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Outcome and Trends in Treatment of Systemic Juvenile Idiopathic Arthritis in the German National Pediatric Rheumatologic Database, 2000–2013

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Objective. **To investigate the clinical presentation and medical treatment of patients with systemic juvenile idiopathic arthritis (JIA) during the first year of illness. Our study focused on 3-year outcomes in a subsample of patients who were followed up longitudinally.**

Methods. **From 2000 to 2013, 597 patients with systemic JIA and a disease duration of ≤12 months were recorded in the National Pediatric Rheumatologic Database. Among those patients, 3-year outcome data were available for 133. These data included the clinical Juvenile Arthritis Disease Activity Score in 10 joints (JADAS-10) and the physician's global assessment score (on a numerical rating scale), as well as assessment of joint involvement, growth retardation, and patient-reported outcomes.**

Results. **The median clinical JADAS-10 declined significantly, from 7 in 2000 to 2 in 2013, while the proportion of patients with inactive disease increased from 19% in 2000 to 41% in 2013. The rate of treatment with systemic glucocorticoids and disease-modifying antirheumatic drugs (DMARDs) remained stable from 2000 to 2013. By 2013, the proportion of patients with systemic JIA who were treated with biologic DMARDs had increased to 20%. At 3-year follow-up, 72% of patients with systemic JIA had inactive disease, and 77% had no functional limitations. Growth retardation was associated with persistently high disease activity and continuing treatment with systemic glucocorticoids. At the 3-year follow-up, one-third of patients were still being treated with systemic glucocorticoids.**

Conclusion. **The proportion of patients with inactive disease has increased over the past decade. Possible explanations may include improved access to specialized care, additional treatment options, and earlier or faster step-up treatment. However, challenges in the management of systemic JIA remain, as ~30% of patients continue to present with ongoing active disease.**

Juvenile idiopathic arthritis (JIA) is the common term for all forms of arthritis that begin before age 16 years, persist for more than 6 weeks, and for which the etiology is unknown. Systemic juvenile idiopathic arthritis (JIA) is 1 of 7 categories of JIA that account for 5–15% of all JIA cases (1–4). The peak age at onset of systemic JIA is between 18 months and 24 months (4). Systemic JIA has a distinct clinical phenotype characterized by daily spiking fevers and is accompanied by a variety of other systemic signs, including evanescent erythematous skin rash, generalized lymphadenopathy, pericarditis, pleuritis, and hepatosplenomegaly (2). Despite its relative rareness,

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systemic JIA is the main contributor to JIA-related mortality and overall morbidity. Serious, life-threatening complications such as macrophage activation syndrome occur more frequently in systemic JIA compared with other JIA categories (5,6). The mortality rate is estimated to be 0.6–4% (7–9) and remains higher than that in other JIA subcategories. Outcome studies have shown that patients with systemic JIA more frequently have osteoporosis, growth failure, cardiovascular disease, joint destruction, and hip endoprosthesis in early adulthood compared with patients with other categories of JIA (10–13).

Newly developed biologic agents that inhibit the cytokines interleukin-1 (IL-1) and IL-6 have demonstrated remarkable effectiveness in the short-term clinical treatment of systemic JIA (14–16). In response to the success shown for these biologic agents, in 2013 the American College of Rheumatology (ACR) updated the treatment recommendations (17) and now recommends the use of IL-1 and IL-6 inhibitors as the first high-dose glucocorticoid-sparing disease-modifying antirheumatic drug (DMARD) therapy in patients with systemic JIA who have active systemic manifestations. Several studies, as well as clinical experience, suggest that methotrexate (MTX) is less effective in systemic JIA than in polyarticular JIA. As reported in the small number of available open studies, the ACR pediatric criteria for 30% improvement (18) response rates are barely above 30% in patients with systemic JIA (19–21). In addition, the randomized controlled trial by Woo and colleagues (22) showed significant improvement in only 2 variables (physician's and patient's global assessment), while the systemic feature score did not substantially differ between the MTX and placebo groups. Treatment with tumor necrosis factor (TNF) receptor antagonists also was not sufficiently effective during the course of systemic inflammatory disease (4,23).

The objective of our study was to compare the clinical presentation and medical treatment of patients with systemic JIA within the first year of disease onset during the period 2000–2013. Cross-sectional data from the National Pediatric Rheumatologic Database (NPRD) (24) in Germany were used. In addition, 3-year outcomes were investigated in a subsample of patients from the total cohort who were followed up longitudinally (longitudinal sample). Finally, possible predictors for attaining a state of inactive disease while not receiving treatment were examined. The physicians who enrolled patients in the NPRD are shown in Appendix A.

PATIENTS AND METHODS

Patients. The NPRD of children and adolescents with rheumatic diseases began in 1997. Today it covers a wide spectrum of juvenile rheumatic diseases and assesses the health care of patients treated by pediatric rheumatologists. Once per year, data on the phenotypes and outcomes of juvenile rheumatic diseases are prospectively collected via standardized physician and patient questionnaires. The number of participating rheumatology centers increased from 27 in 2000 to 60 in 2013. All participating centers consecutively enroll incident and prevalent cases of juvenile rheumatic diseases in the NPRD. The NPRD provides representative data regarding sociodemographic and clinical characteristics, as well as treatment assignments, of children and adolescents with rheumatic diseases who receive routine care in Germany (24). The NPRD has no active study-monitoring to allow longitudinal follow-up of the patients. Approximately 60% of the patients were re-documented the year following enrollment, resulting in a smaller sample size in the longitudinal analyses. The study was approved by the ethics committee of the Charité Medical University of Berlin.

Criteria for inclusion in the cross-sectional study were as follows: 1) a diagnosis of systemic JIA according to the International League of Associations for Rheumatology (ILAR) criteria (2,25), 2) disease duration of $<$12 months, and 3) enrollment in the database between 2000 and 2013. Criteria for inclusion in the longitudinal sample were: 1) a diagnosis of systemic JIA according to the ILAR criteria (2,25), 2) disease duration of $\leq$12 months, 3) enrollment in the database between 2000 and 2010, and 4) availability of a 3-year follow-up assessment.

Measures of function and disease activity. The physician recorded the patient's age, sex, diagnosis, age at disease onset, and body height at each study visit. Systemic symptoms, including spiking fever, evanescent erythematous skin rash, generalized lymphadenopathy, hepatosplenomegaly, or serositis at the time of inclusion in the study were recorded by the physician during the years 2012 and 2013. Unfortunately, this information was not available for previous years. The physician evaluated the patient's disease activity (physician's assessment) on a numerical rating scale (NRS; 0 = no disease activity and 10 = very severe disease activity) and the number of joints with active arthritis. Physician-rated inactive disease (ID_{NRS}) was defined as a patient's disease activity being equivalent to 0 on an NRS. The patient-reported outcomes included an evaluation of pain and overall well-being (patient's global assessment) on an NRS.

Patients ages $\geq$12 years or their parents reported functional ability via the German version of the Childhood Health Assessment Questionnaire (C-HAQ) (26). The resulting disability index ranges from 0 to 3. A value of 0 indicates no functional disability, while higher scores indicate relative degrees of disability. The clinical Juvenile Arthritis Disease Activity Score in 10 joints (JADAS-10) (27) was used as a composite tool for scoring disease activity. The clinical JADAS-10 considers the number of joints with active disease together with the physician's and the patient's/parent's global assessment, without considering the erythrocyte sedimentation rate. Inactive disease based on the clinical JADAS-10 (ID_{cJADAS}) was defined as a clinical JADAS-10 of $\leq$1. It should be noted that Consolaro at al (27) have defined cutoffs for nonsystemic JIA. In the presence of systemic features, one may assume that the physician's and the patient's/parent's global assessment will be $>$0. Consequently, patients with inactive systemic JIA can be identified by a clinical JADAS-10 of $\leq$1. A history of macrophage activation syndrome was reported by the treating physician.

Treatment. The physician recorded current treatment as well as all use of nonsteroidal antiinflammatory drugs (NSAIDs),

Table 1. Characteristics, clinical presentation, and therapy at the first documentation in the 597 patients with systemic JIA with a disease duration of ≤12 months, according to enrollment years*

	2000–2002	2003–2005	2006–2008	2009–2010	2011–2013
No. of patients	94	129	118	94	162
Age, years	7.9 ± 4.3	7.4 ± 4.6	8.1 ± 5.1	9.2 ± 4.8	8.3 ± 5.0
Female, no. (%)	43 (45.7)	68 (52.7)	60 (50.9)	45 (47.9)	85 (52.5)
Disease duration, months	5.6 ± 3.7	5.2 ± 3.4	5.3 ± 3.2	5.7 ± 3.7	5.6 ± 3.6
Time between symptom onset and first visit to pediatric rheumatologist, months	0.9 ± 1.5	0.8 ± 1.8	1.0 ± 2.3	1.3 ± 2.4	1.1 ± 2.1
Age at disease onset, years	7.4 ± 4.2	7.0 ± 4.6	7.7 ± 5.1	8.7 ± 4.8	7.7 ± 4.9
Physician-assessed disease activity†	2.9 ± 2.7	2.4 ± 2.5	1.8 ± 2.4	2.2 ± 2.6	1.6 ± 2.4
ID_{NRS}, no. (%)	17 (20.2)	40 (31.8)	50 (45.9)	33 (36.7)	71 (47.3)
Clinical JADAS-10, median (IQR)	7.0 (0.0–25.0)	3.5 (0.0–28.0)	2.0 (0.0–26.0)	3.0 (0.0–24.0)	1.5 (0.0–24.0)
ID_{cJADAS}, no. (%)	17 (25.4)	33 (31.1)	31 (36.9)	25 (36.8)	60 (48.8)
No. of joints with active disease	2.8 ± 5.3	2.0 ± 4.2	1.1 ± 2.6	1.6 ± 4.1	1.0 ± 2.8
C-HAQ score	0.33 ± 0.55	0.35 ± 0.58	0.30 ± 0.55	0.37 ± 0.64	0.23 ± 0.50
C-HAQ score of 0, no. (%)	35 (48.0)	67 (58.8)	57 (62.6)	41 (54.7)	84 (62.7)
Patient-reported pain†	2.0 ± 2.4	1.2 ± 1.9	1.3 ± 2.1	1.7 ± 2.4	1.4 ± 2.4
Patient-reported well-being†	2.0 ± 2.0	1.7 ± 2.1	1.7 ± 2.2	2.1 ± 2.5	1.4 ± 2.1
Height SDS	ND	−0.68 ± 1.25	−0.87 ± 1.26	−0.71 ± 1.07	−0.68 ± 1.26
Height SDS below the norm, no. (%)	ND	17 (14.5)	21 (19.4)	10 (11.5)	26 (18.1)
Therapy before inclusion in NPRD, no. (%)					
NSAIDs	59 (71.1)	72 (60.5)	64 (66.7)	38 (55.1)	55 (44.0)
Systemic glucocorticoids	65 (78.3)	81 (68.1)	70 (72.2)	45 (65.2)	75 (59.5)
Low-dose systemic glucocorticoids (<0.2 mg/kg/day)	20 (23.8)	23 (18.9)	26 (23.6)	13 (19.1)	20 (23.0)
High-dose systemic glucocorticoids (≥0.2 mg/kg/day)	47 (56.0)	60 (49.2)	65 (58.0)	36 (52.9)	35 (39.8)
Any conventional synthetic DMARD and/or biologic DMARD	50 (59.5)	64 (55.2)	66 (58.4)	44 (50.6)	86 (55.1)
Conventional synthetic DMARD	50 (59.5)	64 (55.2)	65 (57.5)	40 (46.0)	68 (43.6)
Methotrexate	45 (53.6)	56 (48.3)	61 (54.0)	40 (46.0)	68 (43.6)
Other conventional synthetic DMARD	13 (15.5)	11 (9.5)	6 (5.3)	2 (2.3)	3 (1.9)
Biologic DMARD	–	4 (3.4)	10 (8.8)	13 (14.9)	33 (21.2)
Etanercept	–	4 (3.4)	5 (4.4)	7 (8.0)	2 (1.3)
Anakinra	–	–	4 (3.5)	6 (6.9)	17 (10.9)
Tocilizumab	–	–	–	–	12 (7.7)
Canakinumab	–	–	–	–	5 (3.2)

* Except where indicated otherwise, values are the number (%), where % refers to the total number of patients with a valid response for the item. JIA = juvenile idiopathic arthritis; ID_{NRS} = inactive disease defined by a patient's disease activity equivalent to 0 on a numerical rating scale (NRS) with a maximum possible score of 10; JADAS-10 = Juvenile Arthritis Disease Activity Score in 10 joints; IQR = interquartile range; ID_{cJADAS} = inactive disease defined by a clinical JADAS-10 of ≤1; C-HAQ = Childhood Health Assessment Questionnaire; SDS = SD score ([height of patient – average height in the reference population]/SD of the reference population); ND = not determined; NPRD = National Pediatric Rheumatologic Database; NSAIDs = nonsteroidal antiinflammatory drugs; DMARD = disease-modifying antirheumatic drug.
† Assessed on an NRS (maximum score 10).

glucocorticoids, conventional synthetic DMARDs, and biologic DMARDs (including dosage and duration) within the prior 12 months. With respect to systemic glucocorticoids, 3 categories were compared: low-dose (<0.2 mg/kg/day), high-dose (≥0.2 mg/kg/day), and intravenous pulse therapy.

Short stature. Short stature is defined as patient's height minus 2 SD scores (SDS) of the age- and sex-matched general population (SDS = [height of patient – average height in the reference population]/SD of the reference population). Data from the German Health Interview and Examination Survey for Children and Adolescents (28) were used for defining the reference body height for each age group and sex.

Statistical analysis. Categorical variables were reported by absolute and relative frequencies, while continuously distributed variables were reported by the mean ± SD or median and interquartile range, as appropriate. Cross-sectional data from the NPRD for the years 2000–2013 were used to determine the distribution of and changes in sociodemographic and clinical characteristics, as well as treatment of patients with systemic JIA within the first year of disease. Two-level linear mixed-effects models were used to investigate the temporal trend in clinical characteristics between 2000 and 2013 (29,30). Statistical inference in the analyses of longitudinal data was based on logistic regression analysis. In the univariate and multivariate analyses of the outcome in patients with inactive disease while not receiving treatment, and the outcome in patients with inactive disease while not receiving glucocorticoids, possible baseline predictor variables were considered for statistical inference.

A sensitivity analysis was conducted to investigate whether the selection of patients introduced bias in the longitudinal sample. The likelihood of being included in the longitudinal sample was estimated by a logistic regression model including the predictor variables sex, age at the onset of systemic JIA, clinical JADAS-10, treatment with conventional synthetic DMARDs,

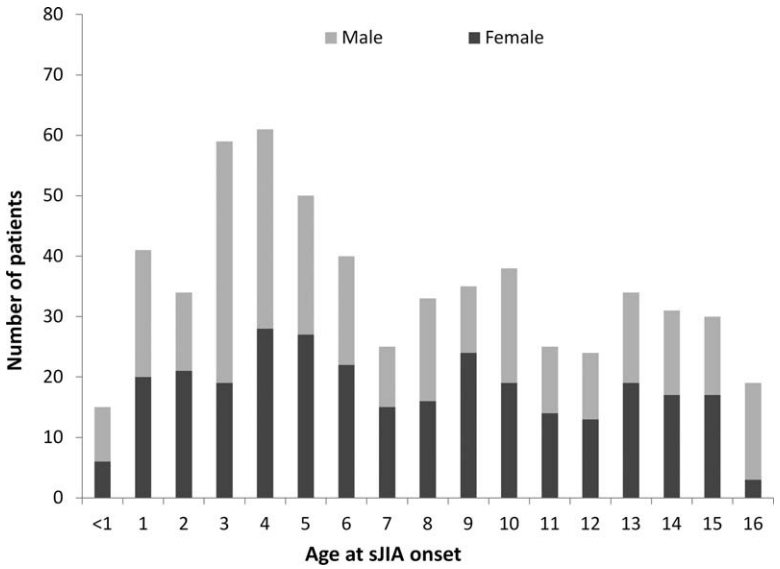

Figure 1. Age at onset of systemic juvenile idiopathic arthritis (sJIA) according to sex.

and treatment with biologic DMARDs. Furthermore, the probability of withdrawal during the 3-year follow-up was estimated with a logistic regression model using the covariates at the considered follow-up from the previous model. Weights were calculated as ratios of the estimated probabilities and were combined for the final weighting, as described by Molenberghs and Kenward (31). Balanced samples of patients were obtained by using inverse probability of weighting, in which weights were estimated as a patient's probability of being included in the study (32). The sensitivity analyses included the weighted analyses of the 3-year outcome data. *P* values less than 0.05 were considered significant. All statistical analyses were conducted using SAS software (version 9.3).

RESULTS

Cross-sectional data on patients with systemic JIA for 2000–2013. Between 2000 and 2013, the number of eligible patients with systemic JIA and a disease duration of ≤1 year ranged from 27 (in 2000) to 51 (in 2013). Cumulatively, this resulted in a total of 597 patients with systemic JIA. The mean ± SD disease duration was 5.5 ± 3.5 months for all patients with systemic JIA. The mean ± SD length of time between symptom onset and first visit to a pediatric rheumatologist was 1 ± 2.0 months. This period of time did not vary significantly between 2000 and 2013. The proportion of systemic JIA patients documented within the first 3 months of disease (35.8% [n = 214]), between months 4 and 6 (27.0% [n = 161), and between months 7 and 12 (37.2% [n = 222]) did not significantly differ ($P = 0.955$) over the course of the 14 years. The mean ± SD age of patients at the onset of systemic JIA was a minimum of 5.9 ± 3.8 years (median 5) in 2002 and a maximum of 9.4 ± 5.5 years (median 8) in 2008 (Table 1 and results not shown). As shown in Figure 1, the most common age range recorded for systemic JIA onset was 3–5 years, with 3 and 4 years being the most common. There was no remarkable difference between boys and girls in this respect.

Clinical activity in patients with systemic JIA within the first year of disease onset and its time trend. In 2012 and 2013 (n = 84 patients providing information about systemic symptoms), the most common systemic symptom at inclusion was fever (n = 59 [70.2%]), followed by skin rash (n = 45 [53.6%]), hepatosplenomegaly (n = 34 [40.5%]), serositis (n = 21 [25.0%]), and generalized lymphadenopathy (n = 14 [16.7%]). The frequency of fever at first documentation was a function of disease duration. Almost all patients with a disease duration of <1 month had fever (88%), while the rate was 8% in patients with systemic JIA with a disease duration of >10 months. The clinical JADAS-10 in the total cohort significantly declined from a mean ± SD of 7.2 ± 5.1 (median 7) in 2000 to 3.7 ± 4.2 (median 2; $\beta = -0.29$ [95% confidence interval (95% CI) −0.42, −0.15], $P < 0.001$) in 2013. The proportion of patients with inactive disease, as defined by the clinical JADAS-10 (ID_{cJADAS}), increased from 19% in 2000 to 41% in 2013 (odds ratio [OR] 1.09 [95% CI 1.04, 1.16], $P = 0.001$).

The clinical JADAS-10 was associated with disease duration at first documentation: patients with systemic JIA with a disease duration of <1 month had a higher clinical JADAS-10 compared with patients in whom documentation occurred between months 7 and 12 after disease onset ($\beta = 2.5$ [95% CI 1.2, 3.8],

$P < 0.001$). The clinical JADAS-10 decreased significantly across the 3 disease-duration strata. During the period 2000–2013, the mean ± SD physician's global assessment of disease activity declined considerably (from 3.0 ± 2.2 in 2000 to 1.6 ± 2.3 in 2013 ($\beta = -0.10$ [95% CI −0.16, −0.05] $P < 0.001$). Meanwhile, the proportion of patients with no functional limitations (C-HAQ = 0) notably increased over time (from 9 [42.9%] in 2000 to 27 [65.9%] in 2013 (OR 1.06 [95% CI 1.02, 1.11], $P = 0.008$). In contrast, however, the proportion of patients with growth retardation (n = 6 [18.8%] in 2000; n = 7 [15.9%] in 2013) and development of macrophage activation syndrome within the first year of systemic JIA disease (n = 1 [2.3%] in 2000; n = 2 [4.6%] in 2013) remained stable over the period (that is, the change was not statistically significant).

Drug treatment. The rates of drug treatment in patients with systemic JIA between 2000 and 2013 are shown in Table 1. NSAIDs were prescribed in 78% of patients (n = 18) in the first year of systemic disease in 2000, whereas the rate of NSAID prescriptions decreased to 42% (n = 16) in 2013. The rate of treatment with systemic glucocorticoids (n = 28 [78%] in 2000 and n = 30 [79%] in 2013) and DMARDs in general (n = 14 [56%] in 2000 and n = 28 [57%] in 2013) remained stable over the period, while treatment with other conventional synthetic DMARDs (e.g., azathioprine or cyclosporin A) decreased, from 15.5% in 2000–2002 to 1.9% in 2011–2013. Since the introduction of biologic DMARDs as a treatment option for systemic JIA in 2002, the rates of DMARD prescriptions have continuously increased (n = 4 [3%] in 2003–2005 and n = 33 [21%] in 2011–2013).

From 2011 to 2013, biologic DMARD therapy was started in 20 patients (28.2%) after a disease duration of >6 months, whereas only a few patients (n = 4 [10%]) were treated with biologic DMARDs within the first 1 month of systemic JIA disease. From 2011 to 2013, 1 of 5 patients was treated with a biologic DMARD within the first year after the diagnosis of systemic JIA. In particular, the IL-1 inhibitors anakinra (n = 17 [10.9%]) and canakinumab (n = 5 [3%]), as well as the IL-6 inhibitor tocilizumab (n = 12 [7.7%]), were the most frequently used biologic DMARDs in 2011–2013. In contrast, the use of etanercept significantly declined in 2011–2013 (n = 2 [1.3%]) compared with 2009–2010 (n = 7 [8%]). Among patients who were treated with a biologic DMARD, almost 60% (n = 31) received treatment in combination with methotrexate.

Three-year outcome in patients with systemic JIA. Among the 435 patients with systemic JIA who were enrolled in the database between 2000 and 2010, 133 (31%) patients with a 3-year follow-up assessment were able to be identified and therefore were included in the longitudinal data analyses. The population of patients with systemic JIA who were not included in the sample that was followed up longitudinally (n = 302) during the corresponding enrollment years, and the subsample of patients who were followed up longitudinally (n = 133), did not significantly differ in sociodemographic characteristics, disease duration at first documentation (mean ± SD 5.0 ± 3.4 versus 5.1 ± 3.2 months; $P = 0.830$), disease activity according to the clinical JADAS-10 (mean ± SD 5.8 ± 6.3 versus 6.3 ± 6.1; $P = 0.547$), or functional ability according to the C-HAQ (mean ± SD 0.36 ± 0.60 versus 0.33 ± 56; $P = 0.600$) (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39796/abstract). However, patients with 3-year follow-up data were slightly less likely to have inactive disease at first documentation (25.7% versus 32.8%; $P = 0.039$).

Treatment at baseline and during follow-up. Treatment was stratified by enrollment years in the sample of patients followed up longitudinally (n = 133). The rates of NSAID treatment (59% at baseline [n = 69] and 31% at 3-year follow-up [n = 35]) and the cumulative use of systemic glucocorticoids during the 12 months before the 3-year follow-up (67% at baseline [n = 79] and 38% at 3-year follow-up [n = 43]) were approximately halved. At 3-year follow-up, patients who continued to be treated with systemic glucocorticoids and high-dose glucocorticoids represented 28% and 8% of the overall cohort, respectively. The proportion of patients with systemic JIA who were treated with biologic DMARDs increased markedly during the 3-year follow-up (10% at baseline [n = 12] and 19% at 3-year follow-up [n = 24]).

Patients with inactive disease (ID_{cJADAS}) at 3-year follow-up less frequently had been treated with systemic glucocorticoids (52.0% versus 27.4%), methotrexate (65.5% versus 43.7%), or biologic DMARDs (34.5% versus 11.3%) in the last 12 months compared with patients with active disease. However, the rate of treatment with biologic DMARDs at baseline depended on the year of enrollment in the NPRD. As shown in Figure 2 (and as described above for the cross-sectional analysis), this reflects changes in the treatment of systemic JIA over the course of the last 10 years. Remarkably, despite the overall treatment response, cumulative steroid use within the prior 12 months, along with contemporaneous use of systemic glucocorticoids—in particular treatment with high-dose glucocorticoids—differed only slightly between enrollment years 2000–2004 and 2005–2010 (Figure 2) at the point of documentation.

Therapy with IL-1 or IL-6 inhibitors was initiated in 14 patients within the first 2-year period and in 4

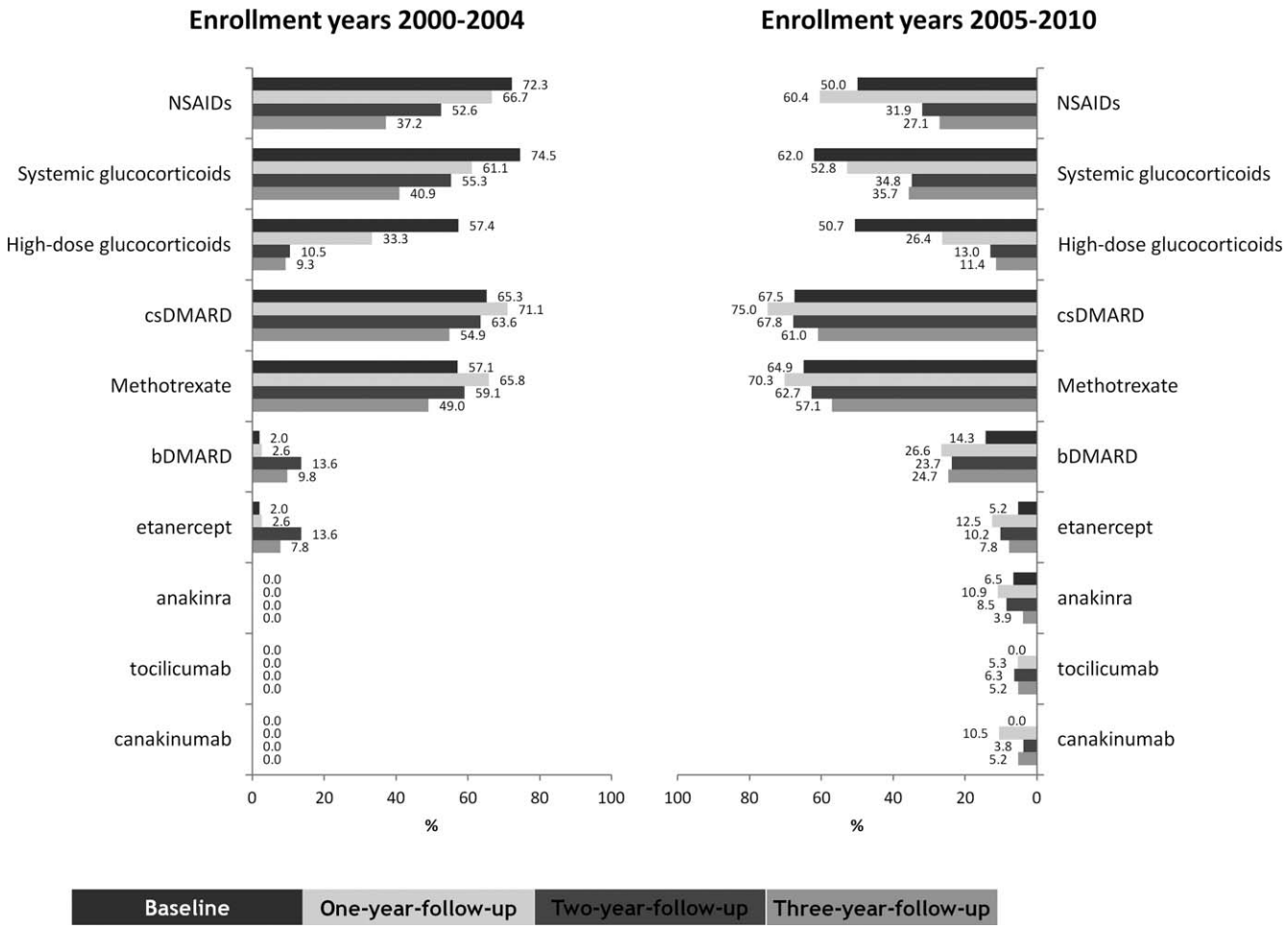

Figure 2. Treatment at baseline and at 1-year, 2-year, and 3-year follow-up in patients with systemic juvenile idiopathic arthritis (n = 133), stratified according to enrollment years. NSAIDs = nonsteroidal antiinflammatory drugs; csDMARD = conventional synthetic disease-modifying antirheumatic drug; bDMARD = biologic DMARD.

patients within the third year. Nearly all patients were treated with systemic glucocorticoids (93%) and high-dose systemic glucocorticoids (79%) before starting treatment with IL-1 or IL-6 inhibitors. In contrast, the rate of glucocorticoid use declined by 50% after starting biologic DMARD therapy (for systemic glucocorticoids, 46%; for high-dose systemic glucocorticoids, 18%) (see Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39796/abstract).

Medium-term (3-year) outcome. According to the clinical JADAS-10, 72% of all patients (n = 133) had inactive disease at the 3-year follow-up. Thirty-five percent were in remission while not receiving medication, and 36% were in remission while receiving medication (Table 2). At study inclusion, 75% of systemic JIA patients had active disease (clinical JADAS-10 of >1). Thirty-four percent of patients (n = 21) still had active disease at the 3-year follow-up (38% treated with systemic glucocorticoids, 51% treated with methotrexate, and 15% treated with biologic DMARDs). In our cohort, the cumulative incidence of macrophage activation syndrome was 4.8% (6 patients with systemic JIA) at the 3-year follow-up. Therapy with systemic glucocorticoids was reported in 2 patients (33.3%), with conventional synthetic DMARDs (MTX) in 3 patients (50%), and with biologic DMARDs (etanercept) in 1 patient (16.7%) after the macrophage activation syndrome event during the 3-year follow-up. Unfortunately however, it was not possible to assess the therapy administered before development of macrophage activation syndrome. Three cases of macrophage activation syndrome (50%) were reported during the baseline year, 1 (16.7%) during the 1-year follow-up, and 2 (33.3%) during the 3-year follow-up.

Growth retardation. The mean ± SD height SDS was −0.78 ± 1.23 at baseline. Fourteen patients (11.0%)

Table 2. Outcomes in the 133 patients with systemic JIA who were followed up longitudinally between 2000 and 2010*

	Baseline	Three-year follow-up
Physician-assessed disease activity, mean ± SD	2.46 ± 2.40	0.65 ± 1.49
ID_{NRS}	34 (26.8)	94 (71.8)
Clinical JADAS-10, median (IQR)	4 (1–9)	0 (0–2)
ID_{cJADAS}	26 (25.7)	73 (71.6)
Receiving medication†		
ID_{NRS}	27 (21.3)	50 (38.2)
ID_{cJADAS}	21 (20.8)	37 (36.3)
Not receiving medication†		
ID_{NRS}	7 (5.5)	44 (33.6)
ID_{cJADAS}	5 (5.0)	36 (35.3)
No. of joints with active disease, mean ± SD	1.97 ± 3.73	0.62 ± 2.44
No joints with active disease	75 (58.6)	112 (86.2)
Pain on NRS, mean ± SD (maximum score 10)	1.35 ± 1.83	0.58 ± 1.40
No pain	52 (49.5)	82 (78.1)
C-HAQ, mean ± SD (0–3 scale)	0.33 ± 0.56	0.17 ± 0.41
C-HAQ score showing no disability	60 (57.7)	81 (77.1)
Height SDS below the norm	14 (14.7)	18 (15.1)

* Except where indicated otherwise, values are the number (%). JIA = juvenile idiopathic arthritis; ID_{NRS} = inactive disease defined by a patient's disease activity equivalent to 0 on a numerical rating scale (NRS) with a maximum possible score of 10; IQR = interquartile range; ID_{cJADAS} = inactive disease defined by a clinical Juvenile Arthritis Disease Activity Score in 10 joints (JADAS-10) of ≤1; C-HAQ = Childhood Health Assessment Questionnaire; SDS = SD score ([height of patient – average height in the reference population]/SD of the reference population).
† Disease-modifying antirheumatic drugs and systemic glucocorticoids.

had a height SDS below the threshold of −2 at baseline. Twelve patients (9.4%) displayed incident growth retardation at the 3-year follow-up (n = 6) or the 2-year follow-up (n = 6), and 1 patient (2.4%) developed growth retardation 3 years after disease onset. In total, 29 patients (22.8%) had a height SDS below the threshold of −2 at any time during the 3-year follow-up interval. Among the 14 patients with short stature at baseline, 5 (35.7%) caught up on growth by the time of the 3-year follow-up, while 9 patients (64.2%) continued to have short stature. The latter group of patients had a significantly higher rate of glucocorticoid treatment (high-dose glucocorticoids, 56% versus 20%; systemic glucocorticoids in total, 88.9% versus 20%) and significantly higher disease activity (clinical JADAS-10, 3.0 versus 0.9) during the 3-year interval, as compared with patients in whom catch-up growth occurred (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39796/abstract).

Patients who developed short stature during follow-up (n = 12) had continuing high disease activity before the onset of growth retardation. Compared with patients with normal growth, however, there was no significant difference in the history of treatment with glucocorticoids (see Supplementary Figure 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39796/abstract). Approximately one-half of the patients with incident growth retardation during follow-up did not experience catch-up growth until the 3-year follow-up. Ongoing short stature in these 6 patients was significantly associated with high rates of glucocorticoid treatment (systemic glucocorticoids, 83.3% versus 40%; high-dose glucocorticoids, 50% versus 0%) and long-lasting high disease activity (clinical JADAS-10, 7.1 versus 1.0) as compared with the 5 patients who experienced catch-up growth (see Supplementary Figure 2) until the 3-year follow-up. Fourteen patients started treatment with IL-1 or IL-6 inhibitors within the first 2 years of systemic JIA disease. Among those, 4 patients had short stature in the year when biologic DMARD therapy was started. Only 1 of the 10 patients without short stature at the initiation of biologic DMARD treatment had short stature at the 3-year follow-up. This patient was treated with high-dose glucocorticoids at each follow-up assessment.

Medium-term predictors of outcome. The outcome variables for inactive disease while not receiving medication (n = 44 [33.6%]) and inactive disease while not receiving glucocorticoid treatment (n = 68 [58.6%]) were investigated at 3-year follow-up. Patients who had an onset of systemic JIA before age 18 months (OR 2.8 [95% CI 1.05, 7.45], $P = 0.04$), who had no joint involvement at baseline (OR 2.1 [95% CI 1.02, 4.49], $P = 0.045$), and in whom systemic symptoms were absent (OR 3.1 [95% CI 1.06, 9.10], $P = 0.039$) were more likely to have inactive disease

Table 3. Univariate baseline predictors of inactive disease in the 133 patients followed up longitudinally who were not receiving medications and those who were not receiving glucocorticoids at 3-year follow-up*

Variable	Inactive disease off medications			Inactive disease off glucocorticoids		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.02	0.93, 1.11	0.700	1.07	1.00, 1.14	0.062
Female sex	0.95	0.46, 1.96	0.898	1.06	0.61, 1.86	0.833
Duration of systemic JIA	1.04	0.93, 1.16	0.527	1.10	1.01, 1.20	0.035
Age at onset of systemic JIA	1.01	0.93, 1.11	0.744	1.06	0.99, 1.14	0.088
Disease onset before age 18 months	2.80	1.05, 7.45	0.040	2.08	0.94, 4.63	0.072
No systemic symptoms at inclusion†	3.10	1.06, 9.10	0.039	1.59	0.57, 4.43	0.379
No. of joints with active disease	0.87	0.77, 0.99	0.028	0.85	0.77, 0.93	<0.001
No joint involvement	2.13	1.02, 4.49	0.045	2.59	1.49, 4.50	0.001
Physician-assessed disease activity‡	0.89	0.77, 1.03	0.118	0.81	0.73, 0.91	<0.001
Clinical JADAS-10	0.92	0.85, 1.00	0.050	0.89	0.84, 0.94	<0.001
Patient-reported pain‡	0.78	0.59, 1.02	0.067	0.75	0.61, 0.92	0.005

* OR = odds ratio; 95% CI = 95% confidence interval; JIA = juvenile idiopathic arthritis; JADAS-10 = Juvenile Arthritis Disease Activity Score in 10 joints.
† Systemic symptoms included spiking fever, evanescent erythematous skin rash, generalized lymphadenopathy, hepatosplenomegaly, and serositis.
‡ Assessed on a numerical rating scale (maximum score 10).

while not receiving medication. No variable showed a significant association in the multivariate analysis. Patients with no joint involvement at the time of study inclusion more often had inactive disease while not receiving glucocorticoids (OR 2.6 [95% CI 1.49, 4.50], $P = 0.001$). Patients with lower disease activity and a lower pain level at baseline had a significantly higher likelihood of having inactive disease while not receiving glucocorticoids (Table 3).

Sensitivity analysis. In the sensitivity analysis, we examined whether the results of the longitudinal analyses are retained when taking into account the potential selection bias for the longitudinally followed sample. The mean weight was 0.96 (median 0.89). For instance, systemic JIA patients with higher disease activity were assigned (in means) to weights lower than that in the longitudinally followed cohort. It might be an indication that these patients were going to have a more-severe disease course compared with that in the total cohort. The weighted 3-year outcome analysis showed a slightly more favorable outcome (see Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39796/abstract) compared with the results shown in Table 2. For example, the proportion of patients with inactive disease at 3-year follow-up was slightly higher (inactive disease clinical JADAS-10, 73.2% versus 71.6%; inactive disease clinical JADAS-10 while not receiving medication, 42.4% versus 35.3%). The weighted analysis of predictors for inactive disease while not receiving medications or glucocorticoids (see Supplementary Table 4, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39796/abstract) showed associations comparable with those shown in Table 3.

DISCUSSION

Systemic JIA is known as a potentially life-threatening disease (1). In our cohort, the overall clinical condition of patients with systemic JIA in the first year after diagnosis significantly changed between the years 2000 and 2013. This was shown by a decrease in disease activity and the number of joints with active disease, as well as by better functional capacity in the NPRD. However, between 2000 and 2010, a remarkable proportion of patients with systemic JIA in our cohort still were being treated with systemic glucocorticoids or high-dose glucocorticoids (38% and 11%, respectively) during the third year of disease. Given the risk of serious side effects with glucocorticoid treatment (23), particularly in children, this is notable.

Achieving inactive disease status is one of the major goals of treatment in JIA. The proportion of patients with inactive disease (clinical JADAS-10 of ≤ 1, physician's global assessment of <1) increased significantly between 2000 and 2013. Almost every second patient achieved a state of inactive disease in the first year of systemic JIA disease between 2011 and 2013. This reflects overall improvements in the treatment of patients with systemic JIA over the last decade. As of 2014, 95 specialized centers and pediatric rheumatologists are available for medical care of patients with juvenile rheumatic diseases. The introduction of treatment guidelines (17,32,33) and their

implementation in routine care, the early involvement of experienced multidisciplinary teams, as well as the trend toward earlier and faster step-up treatment regimens with systemic and intraarticular glucocorticoids, conventional systemic DMARDs, and biologic DMARDs (34,35) can be seen as being associated with more favorable prognoses for patients with systemic JIA. A trend toward earlier and/or faster step-up treatment also can be observed in our study cohort. In 2013, 1 of every 5 patients was treated with a biologic DMARD that inhibits IL-1 or IL-6.

In our longitudinal study, ~72% of the patients with systemic JIA had inactive disease at the 3-year follow-up. A variety of studies have shown (11,13,36–38) a comparable proportion of patients with systemic JIA achieving clinical disease remission. In contrast, almost 30% of systemic JIA patients had active disease at 3-year follow-up. Similar rates (10–50%) of patients with active systemic JIA can be found in the literature (36–39), depending on the cohort and era. Patients with no joint involvement and an absence of systemic symptoms at baseline had a higher likelihood of experiencing inactive disease while not being treated with medications. This was also shown by Russo and Katsicas (40). In contrast to the findings in another study by Russo and Katsicas (41), however, we observed that onset of systemic JIA before age 18 months was associated with a higher likelihood of having inactive disease while not receiving medications at the 3-year follow-up. The number of patients with early-onset systemic JIA in our cohort (n = 18 [13.6%] was similar to that in the later study by Russo and Katsicas (n = 19 [14%]) (41). The possibility that early-onset systemic JIA is a risk factor needs to be studied in larger cohorts in order to limit the random effect of small group and sample sizes.

We did not analyze the treatment effect of systemic glucocorticoids and (nonbiologic/biologic) DMARDs on the likelihood of having inactive disease while not receiving medications and/or glucocorticoids. Our data show that patients with a more-severe disease course (higher disease activity, presence of systemic symptoms) were more likely to be treated with conventional synthetic DMARDs and biologic DMARDs. Unfortunately, the use of statistical methods such as propensity scores does not allow us to address the indication bias caused by the observational study design. Annual data collection prevents the identification of relevant variables for estimating the propensity score to model treatment decisions (e.g., clinical characteristics at treatment start). Head-to-head trials of different treatment strategies in systemic JIA are not available (42). To prove the comparative effectiveness of different treatment strategies in systemic JIA, such studies remain necessary.

Nearly all patients who started treatment with IL-1 or IL-6 inhibitors had previously been treated with high-dose systemic glucocorticoids. Among those, only 1 patient was treated with high-dose systemic glucocorticoids at follow-up. Woerner et al (3,43) hypothesized that the early use of IL-1 and IL-6 inhibitors is beneficial and may rescue patients from the need for long-term treatment with high-dose glucocorticoids. This is significant because of the associated risks of serious side effects, including excessive weight gain, osteoporosis, fractures, arterial hypertension, and growth failure (23).

The most serious complication of systemic JIA is macrophage activation syndrome. Approximately 5% of patients with systemic JIA developed macrophage activation syndrome within the first year of disease. Over the last decade, there has been no trend toward a decline in this rate. A similar rate was observed in our sample that was followed up longitudinally, while other studies have shown even higher rates of macrophage activation syndrome (10–15%) (6,44). This difference may be explained by the difference in study designs. Our study is a population-based registry, whereas other studies (6,44) have been based on systemic JIA disease registries and retrospective chart reviews.

Due to persistent systemic inflammation during the course of systemic JIA as well as long-term glucocorticoid therapy (4), growth failure is a major problem among patients with systemic JIA. The degree of growth retardation correlates with both the severity and the duration of acute symptoms in patients with systemic JIA and to the cumulative glucocorticoid exposure (45), as our data also show. Some children with systemic JIA catch up on growth following effective disease control and a resulting reduction in glucocorticoid doses (46). In our cohort, we identified growth deficits in 29 patients (23%) at the 3-year follow-up. These patients had a prolonged history of both active systemic JIA disease and treatment with high-dose glucocorticoids. Other studies of growth retardation in JIA have shown similar rates of continuing growth deficit (i.e., 10–20%) (46,47). Despite variability in the response pattern, the use of growth hormones showed promising results for the treatment of growth failure in patients with severe systemic JIA or nonsystemic polyarticular JIA (48). Future research should address the question of whether the ACR recommendations (17) for treatment of systemic JIA—in particular the use of IL-1 and IL-6 inhibitors in patients with continuing disease activity—are more effective in terms of reducing growth deficits in patients with systemic JIA. De Benedetti et al (49) recently reported on catch-up growth and normalization of insulin-like growth factor 1 levels in patients treated with tocilizumab.

Composite disease activity scores (such as the clinical JADAS-10) evaluate different dimensions of disease activity in order to produce a single numerical value. Given the heterogeneity in the clinical presentation of JIA patients (27,50), composite scores may be more reliable for summarizing overall disease activity. Indeed, in our study, inactive disease was defined by a clinical JADAS-10 of ≤1. However, the clinical JADAS-10 has weaknesses, because it does not incorporate systemic features such as fever, rash, serositis, organomegaly, or lymphadenopathy. A disease activity score for systemic JIA should include these features. Consolaro et al (27) established the clinical JADAS-10 cutoff values for nonsystemic JIA. However, the physician's and the patient's/parent's global assessment scores may not equal zero in the presence of systemic features. Consequently, the group of patients with inactive systemic JIA disease may be identified correctly by a clinical JADAS-10 of ≤1. In view of the limited evidence for the clinical JADAS-10 cutoff values in systemic JIA, we did not consider moderate or high disease activity.

Thus, our study has several limitations. For instance, due to the nature of observational registry data, we were unable to properly evaluate the role of single drugs (e.g., anti-TNF agents and IL-1 or IL-6 inhibitors) in predicting disease activity and functional outcome at 3-year follow-up. Our study was not designed to assess or compare the effectiveness of therapeutic agents; because of this, our results must be interpreted with caution. Systemic JIA has a heterogeneous disease course regarding severity and outcome.

Within our registry, it is not possible to distinguish between patients with a monocyclic course and those with a polycyclic course, including recurrent episodes of active disease and a persistent course. The NPRD provides representative data on the treatment and disease characteristics of patients with rheumatic diseases (24). Only one-third of the patients with systemic JIA (133 of 435) provided 3-year follow-up data. It is possible that patients in the sample that was followed up longitudinally appeared to be on a course for more-severe disease due to the periodic documentation at their specialized center. Patients with systemic JIA having a monocyclic course, with expected remission within 2–4 years (4), may be less likely to be included in the sample followed up longitudinally compared with patients with a polycyclic disease course. The sensitivity analyses revealed some support for this hypothesis, because the analysis weighted for the potential selection bias resulted in a slightly higher rate of inactive disease at 3-year follow-up. It should be noted, however, that the potential selection bias only mildly affected the results. Physicians report on current treatment and treatment within the last 12 months. In the NPRD, the exact dates of treatment start and discontinuation were not documented in most years. Finally, the duration and dosage of drugs used is not described in the NPRD. Because of this, the cumulative dosage of systemic glucocorticoids cannot be determined. The physician indicated the dosage according to the categories <0.2 mg/kg/day and ≥0.2 mg/kg/day.

In conclusion, our prospective disease registry provides data on outcome and predictors of outcome in a representative subset of patients with systemic JIA in Germany. Disease activity in patients with systemic JIA during the first year of disease has significantly improved over the last decade. From 2010 to 2013, half of patients with systemic JIA attained an inactive disease state within the first year of disease. The disease burden appears to have changed due to improved access to specialized care, implementation of treatment guidelines, more treatment options including biologic DMARDs (and in particular IL-1 and IL-6 inhibitors), as well as the trend toward earlier and/or faster step-up treatment. However, challenges in the management of systemic JIA remain. For instance, ~15% of patients with systemic JIA still experience growth retardation, and this has potentially negative health consequences in adulthood.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Klotsche and Raab had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Nigrovic PA. Is there a window of opportunity for treatment of systemic juvenile idiopathic arthritis? [review]. Arthritis Rheumatol 2014;66:1405–13.
2. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390–2.
3. Woerner A, von Scheven-Gete A, Cimaz R, Hofer M. Complications of systemic juvenile idiopathic arthritis: risk factors and management recommendations. Expert Rev Clin Immunol 2015; 11:575–88.

4. Woo P. Systemic juvenile idiopathic arthritis: diagnosis, management, and outcome. Nat Clin Pract Rheumatol 2006;2:28–34.
5. De Benedetti F. Inflammatory cytokines in the pathogenesis and treatment of systemic juvenile idiopathic arthritis: basic science for the clinician. Pediatr Rheumatol Online J 2005;3:122–36.
6. Sawhney S, Woo P, Murray KJ. Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. Arch Dis Child 2001;85:421–6.
7. Hashkes PJ, Wright BM, Lauer MS, Worley SE, Tang AS, Roettcher PA, et al. Mortality outcomes in pediatric rheumatology in the US. Arthritis Rheum 2010;62:599–608.
8. Ramanan AV, Rosenblum ND, Feldman BM, Laxer RM, Schneider R. Favorable outcome in patients with renal involvement complicating macrophage activation syndrome in systemic onset juvenile rheumatoid arthritis. J Rheumatol 2004;31:2068–70.
9. Schneider R, Laxer RM. Systemic onset juvenile rheumatoid arthritis. Baillieres Clin Rheumatol 1998;12:245–71.
10. Bertilsson L, Andersson-Gare B, Fasth A, Forsblad-d'Elia H. A 5-year prospective population-based study of juvenile chronic arthritis: onset, disease process, and outcome. Scand J Rheumatol 2012;41:379–82.
11. Nordal E, Zak M, Aalto K, Berntson L, Fasth A, Herlin T, et al. Ongoing disease activity and changing categories in a long-term nordic cohort study of juvenile idiopathic arthritis. Arthritis Rheum 2011;63:2809–18.
12. Raab A, Sengler C, Niewerth M, Klotsche J, Horneff G, Zink A, et al. Comorbidity profiles among adult patients with juvenile idiopathic arthritis: results of a biologic register. Clin Exp Rheumatol 2013;31:796–802.
13. Selvaag AM, Aulie HA, Lilleby V, Flatø B. Disease progression into adulthood and predictors of long-term active disease in juvenile idiopathic arthritis. Ann Rheum Dis 2016;75:190–5.
14. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367:2385–95.
15. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis 2011;70:747–54.
16. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367:2396–406.
17. Ringold S, Weiss PF, Beukelman T, DeWitt EM, Ilowite NT, Kimura Y, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Rheum 2013;65:2499–512.
18. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40:1202–9.
19. Albers HM, Wessels JA, van der Straaten RJ, Brinkman DM, Suijlekom-Smit LW, Kamphuis SS, et al. Time to treatment as an important factor for the response to methotrexate in juvenile idiopathic arthritis. Arthritis Rheum 2009;61:46–51.
20. Halle F, Prieur AM. Evaluation of methotrexate in the treatment of juvenile chronic arthritis according to the subtype. Clin Exp Rheumatol 1991;9:297–302.
21. Speckmaier M, Findeisen J, Woo P, Hall A, Sills JA, Price T, et al. Low-dose methotrexate in systemic onset juvenile chronic arthritis. Clin Exp Rheumatol 1989;7:647–50.
22. Woo P, Southwood TR, Prieur AM, Dore CJ, Grainger J, David J, et al. Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. Arthritis Rheum 2000;43:1849–57.
23. Beukelman T. Treatment advances in systemic juvenile idiopathic arthritis. F1000Prime Rep 2014;6:21.
24. Minden K, Niewerth M, Listing J, Zink A, German Study Group of Pediatric Rheumatologists. Health care provision in pediatric rheumatology in Germany: national rheumatologic database. J Rheumatol 2002;29:622–8.
25. Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 1998;25:1991–4.
26. Foeldvari I, Ruperto N, Dressler F, Hafner R, Kuster RM, Michels H, et al. The German version of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ). Clin Exp Rheumatol 2001;19 Suppl 23:S71–5.
27. Consolaro A, Negro G, Chiara Gallo M, Bracciolini G, Ferrari C, Schiappapietra B, et al. Defining criteria for disease activity states in nonsystemic juvenile idiopathic arthritis based on a three-variable juvenile arthritis disease activity score. Arthritis Care Res (Hoboken) 2014;66:1703–9.
28. Kurth BM, Schaffrath Rosario A. The prevalence of overweight and obese children and adolescents living in Germany: results of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2007;50:736–43. In German.
29. Breslow NE, Clayton DG. Approximate inference in generalized linear mixed models. J Am Stat Assoc 1993;88:9–25.
30. Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics 1982;38:963–74.
31. Molenberghs G, Kenward MG. Missing data in clinical studies. Hoboken (NJ): John Wiley & Sons; 2007.
32. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550–60.
33. Bertilsson L, Andersson-Gare B, Fasth A, Petersson IF, Forsblad-D'elia H. Disease course, outcome, and predictors of outcome in a population-based juvenile chronic arthritis cohort followed for 17 years. J Rheumatol 2013;40:715–24.
34. Svantesson H, Akesson A, Eberhardt K, Elborgh R. Prognosis in juvenile rheumatoid arthritis with systemic onset: a follow-up study. Scand J Rheumatol 1983;12:139–44.
35. Wulffraat NM, Brinkman D, Ferster A, Opperman J, ten Cate R, Wedderburn L, et al. Long-term follow-up of autologous stem cell transplantation for refractory juvenile idiopathic arthritis. Bone Marrow Transplant 2003;32 Suppl 1:S61–4.
36. Hafner R, Truckenbrodt H. Course and prognosis of systemic juvenile chronic arthritis: retrospective study of 187 patients. Klin Padiatr 1986;198:401–7. In German.
37. Nigrovic PA, White PH. Care of the adult with juvenile rheumatoid arthritis. Arthritis Rheum 2006;55:208–16.
38. Oen K, Duffy CM, Tse SM, Ramsey S, Ellsworth J, Chedeville G, et al. Early outcomes and improvement of patients with juvenile idiopathic arthritis enrolled in a Canadian multicenter inception cohort. Arthritis Care Res (Hoboken) 2010;62:527–36.
39. Prieur AM, Bremard-Oury C, Griscelli C, Mozziconacci P. Prognosis of the systemic forms of juvenile chronic arthritis: apropos of 100 cases. Arch Fr Pediatr 1984;41:91–7. In French.
40. Russo RA, Katsicas MM. Clinical remission in patients with systemic juvenile idiopathic arthritis treated with anti-tumor necrosis factor agents. J Rheumatol 2009;36:1078–82.
41. Russo RA, Katsicas MM. Patients with very early-onset systemic juvenile idiopathic arthritis exhibit more inflammatory features and a worse outcome. J Rheumatol 2013;40:329–34.
42. Otten MH, Anink J, Spronk S, van Suijlekom-Smit LW. Efficacy of biological agents in juvenile idiopathic arthritis: a systematic review using indirect comparisons. Ann Rheum Dis 2013;72:1806–12.
43. Woerner A, Uettwiller F, Melki I, Mouy R, Wouters C, Bader-Meunier B, et al. Biological treatment in systemic juvenile idiopathic

arthritis: achievement of inactive disease or clinical remission on a first, second or third biological agent. RMD Open 2015;1:e000036.
44. Behrens EM. Macrophage activation syndrome in rheumatic disease: what is the role of the antigen presenting cell? Autoimmun Rev 2008;7:305–8.
45. Simon D, Fernando C, Czernichow P, Prieur AM. Linear growth and final height in patients with systemic juvenile idiopathic arthritis treated with longterm glucocorticoids. J Rheumatol 2002;29:1296–300.
46. Bechtold S, Simon D. Growth abnormalities in children and adolescents with juvenile idiopathic arthritis. Rheumatol Int 2014;34:1483–8.
47. Bechtold S, Roth J. Natural history of growth and body composition in juvenile idiopathic arthritis. Horm Res 2009;72 Suppl 1:13–9.
48. Bechtold S, Ripperger P, Hafner R, Said E, Schwarz HP. Growth hormone improves height in patients with juvenile idiopathic arthritis: 4-year data of a controlled study. J Pediatr 2003;143:512–9.
49. De Benedetti F, Brunner H, Ruperto N, Schneider R, Xavier R, Allen R, et al. Catch-up growth during tocilizumab therapy for systemic juvenile idiopathic arthritis: results from a phase III trial. Arthritis Rheumatol 2015;67:840–8.
50. McErlane F, Beresford MW, Baildam EM, Thomson W, Hyrich KL. Recent developments in disease activity indices and outcome measures for juvenile idiopathic arthritis. Rheumatology (Oxford) 2013;52:1941–51.

APPENDIX A: CONTRIBUTORS TO THE NPRD

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