3	8–3	6–3	5–13	1–1
Age at disease onset, median (range), years	7 (1–15.5)	6 (1.5–10)	7.8 (1–13)	3.8 (1.5–13.5)	6.5 (1.5–15.5)	10 (4–14)	6.5 (2–11)	11.3 (6–15.5)	13.8 (13.5–14)
Disease duration, median (range), years	17 (5–31.5)	21 (8–31)	24.8 (14.5–31)	16.8 (5–31.5)	17.5 (6–24)	17 (6–29)	16.5 (9–27.5)	13 (5–25)	11.3 (8.5–14)
Age at study visit, median (range), years	24 (18–41)	27 (18–39)	32 (18–41)	20.5 (18–35)	22 (18–30)	28 (18–37)	23 (19–31)	24.5 (18–36)	25 (22–28)
Polyarticular course, n (%)	84 (82.4)	10 (76.9)	NA	22 (100)	19 (100)	11 (100)	5 (55.6)	15 (83.3)	2 (100)
Axial involvement, n (%)	12 (11.8)	0	0	0	0	0	1 (11.1)	11 (61.1)	0
Hip involvement, n (%)	45 (44.1)	8 (61.5)	0 (0)	5 (22.7)	11 (57.9)	7 (63.6)	6 (66.7)	8 (44.4)	0 (0)
History of uveitis, n (%)	11 (10.8)	NA	2 (25)	7 (31.8)	1 (5.3)	NA	NA	1 (5.6)	NA
ANA positive, n (%)[a]	33/99 (33.3)	0/13 (0)	4/8 (50)	12/21 (57.1)	4/18 (22.2)	5/11 (45.5)	5/9 (55.6)	3/17 (17.6)	0/2 (0)
Anti-CCP positive, n (%)[a]	11/81 (13.6)	1/12 (8.3)	1/8 (12.5)	2/17 (11.8)	2/14 (14.3)	4/7 (57.1)	0/6 (0)	0/15 (0)	1/2 (50)
Achievement CRM during the disease course, n (%)[a]	87/98 (88.8)	8/11 (72.7)	6/8 (75)	20/22 (90.9)	18/19 (94.7)	9/11 (81.8)	9/9 (100)	15/16 (93.8)	2/2 (100)
Achievement CR during the disease course, n (%)[a]	37/98 (37.8)	4/11 (36.4)	7/8 (87.5)	8/22 (36.4)	6/19 (31.6)	0/11 (0)	3/9 (33.3)	7/16 (43.8)	2/2 (100)
Proportion of disease course spent in active disease (%)									
Mean (S.D.)	52.7 (27.7)	57.2 (31)	32.4 (25.8)	47.8 (24.7)	58.7 (25.9)	78.6 (18.3)	44.7 (28)	43.7 (29.1)	58.4 (24.3)
Range	3.6–100	7.2–100	5.4–68.6	6.3–91.9	3.6–100	50.8–100	14.7–81.6	8.2–100	41.2–75.6
Proportion of disease course spent in CR (%)									
Mean (S.D.)	17.8 (28.7)	23.0 (34.4)	51.6 (37.6)	18.2 (30.3)	8.2 (17.5)	0	11.6 (17.6)	22.5 (30.8)	29.6 (31.7)
Range	0–93.8	0–83.3	0–87.5	0–93.8	0–61.9		0–39.6	0–83.8	7.1–52
Active disease duration during the first 5 years after disease onset, months									
Mean (S.D.)	36.5 (35.5)	43 (18.6)	31 (15.3)	36.5 (13.6)	34 (15.6)	52 (14.3)	39 (12.6)	29.5 (13.1)	33 (2.8)
Range	6–60	9–60	6–53	9–56	10–58	14–60	8–45	13–60	31–35
Achievement CR during the first 5 years after disease onset, n (%)[a]	12/100 (12)	2/13 (15.4)	3/8 (37.5)	2/22 (9.1)	2/19 (10.5)	0/11 (0)	1/9 (11.1)	1/16 (5.6)	1/2 (50)

Proportion of disease course spent in active disease (%). Active disease duration was the sum of periods of active disease. Proportion of disease course spent in CR (%). CR duration was the sum of periods of CR (12 months of inactive disease off all anti-rheumatic medications defines clinical remission off medication according to Wallace's criteria). [a]Number of patients/number of patients assessed. CR: clinical remission off medication; CRM: clinical remission on medication; NA = not applicable.

Table 2 Data of disease activity status at the final follow-up visit, 17 year post-diagnosis

Data of disease activity	Total cohort (n = 102)	Systemic arthritis (n = 13)	Oligoarthritis persistent (n = 8)	Oligoarthritis extended (n = 22)	Polyarticular RF negative (n = 19)	Polyarticular RF positive (n = 11)	PsA (n = 9)	Enthesitis-related (n = 18)	Undifferentiated (n = 2)
ESR, mean (S.D.)[a], mm/h	19.9 (20.0)	19.7 (28.3)	16.4 (12.1)	23.1 (18.3)	18.9 (15.2)	20.7 (21.1)	22.7 (21.6)	18.5 (23.5)	4.0 (4.2)
CRP, mean (S.D.)[b], mg/l	7.5 (19.4)	18.1 (43.8)	0.1 (0)	4.0 (7.0)	5.1 (7.6)	7.4 (10.6)	11.1 (15.1)	9.3 (20.6)	0.1 (0.0)
Active arthritis joint count, mean (S.D.)	1.9 (3.7)	3.1 (6.5)	0.3 (0.5)	2.0 (3.5)	1.6 (2.4)	4.3 (5.6)	1.7 (2.5)	1.0 (1.9)	0.0 (0.0)
Duration of morning stiffness, mean (S.D.), min	23.9 (31.9)	21.2 (31.1)	7.5 (10.7)	26.8 (33.0)	18.7 (18.1)	40.9 (26.2)	26.7 (36.7)	25.6 (46.5)	2.5 (0.0)
Physician's global assessment of overall DAS, mean (S.D.), 0–10 point VAS	2.1 (2.3)	2.4 (2.8)	1.5 (2.4)	1.9 (2.1)	2.0 (2.2)	3.4 (2.0)	2.2 (2.5)	1.8 (2.6)	0.3 (0.4)
Patient's global assessment of overall DAS, mean (S.D.), 0–10 point VAS	1.9 (2.2)	2.0 (2.4)	1.6 (2.2)	1.6 (1.7)	1.8 (2.0)	2.9 (2.1)	2.4 (2.5)	1.7 (2.6)	0.3 (0.4)
Active uveitis, n (%)	1 (1)	0	0	1 (4.5)	0	0	0	0	0
JADAS-10, mean (S.D.)	6.3 (7.5)	7.3 (10)	3.5 (5.5)	6.0 (6.7)	5.9 (6.2)	10.9 (7.0)	7.0 (7.7)	5.2 (8.7)	0.5 (0.7)
ASDAS, mean (S.D.)	2.1 (1.5)	—	—	—	—	—	2.2 (1.5 (11)	2.0 (1)	—
Active disease, n (%)[c]	53 (52)	7 (53.8)	2 (25)	11 (50)	10 (52.6)	10 (90.9)	5 (55.6)	8 (44.4)	0 (0)
Inactive disease, n (%)[c]	49 (48)	6 (46.2)	6 (75)	11 (50)	9 (47.4)	1 (9.1)	4 (44.4)	10 (55.6)	2 (100)
CRM, n (%)[c]	19 (18.6)	2 (15.4)	2 (25)	4 (18.2)	4 (21)	0 (0)	3 (33.3)	4 (22.2)	0 (0)
CR, n (%)[c]	24 (23.5)	3 (23.1)	4 (50)	5 (22.7)	3 (15.8)	0 (0)	1 (11.1)	6 (33.3)	2 (100)
Inactive disease <6 months, n (%)[c]	6 (5.9)	1 (7.7)	0 (0)	2 (9.1)	2 (10.5)	1 (9.1)	0 (0)	0 (0)	0 (0)

[a]Normal value <20 mm/h. [b]Normal value <3 mg/l (all values below the threshold were converted to 1 mg/l). [c]Definition according to Wallace's criteria. VAS: visual analogue scale; JADAS-10: juvenile arthritis DAS-10; CRM: clinical remission on medication; CR: clinical remission off medication.

Table 3 Results of physical ability and damage at the final follow-up visit, 17 years post-diagnosis

scores	Total cohort (n = 102)	Systemic arthritis (n = 13)	Oligoarthritis persistent (n = 8)	Oligoarthritis extended (n = 22)	Polyarticular RF negative (n = 19)	Polyarticular RF positive (n = 11)	PsA (n = 9)	Enthesitis-related (n = 18)	Undifferentiated (n = 2)
JADI-A, scale 0–72, median (range)	6 (0–67)	11 (0–63)	0.5 (0–1)	6 (0–41)	15 (2–67)	22 (0–59)	11 (0–48)	4 (0–26)	4 (3–5)
JADI-E, scale 0–17, median (range)	1 (0–5)	1 (0–5)	0 (0–5)	1 (0–5)	1 (0–5)	1 (0–2)	1 (0–3)	1 (0–2)	0 (0)
TmSvdHS, scale 0–448, median (range)	112.5 (0–448)	166 (0–448)	0 (0–18)	150 (0–364)	218 (18–448)	326 (50–448)	112 (0–386)	59 (0–271)	98.5 (96–101)
mSvdHS-E, scale 0–280, median (range)	56.5 (0–280)	98 (0–280)	0 (0–10)	76 (0–228)	132 (4–280)	204 (30–280)	42 (0–240)	28 (0–158)	60 (50–70)
mSvdHS-JSN, scale 0–168, median (range)	59 (0–168)	62 (0–168)	0 (0–12)	72 (0–136)	86 (12–168)	120 (20–168)	70 (0–146)	25 (0–106)	38.5 (31–46)
mSvdHS–hands, scale 0–280, median (range)	74.5 (0–280)	104 (0–280)	0 (0–18)	94.5 (0–250)	154 (0–280)	207 (50–280)	72 (0–250)	12 (0–148)	44.5 (31–58)
mSvdHS–feet, scale 0–168, median (range)	40 (0–168)	40 (0–168)	0	36 (0–168)	58 (0–168)	89 (0–168)	40 (0–136)	29 (0–132)	54 (38–70)
Leg-length inequality $\geqslant$0.5 cm, n (%)	30 (29.4)	3 (23.1)	2 (25)	11 (50)	5 (26.3)	2 (18.2)	3 (33.3)	4 (22.2)	0 (0)
Mandibular dysfunction, n (%)	37 (36.3)	3 (23.1)	0 (0)	9 (40.9)	13 (68.4)	5 (45.5)	3 (33.3)	3 (16.7)	1 (50)
HAQ-DI, scale 0–3, median (range)	0 (0–2.75)	0.375 (0–2.75)	0 (0–0.13)	0 (0–1.63)	0.25 (0–2.5)	0.5 (0–1.25)	0 (0–2)	0 (0–2.5)	0 (0)

HAQ-DI: HAQ Disability Index; JADI-A: juvenile arthritis damage index – articular; JADI-E: juvenile arthritis damage index – extra-articular; mSvdHS-E: modified Sharp–van der Heijde score – erosions; mSvdHS – feet: modified Sharp/van der Heijde score – feet; mSvdHS – hands: modified Sharp–van der Heijde score – hands; mSvdHS-JSN: modified Sharp–van der Heijde score – joint space narrowing; TmSvdHS: total modified Sharp–van der Heijde score.

were observed in 29.4% of the patients. A leg-length discrepancy $\geqslant 0.5$ cm was evident in 37/102 patients (36.3%) (Table 3).

Physical disability

Fifty-four (52.9%) of the patients had no disability, while abnormal HAQ-DI (scores > 0) were found in 48 (47.1%) patients with JIA. The median HAQ-DI score was 0, while severe disability (>1.5) was found in only 4.9% of the cohort (Table 3).

Visual outcome in patients with uveitis

Established blindness in one of the eyes developed in 2/11 patients (18.2%) while the rest had a good visual acuity in both eyes.

Medication

The history of the regimens ever received with respect to drug type is shown in Table 4. Biologic therapy was administered to 52 of 102 patients (51%). Within this cohort of patients who received biologic therapy, 13 were diagnosed after 2000, while 39 were diagnosed before 2000. These two groups of patients did not differ in terms of their basic demographic characteristics and on the risk factors. The group of patients who had access to biologic treatment promptly after the disease onset (n = 13) was found to have a significantly more favourable outcome concerning the radiographic damage (TmSvdH score), JADI-A, JADI-E and functional ability (HAQ-DI) ($P = 0.001$, $P < 0.00$, $P = 0.002$ and $P = 0.002$, respectively) compared with the group of patients who received biologic treatment, but their disease onset was recorded before 2000 (n = 39).

Independent predictors of outcome

In regard to radiographic damage, female sex, polyarticular type of disease onset and longer duration of active disease within the first 5 years were all independent risk factors for a worse final TmSvdH score ($P < 0.05$ for all) (Table 5).

In regard to persistent disease, in the multivariate analysis, predictive factors for higher duration spent in active disease and lower percentage time spent in CR over the entire disease course were found to be the polyarticular subtype of onset ($P = 0.004$ and $P = 0.006$, respectively) and the longer duration of disease activity within the first 5 years of onset ($P = 0.002$ and $P = 0.001$, respectively). Residence in suburban or rural areas was found to be a risk factor for higher proportion of disease course spent with active disease ($P = 0.009$) (Table 5).

In regard to physical disability, active disease at the last follow-up visit was the only independent predictor of disability (HAQ-DI score at the last follow-up) (Table 5).

Inter-correlations of the disease outcome measures

TmSvdH score was highly and significantly correlated with JADI-A ($r = 0.894$, $P < 0.001$). Additionally, TmSvdH score was also positively and significantly correlated with the proportion of disease course spent with active disease ($r = 0.435$, $P < 0.001$), the presence of mandibular dysfunction ($P < 0.001$), hip involvement ($P < 0.001$) and greater number of joint surgeries ($P < 0.001$), and it inversely correlated with the proportion of disease course spent in CR ($r = -0.313$, $P = 0.002$). HAQ-DI score was positively correlated with TmSvdH score ($r = 0.451$, $P < 0.001$), JADI-A ($r = 0.536$, $P < 0.001$) and the proportion of disease course spent with active disease ($r = 0.410$, $P < 0.001$), and negatively correlated with the proportion of disease course spent in CR ($r = -0.239$, $P = 0.018$).

Data from the cohort that participated by telephone interview

From the 285 eligible patients, 205 responded to the call and were further assessed by questionnaires after a mean of 17.5 years' disease duration. Their mean age was 25.9 years and 109/205 (53.2%) were females. The JIA subtype was mainly persistent oligoarthritis (103/205, 50.2%), followed by enthesitis-related arthritis (32/205, 15.6%) and systemic arthritis (29/205, 14.1%). Overall, 122/205 patients (59.5%, 72 females) were found to be in a CR state, mainly those with persistent oligoarthritis (88/103, 85.4%). Abnormal HAQ-DI score > 0 was recorded in 45/205 patients (22%). Of the total population of adult patients with JIA (n = 307) [both cohorts, those who never stopped their follow-up in our hospital (n = 102) and those who participated by telephone (n = 205)], 146/307 patients (47.6%) were found to be in a CR state 17 years post-diagnosis. Physical disability (HAQ-DI score > 0) was recorded in 93/307 patients (30.3%).

Discussion

This is one of the few studies so far involving a sizeable sample of JIA patients who had a long follow-up assessment (mean 17.2 years); based on Wallace's criteria, the study longitudinally and uninterruptedly captured the disease profile. One of the most significant findings was the documentation of long-term inflammatory activity as patients spent more than half of the follow-up period (52.7%) in a state of active disease, while only a short, but considerable, time (mean 17.8%) was spent in a state of CR. Polyarthritis RF^+ was indeed the subtype with the worse disease course and persistent oligoarthritis the subtype with the best one.

These observations align with those from an American publication (Wallace *et al.* [18]). However, in the previous study, fewer patients achieved a 5-year CR (3.4%) than in this one (19.4%), a difference that may be attributed to the longer follow-up period of the Greek patients. The results of our study suggest that in the modern treatment era the long-term outcomes of JIA patients have significantly improved and such conclusions are probably associated with the initiation of biologic drugs and better management strategies. For example in our study the relatively high percentage of patients achieving 5 years' CR may be associated with the fact that almost half of them received biologic DMARDs during the course of the disease. At the final evaluation, 23.5% of this cohort of

Table 4 Drug treatment received by patients in the Greek JIA cohort

Treatment	During the study period (n = 102)	At the final study visit (n = 102)
No medications	0	35 (34.3)
NSAIDs	102 (100)	19 (18.6)
Systemic corticosteroids	70 (68.6)	18 (17.6)
DMARDS	87 (85.3)	43 (42.2)
MTX	71 (69.6)	28 (27.5)
Ciclosporin	43 (42.2)	5 (4.9)
SSZ	29 (28.4)	3 (2.9)
HCQ	24 (23.5)	6 (5.9)
LEF	13 (12.7)	5 (4.9)
D-Pen	10 (9.8)	0
Gold	8 (7.8)	0
AZA	4 (3.9)	1 (0.9)
Biologic agents	52 (51)	42 (41.2)
Inh-TNFα agents	52 (51)	38 (37.3)
Etanercept	31 (30.4)	19 (18.6)
Adalimumab	27 (26.5)	15 (14.7)
Infliximab	21 (20.6)	3 (2.9)
Golimumab	1 (0.9)	1 (0.9)
Non-inh-TNFα agents	6 (5.9)	4 (3.9)
Anakinra	2 (1.9)	0
Rituximab	4 (3.9)	2 (1.9)
Tocilizumab	2 (1.9)	2 (1.9)

Values are n (%) of the patients.

patients with continuous follow-up since the disease onset were found in CR, similar to publications from other geographical areas [19–24]. Of the total group of 307 adult JIA patients, including adults who had been lost to follow-up, a higher percentage of the patients, 47.6%, were found to be in CR at the final evaluation. Apparently, this better outcome is more representative for the whole JIA spectrum.

Polyarticular subtype, female gender and length of active disease during the first 5 years were all independent predictors of structural damage at the end of the follow-up. Moreover, it appears that the TmSvdH score is indicative of more generalized structural damage as demonstrated by the associations established between the TmSvdH score and JADI-A and also between TmSvdH score and the presence of mandibular dysfunction, hip involvement and the number of joint surgeries, which are all parameters indicative of structural damage in joints other than those of hands and feet. A significant positive correlation between the TmSvdH score and disability (HAQ-DI) was found in our study. In the multivariate analysis, we found a trend (P = 0.08) towards reduced physical ability in the patients with greater JSN score.

Importantly, the main parameter affecting physical disability (HAQ-DI) was the current presence of active disease and not the structural damage. This is probably explained by the patients' adaptation to the restriction of motion between periods of disease activity. Our findings are in line with those of Oen *et al*. [25] and Minden *et al*. [23]. There are few studies in the literature correlating the degree of radiographic damage and physical disability in patients with JIA [26, 27]. In the present study more than half of the patients (52.9%), after 17 years' disease duration, had no disability in their daily activities. Severe disability was recorded in only a small percentage of this group of patients with continuous follow-up (4.9%). In the extended cohort of patients, the percentage of those without any disability rose to ~70% (69.7%), observations which concur with those of previous studies [19, 20, 23, 24, 28, 29].

In our study, the duration of disease activity during the first 5 years after disease onset was identified as an important prognostic factor that can affect both future inflammatory status and long-term outcome regarding structural damage. Currently, only two studies have investigated long-term outcome with patients' characteristics at the first 5 years after disease onset [21, 30]. We consider our data of higher quality since we applied disease activity duration as a continuous variable and we applied currently used classification and clinical remission criteria.

In the present study more than half of the patients (51%) have received biologic therapy as data arising from international studies emphasized their effectiveness and safety. However, besides the frequent biologic use, a high percentage of the total cohort developed radiographic abnormalities. It is important to underline that the outcome of those who received biologic agents promptly after the disease onset was significantly more favourable. A potential explanation of the rather low median of the TmSvdH score noticed in our study is the broad range of radiographic abnormalities including even mild JSN.

Our findings should be considered against the background of limitations. First, despite the prospective and continuous data collection of JIA outcome measures between paediatric and adult services, this remains a retrospective study. Secondly, there is a selection bias since the study sample originally consisted of adult patients who were still followed by a tertiary centre, where individuals with more severe disease are commonly over-presented. We allowed a 4-year period (2008–11) for patient recruitment in order to include a more representative population of JIA subjects since some of them, being in CR, come once a year for their annual evaluation. In order to enhance the generalizability of our study, we included a second group of patients that had been lost to follow-up; this subgroup was more likely to include most of the milder forms of the disease. We acknowledge that patient-reported outcome may not reliably reflect 'real' disease activity at the time of the telephone-based interview as individuals are normally not able to evaluate parameters of JIA in the same way as health professionals do. In the light of these limitations CR status in this group should be interpreted with caution. On the other hand studies on rheumatoid arthritis have shown moderate-to-high correlation between patient- and rheumatologist-performed joint count assessment [30] and reports assessing JIA outcomes have also included telephone-based cohorts [19, 31]. Taken altogether we believe that the

Table 5 Predictors of long term outcome

Variables	TmSvdH score		Proportion of disease course spent in active disease[a] (%)		Proportion of disease course spent in CR[b] (%)		HAQ-DI	
	B (95% CI)	P-value*	B (95% CI)	P-value*	B (95% CI)	P-value*	B (95% CI)	P-value*
Intercept	−81.383 (−224.916, 62.150)	0.266	0.262 (0.079, 0.445)	0.05	59.445 (38.240, 80.650)	<0.001	−1.911 (−3.478, −0.344)	0.017
Female sex	93.718 (17.039, 170.397)	0.017	—	—	−11.442 (−27.597, −4.713)	NS	—	—
Onset age, years	−4.973 (−12.643, 2.697)	NS	—	—	—	—	—	—
Onset type	Reference		Reference		Reference		Reference	
Oligoarticular								
Polyarticular	126.917 (56.114, 197.721)	<0.001	0.161 (0.052, 0.270)	0.004	−20.495 (−34.982, −6.008)	0.006	0.027 (−1.243, 1.927)	NS
Systemic	79.815 (−2.372, 162.001)	0.057	0.042 (−0.106, 0.190)	NS	−2.738 (−21.568, 16.092)	NS	0.701 (−0.989, 2.391)	NS
Positive IgM RF	49.423 (−45.200, 144.046)	NS	0.109 (−0.056, 0.275)	NS	−0.510 (−20.019, −18.999)	NS	—	—
Positive anti-CCP	—	—	—	—	—	—	—	—
ANA	—	—	—	—	—	—	—	—
Active disease duration within 5 years of onset, months	3.488 (1.300, 5.676)	0.002	0.006 (0.002, 0.010)	0.002	−0.653 (−1.046, −0.261)	0.001	−0.002 (−0.041, 0.037)	NS
No achievement of clinical remission (CRM or CR) within 2 years of onset	42.833 (−30.344, 116.111)	NS	−0.090 (−0.216, 0.035)	NS	—	—	—	—
Active disease duration, months	—	—	—	—	—	—	0.004 (−0.005, 0.013)	NS
Current presence of active disease[c]	—	—	—	—	—	—	1.461 (0.358, 2.563)	0.009
mSvdH-JSN	—	—	—	—	—	—	0.011 (−0.002, 0.024)	NS
Residence								
Urban	—	—	Reference		—	—	Reference	
Suburban/rural	—	—	—	—	—	—	—	—

Multivariate analysis. [a]Proportion of active disease duration/disease duration is the percentage of the whole disease course spent in a state of active disease. Active disease duration was the sum of periods of active disease. [b]Proportion of CR duration/disease duration is the percentage of the whole disease course spent in state of CR. CR duration was the sum of periods of CR (12 months of inactive disease off all anti-rheumatic medications defines clinical remission off medication according to Wallace's criteria). [c]According to Wallace's criteria. *Significant at $P < 0.05$. CR: clinical remission off medication; CRM: clinical remission on medication; HAQ-DI: HAQ Disability Index; mSvdHS-JSN: modified Sharp–van der Heijde score – joint space narrowing; TmSvdHS: total modified Sharp–van der Heijde score; NS: non-significant.

additional information provided by telephone-based interview outweighs the metrological weaknesses of such a type of assessment highlighting the increasing need for long-term data in JIA population. Last but not least, Wallace's criteria have not been evaluated for psoriatic, enthesitis-related and undifferentiated JIA. Nevertheless, several studies have applied them to their total patient groups [32–36].

The strengths of our study are that it is the first to characterize phenotypically Greek JIA patients at disease onset and disease course during a prolonged follow-up period and finally evaluate the predictors of long-term outcome This is one of the largest studies in a well-clinically and -serologically characterized JIA population according to the current ILAR classification criteria with the implementation of modern tools of disease activity and disease course assessment and adequate evaluation of functional ability and joint damage.

In conclusion, our study suggests that almost half of the adult JIA patients were found in CR at the last follow-up. In approximately two-thirds of the total group there was recorded no disability in daily activities with only a small number of patients having developed severe disability. The reported outcomes concerning the structural damage and the disease course refer to a severely affected group of patients with a need for specialty care into adulthood. Although, almost one-fifth of these patients spent a considerable percentage of their disease course in CR, JIA cannot be regarded as a benign disease because a significant proportion of patients develop structural damage and enter adulthood with persistent active disease Altogether, the available data indicate that JIA as a whole is a heterogeneous disease with significant variability in long-term outcome ranging from very mild to very severe. The early identification of the prognostic risk factors implicated in disease severity is crucial, since prompt therapeutic interventions may provide a better outcome.

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