EXTENDED REPORT

The risk and nature of flares in juvenile idiopathic arthritis: results from the ReACCh-Out cohort

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ABSTRACT

Objective To describe probabilities and characteristics of disease flares in children with juvenile idiopathic arthritis (JIA) and to identify clinical features associated with an increased risk of flare.

Methods We studied children in the Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh-Out) prospective inception cohort. A flare was defined as a recurrence of disease manifestations after attaining inactive disease and was called significant if it required intensification of treatment. Probability of first flare was calculated with Kaplan–Meier methods, and associated features were identified using Cox regression.

Results 1146 children were followed up a median of 24 months after attaining inactive disease. We observed 627 first flares (54.7% of patients) with median active joint count of 1, physician global assessment (PGA) of 12 mm and duration of 27 weeks. Within a year after attaining inactive disease, the probability of flare was 42.5% (95% CI 39% to 46%) for any flare and 26.6% (24% to 30%) for a significant flare. Within a year after stopping treatment, it was 31.7% (28% to 36%) and 25.0% (21% to 29%), respectively. A maximum PGA >30 mm, maximum active joint count >4, rheumatoid factor (RF)-positive polyarthritis, antinuclear antibodies (ANA) and receiving disease-modifying antirheumatic drugs (DMARDs) or biological agents before attaining inactive disease were associated with increased risk of flare. Systemic JIA was associated with the lowest risk of flare.

Conclusions In this real-practice JIA cohort, flares were frequent, usually involved a few swollen joints for an average of 6 months and 60% led to treatment intensification. Children with a severe disease course had an increased risk of flare.

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INTRODUCTION

In current practice, inactive disease is attained in most children with juvenile idiopathic arthritis (JIA) and many discontinue antirheumatic treatments.[1] In these circumstances, recurrences are a major concern for parents and clinicians, particularly when they lead to intensification of treatment.[2] Conversely, prolonged treatment of patients with inactive disease may result in unnecessary exposure to adverse side effects. For these reasons, accurate estimates of the probability of disease flares and identification of clinical features associated with increased risk would be helpful when counselling families and when deciding on discontinuing treatment.

There is no universally accepted definition of flare applicable to all JIA categories.[3] Flare has been defined as recurrence of synovitis requiring treatment,[4 5] loss of criteria for inactive disease[6] or worsening of at least three of the six American College of Rheumatology juvenile arthritis core variables by at least 30% without concomitant improvement of more than one variable by 30% or more.[7 8]

To our knowledge, no descriptions of the probability and characteristics of disease flares in patients with all JIA categories followed prospectively in contemporary practice have been published. Our aims were to: (1) determine the probabilities and characteristics of first flares, defined as the recurrence of any disease manifestation after attainment of inactive disease or after medication discontinuation, in children with JIA enrolled in a prospective inception cohort and (2) identify clinical features associated with a higher risk of flare.

METHODS

We used data from the Research in Arthritis in Canadian Children emphasizing Outcomes study (ReACCh-Out), which recruited consecutive newly diagnosed patients with JIA[3] from all 16 Canadian paediatric rheumatology centres between January

2005 and December 2010.[9] Full study visits occurred at enrolment, 6, 12, 18, 24, 36, 48 and 60 months. Data collected at these visits included juvenile arthritis core variables,[10] extra-articular signs, medications and quality-of-life measures. At interim visits (clinic visits between full study visits), active joint count, enthesitis count, medications and physician global assessment (PGA) of disease activity measured on a 100 mm visual analogue scale (VAS) were recorded. Treatment decisions, including those regarding treatment discontinuation, were at the discretion of the paediatric rheumatologist and the family. Patients receiving multiple medications usually discontinued one medication at a time. The study was approved by research ethics boards at each institution and performed in conformity with the Declaration of Helsinki. Parents provided informed written consent, and patients provided assent where appropriate.

Patients

We included all children with JIA enrolled in the ReACCh-Out cohort who had at least one full study visit documenting inactive disease. The closing date for this analysis was 30 May 2012.

Definitions

Details of assignment of JIA categories[3] and implementation of study definitions are provided as online supplementary material. Children with oligoarthritis were categorised into persistent or extended course[3] as determined by site investigators at the time of first attainment of inactive disease.

We defined inactive disease as an active joint count of 0, absence of systemic manifestations (for systemic arthritis), absence of enthesitis (for enthesitis-related arthritis (ERA) and psoriatic arthritis), absence of uveitis and a PGA <10 mm. This definition was based on Wallace *et al*,[11] with modifications.[1] We defined a flare as a recurrence of any of the above manifestations or a PGA ≥10 mm, and a significant flare as one requiring treatment intensification, analogous to the proposed definition of flare in rheumatoid arthritis.[12]

Treatment intensification was defined as the start of a new antirheumatic medication in addition to, or instead of, previous medications or reinitiation of antirheumatic drugs in children off treatment. Because dosing information was not systematically recorded, dose increases were not included in our definition of treatment intensification. The date of attainment of inactive disease was the date of the first study visit where criteria for inactive disease were fulfilled. The date of treatment discontinuation was the date of the first study visit where the patient had inactive disease, was not on antirheumatic medications and had not received any corticosteroid injection in at least 12 months.

Antirheumatic treatments were categorised as non-steroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids, disease-modifying antirheumatic drugs (DMARDs), biological agents, intra-articular corticosteroid injections and ophthalmic corticosteroids. Provision of corticosteroids by injection or eye-drops was considered evidence of a flare.

The date of flare was the date of the first documentation of recurrence of disease manifestations. For significant flares, treatment intensification could be documented at a subsequent visit. The date of flare resolution was the date of the first visit after flare where the active joint count was zero, enthesitis was absent, PGA was <10 mm and the patient was not on ophthalmic corticosteroids. Since systemic JIA symptoms and uveitis were recorded at study visits, absence of these manifestations was required when resolution occurred at a study visit. When resolution occurred at an interim visit, we assumed a PGA <10 mm excluded systemic symptoms, and absence of ophthalmic steroids excluded active uveitis.

Analysis

Kaplan–Meier methods were used to estimate the cumulative probability of the first occurrence of flare. Survival curves were constructed separately for each JIA category from the dates of attainment of inactive disease and treatment discontinuation using STATA software V.12 (STATA). Data on each subject were analysed until the occurrence of flare or their last available visit by the closing date for this report. χ^2 tests were used to compare flare characteristics and log-rank tests to compare survival curves. A p value of <0.05 on two-tailed tests was considered statistically significant.

Cox proportional hazard models were used to identify clinical features associated with risk of flare. Crude HRs were calculated for each candidate feature, and adjusted HRs were calculated by including features with significant associations ($p<0.05$) simultaneously in one model. Features considered were selected a priori and included JIA categories, features associated with poor outcomes in literature reviews,[13–16] prolonged time to inactive disease, and maximum joint count, maximum PGA and medications used prior to inactive disease. All features were dichotomised (present or absent) so that HRs may be interpreted as relative risks.

RESULTS

Patients

ReACCh-Out recruited 1497 newly diagnosed patients with JIA; 77 patients only had one visit, 5 had insufficient information to assign a JIA category and 269 did not attain inactive disease during the study (figure 1). The remaining 1146 patients (76.5%) were included in the present analysis (see online supplementary table S1). Median time from diagnosis to inactive disease was 10.9 months (25, 75 centiles: 6, 17 months). The median follow-up after attaining inactive disease was 24.0 (12, 39) months. Online supplementary table S2 reports characteristics of excluded patients.

Characteristics of flares

A total of 627 patients (54.7%) had at least one flare after attaining inactive disease; 401 (35%) had one, 151 (13.2%) had two and 75 (6.5%) had more than two flares. Overall, 72.7% of first flares occurred while the patient was receiving antirheumatic treatment. First flares had median active joint counts of 1–2 active joints, PGA of 10–13.5 mm and duration of 21–30 weeks across JIA categories (see online supplementary table S3).

First flares included at least one active joint in 82.1%, varying from 53.3% to 95.8% depending on JIA category ($p<0.001$). A total of 108 flares (17.2%) involved no active joints (a PGA ≥10 mm in 58, isolated uveitis in 21, enthesitis in 24 and systemic symptoms in 5). The majority (60.3%) were significant flares with treatment intensification involving NSAIDs in 41%, intra-articular corticosteroids in 19.8% and DMARDs in 17.7%. Treatment intensification in children with rheumatoid factor (RF)-positive polyarthritis more often involved systemic corticosteroids (16%, $p=0.07$) and biological agents (20%, $p<0.001$), relative to all other JIA categories (see online supplementary table S3).

Probability of flare

Within 1 year of attaining inactive disease, the probability of flare for the whole cohort was 42.5% for any flare and 26.6% for a significant flare (table 1). Probabilities of any flare differed

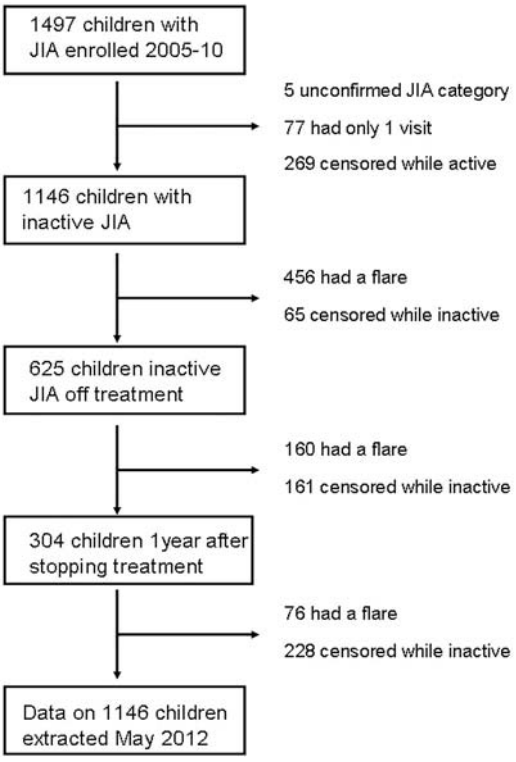

Figure 1 Flow chart of study subjects during the study. Of the 1497 children with juvenile idiopathic arthritis (JIA) enrolled in the Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh-Out) cohort, 1146 children were eligible for the present study. Study subjects were censored at their last available visit by the study closing date (30 May 2012). The total of flares listed in this figure exceeds 627 because some children contributed more than one flare.

across JIA categories (p=0.003 log-rank test, figure 2A). Children with RF-positive polyarthritis had the highest probability of flare and children with systemic JIA, the lowest. Differences were of borderline statistical significance for significant flares (p=0.056, figure 2B).

Within the first year after discontinuing treatment, the probability of any flare for the whole cohort was 31.7% and of a significant flare, 25.0%, but only 6.2% and 3%, respectively, for children with systemic JIA (table 2 and figure 2C, D).

Clinical features associated with the risk of flare

Table 3 shows clinical features significantly associated with risk of any flare after attaining inactive disease. RF-positive polyarthritis had the highest HR (1.92, CI 1.29 to 2.87) while systemic JIA had the lowest (0.67, 0.46 to 0.97), but no feature increased or decreased the hazard by a factor >2. Several features reflecting a severe disease course before attaining inactive disease (eg, maximum PGA >30, maximum active joint count >4, use of biological agents) were associated with an increased risk of flare. Antinuclear antibodies (ANA, above the cut-off for the local laboratory) were associated with an increased HR of 1.21 (1.03 to 1.43). This was 1.21 (1.03 to 1.42) when uveitis-only flares were excluded, and 1.16 (0.98 to 1.36) when all flares with uveitis were excluded. In multivariable analysis, significant associations remained only for a maximum PGA >30 mm (positive correlation) and systemic JIA (negative correlation). Kaplan–Meier curves for PGA >30 mm, active joints >4, use of DMARD, use of biological agents, >52 weeks to inactive disease, involvement of a high-risk joint[16] and ANA are available in online supplementary figure S1. The full results of all Cox regression analyses are reported in online supplementary tables S4–S7.

DISCUSSION

We previously found that most children with JIA in the ReACCh-Out cohort attained inactive disease with contemporary treatments.[1] Here, we investigated the probability and characteristics of flares occurring after attaining inactive disease and features associated with increased risk of flare. We calculated a 42.5% probability of any flare within a year of attaining inactive disease and a 26.6% probability of a significant flare requiring treatment intensification. After treatment discontinuation, the corresponding figures were 31.7% and 25.0%. Children with RF-positive polyarthritis had the highest probability of flare, and children with systemic JIA, the lowest.

Table 1 Cumulative probabilities of flare within 6, 12 and 24 months after attaining a state of inactive disease for different JIA categories

		Probability of flare after attaining inactive disease (95% CI)					
		Within 6 months		Within 12 months		Within 24 months	
	N*	Any flare	Significant flare	Any flare	Significant flare	Any flare	Significant flare
Whole cohort	1146	0.254 (0.229 to 0.282)	0.154 (0.133 to 0.178)	0.425 (0.394 to 0.456)	0.266 (0.240 to 0.295)	0.603 (0.570 to 0.636)	0.400 (0.368 to 0.434)
Systemic arthritis	68	0.268 (0.176 to 0.396)	0.127 (0.065 to 0.238)	0.387 (0.278 to 0.520)	0.179 (0.103 to 0.300)	0.486 (0.366 to 0.621)	0.222 (0.135 to 0.354)
Oligoarthritis persistent	457	0.226 (0.189 to 0.269	0.143 (0.113 to 180)	0.402 (0.356 to 0.451)	0.279 (0.238 to 0.325)	0.594 (0.542 to 0.646)	0.412 (0.362 to 0.466)
Oligoarthritis extended	31	0.337 (0.192 to 0.549)	0.226 (0.108 to 0.435)	0.415 (0.255 to 0.624)	0.269 (0.138 to 0.484)	0.537 (0.343 to 0.757)	0.467 (0.268 to 0.717)
RF-negative polyarthritis	212	0.251 (0.196 to 0.319)	0.163 (0.117 to 0.224)	0.445 (0.376 to 0.521)	0.263 (0.205 to 0.334)	0.618 (0.542 to 0.694)	0.390 (0.318 to 0.471)
RF-positive polyarthritis	35	0.389 (0.242 to 0.583)	0.192 (0.091 to 0.379)	0.598 (0.429 to 0.772)	0.329 (0.192 to 0.526)	0.770 (0.595 to 0.908)	0.515 (0.338 to 0.719)
Psoriatic arthritis	75	0.266 (0.174 to 0.393)	0.171 (0.098 to 0.287)	0.432 (0.319 to 0.564)	0.253 (0.163 to 0.380)	0.609 (0.483 to 0.738)	0.408 (0.292 to 0.549)
ERA	155	0.259 (0.192 to 0.345)	0.126 (0.079 to 0.197)	0.429 (0.347 to 0.522)	0.237 (0.171 to 0.323)	0.628 (0.532 to 0.725)	0.394 (0.306 to 0.497)
Undifferentiated arthritis	113	0.290 (0.213 to 0.388)	0.194 (0.129 to 0.284)	0.444 (0.353 to 0.547)	0.297 (0.218 to 0.397)	0.617 (0.515 to 0.720)	0.429 (0.333 to 0.540)

*Number of subjects who attained inactive disease.
ERA, enthesitis-related arthritis; JIA, juvenile idiopathic arthritis; RF, rheumatoid factor.

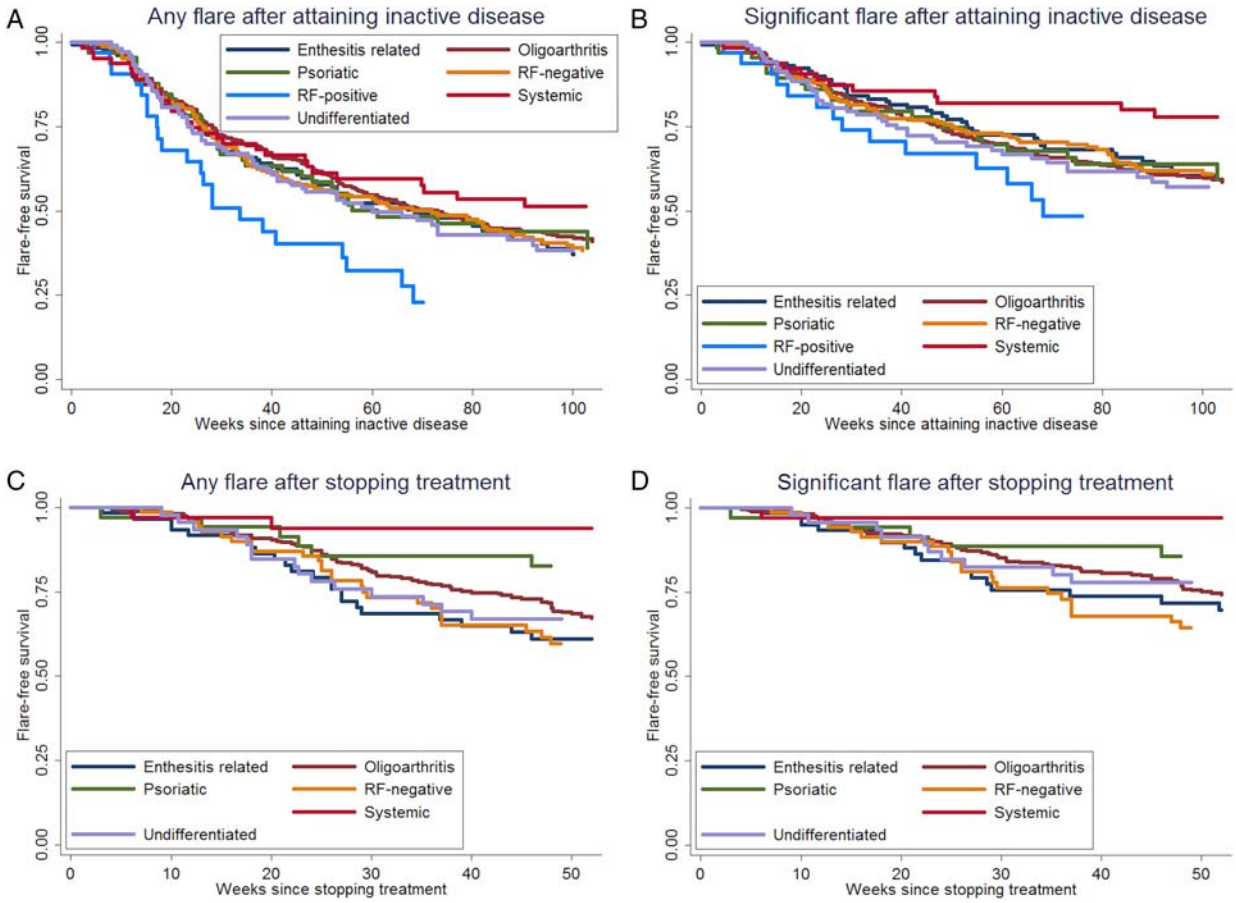

Figure 2 Kaplan–Meier curves for the risk of any flare (A) and significant flare (B) for seven JIA categories after attaining inactive disease. Panels (C) and (D) show corresponding Kaplan–Meier curves for any flare (C) and significant flare (D) after stopping treatment. Significant flares were those requiring intensification or reinitiation of treatment. Persistent and extended oligoarthritis are combined. JIA, juvenile idiopathic arthritis; RF, rheumatoid factor.

The latter is compatible with the high frequency of a monophasic course in systemic JIA.[17] Children with a severe disease course, high treatment requirements or positive ANA were at increased risk of flare.

Trials of biological therapies have reported a cumulative incidence of flare between 50% and 80% within 6 months of discontinuing the biological agent, defining flare as 30% worsening in three or more juvenile arthritis core variables without

Table 2 Cumulative probabilities of flare within 3, 6 and 12 months after stopping all antirheumatic treatments

		Probability of flare after stopping treatment (95% CI)					
		Within 3 months		Within 6 months		Within 12 months	
Patients	N*	Any flare	Significant flare	Any flare	Significant flare	Any flare	Significant flare
Whole cohort	625	0.060 (0.043 to 0.084)	0.053 (0.037 to 0.075)	0.172 (0.142 to 0.207)	0.137 (0.110 to 0.170)	0.317 (0.278 to 0.360)	0.250 (0.214 to 0.290)
Systemic arthritis	37	0.030 (0.004 to 0.196)	0.030 (0.004 to 0.196)	0.062 (0.016 to 0.225)	0.030 (0.004 to 0.196)	0.062 (0.016 to 0.225)	0.030 (0.004 to 0.196)
Oligoarthritis persistent	310	0.058 (0.036 to 0.092)	0.054 (0.033 to 0.088)	0.156 (0.118 to 0.205)	0.127 (0.093 to 0.173)	0.330 (0.277 to 0.391)	0.259 (0.210 to 0.316)
Oligoarthritis extended†	8	–	–	–	–	–	–
RF-negative polyarthritis	85	0.071 (0.030 to 0.163)	0.057 (0.022 to 0.145)	0.217 (0.137 to 0.334)	0.188 (0.114 to 0.302)	0.402 (0.293 to 0.534)	0.355 (0.251 to 0.486)
RF-positive polyarthritis†	4	–	–	–	–	–	–
Psoriatic arthritis	44	0.057 (0.015 to 0.210)	0.057 (0.015 to 0.210)	0.143 (0.062 to 0.310)	0.114 (0.044 to 0.276)	0.172 (0.081 to 0.344)	0.144 (0.062 to 0.312)
ERA	77	0.083 (0.035 to 0.188)	0.066 (0.025 to 0.167)	0.242 (0.151 to 0.374)	0.190 (0.110 to 0.317)	0.389 (0.275 to 0.529)	0.302 (0.199 to 0.441)
Undifferentiated arthritis	60	0.065 (0.021 to 0.189)	0.043 (0.011 to 0.160)	0.219 (0.124 to 0.369)	0.153 (0.076 to 0.294)	0.331 (0.214 to 0.488)	0.222 (0.126 to 0.373)

*Number of subjects who discontinued treatment.
†The probability of flares after stopping treatment is not reported because few subjects stopped treatment in this JIA category.
ERA, enthesitis-related arthritis; JIA, juvenile idiopathic arthritis; RF, rheumatoid factor.

Table 3 Association of clinical features with the risk of any flare after attaining inactive disease

Characteristic	Patients with feature (%)	Crude HR*	95% CI	p Value	Adjusted HR*	95% CI	p Value
Systemic arthritis	5.9	0.67	0.46 to 0.97	0.033	0.60	0.40 to 0.91	0.015
RF-positive polyarthritis	3.0	1.92	1.29 to 2.87	0.001	1.53	0.99 to 2.39	0.057
DMARD before inactive disease	42.1	1.28	1.09 to 1.50	0.002	0.96	0.77 to 1.21	0.762
Biological agents before inactive disease	6.7	1.65	1.22 to 2.23	0.001	1.31	0.94 to 1.84	0.115
Greater than 52 weeks to attain inactive disease	33.1	1.28	1.09 to 1.50	0.002	1.15	0.95 to 1.39	0.146
Maximum joint count before inactive disease >4	35.3	1.46	1.23 to 1.74	<0.001	1.15	0.90 to 1.46	0.270
Maximum PGA before inactive disease >30 mm	50.6	1.50	1.27 to 1.78	<0.001	1.32	1.08 to 1.62	0.007
Involvement of a high-risk joint†	48.9	1.26	1.08 to 1.47	0.004	1.01	0.82 to 1.25	0.913
ANA positive‡	43.7	1.21	1.03 to 1.43	0.017	1.15	0.96 to 1.37	0.122

*Crude HRs were calculated in Cox regression models that included only one independent variable at a time. Adjusted HRs were calculated in a multivariable Cox regression model that included all statistically significant variables (p<0.05) at once. All variables were dichotomised so that HRs may be interpreted as relative risks. For JIA categories, the HR compares children in that JIA category with children in all other JIA categories. A round number close to the median was chosen to dichotomise continuous variables. The HRs of continuous variables without dichotomisation were examined in separate models and did not change the statistical significance of the association (data not shown).
†High-risk joints included any of neck, wrist, sacroiliac, hip or ankle.[16]
‡An ANA titre above the cut-off for the local laboratory (usually 1:80).
ANA, antinuclear antibodies; DMARD, disease-modifying antirheumatic drug; JIA, juvenile idiopathic arthritis; PGA, physician global assessment; RF, rheumatoid factor.

improvement of more than one variable by 30%.[7 18 19] However, these results cannot be extrapolated to real-practice populations because most of these trials selected patients with a severe polyarticular course. Furthermore, 30% worsening in joint counts has questionable relevance in JIA categories with few joints involved, and in current practice, where most children with JIA attain joint counts of zero.

The trial reported by Foell *et al*[6] may be closer to real practice. Foell *et al* randomised children with JIA with inactive disease for 3 months while on methotrexate, to stop all treatment 6 or 12 months later. They defined flare as loss of criteria for inactive disease according to Wallace *et al*.[11] The rates of flare within 24 months after entering the study were 56.7% and 55.6%, respectively; comparable to our calculated probability of 60.3% within 24 months of attaining inactive disease. The rates of flare within 12 months of stopping medication were 39.6% and 39.5%, respectively; slightly higher than our calculated probability of flare of 31.7%.

To identify clinical features associated with the risk of flare, we calculated Cox HRs for dichotomised clinical variables. Dichotomisation increases clinical applicability, although it reduces statistical power. Crude HRs and CIs can identify markers of increased risk, without inferring causality. Others may prefer to emphasise features that retain statistical significance in multivariable analysis as independent determinants of flare. The only significant associations in multivariable analysis were an increased risk of flare with greater disease severity as signalled by a PGA >30 mm and a protective effect of systemic JIA compared with other JIA categories. The association of the use of DMARD or biological agents with increased risk of flare loses significance in multivariable analysis, suggesting that high treatment requirements are markers of a more severe disease and not independent determinants of flare. Our results suggest that ANA are also markers of an increased risk of flare, partly explained by their association with uveitis. ANA have been proposed as a marker of a homogeneous subgroup of patients encompassing several JIA categories.[20]

Implications for practice

Families should know there is a steadily increasing risk of flare after inactive disease is attained that reaches over 40% within a year, but about 40% of flares may not require treatment intensification. The risk is higher for children with a severe disease course, RF-positive polyarthritis or ANA. Flares will often consist of a few swollen joints for an average of 6 months.

When considering treatment discontinuation, families should know that the chance of a flare requiring treatment reinitiation is one in four during the first year after stopping treatment. This does not apply to children with RF-positive polyarthritis or extended oligoarthritis who rarely discontinued treatment in our cohort. Children with systemic JIA had the lowest risk of flare and only a 1-in-33 chance of requiring reinitiation of treatment. With this information at hand, the risk of flare can be meaningfully compared with the inconveniences and risks of continuing on antirheumatic treatment.

Study strengths and limitations

This is the largest prospective inception cohort of JIA published to date. We were able to enrol and follow all these children because of the close collaboration among all Canadian paediatric rheumatology centres. Our definition of flare as any recurrence of disease manifestations is simple and requires only a few variables: a standard active joint count, a PGA and presence of extra-articular manifestations. However, it does not consider important patient-reported outcomes such as pain or quality of life.[2] Furthermore, it excludes worsening in children who have improved, but did not attain inactive disease; conversely, it may include flares of doubtful clinical relevance. Our definition of significant flare may be more clinically meaningful than any flare, as it implies a situation serious enough to intensify treatment. However, due to limitations of data collection in our study, flares treated only by increasing medication doses or changing mode of administration were not called significant, while medication changes partly due to side effects may be included in some significant flares. These latter limitations do not apply to flares after discontinuing treatment.

Data from this real-practice cohort may not be comparable with studies using the recently validated definition of inactive disease.[21] The main differences are that we required an absence of enthesitis in children with ERA and psoriatic arthritis, and a PGA <10 mm rather than 0 mm to avoid counting as active disease small values that could be due to unintentional markings or a reluctance to mark the extreme end-point of the VAS. This is the same cut-off used by Ruperto *et al*.[22] We did not require normal levels of acute phase reactants since the study was carried out in clinical practice settings where ethical considerations discouraged blood draws in children without clinical

indication. We did not require morning stiffness <15 min as this was not recorded in all visits. It is possible that a stricter definition of inactive disease would result in a lower number of subjects attaining inactive disease and higher estimates of the risk of flare.

We estimated the probability of flare after first attainment of inactive disease and after discontinuation of treatment because these were important milestones where counselling of families was critical. However, the data provided can also be used to approximate the chance of flare after 6 months of inactive disease by subtracting the probabilities presented in the 6-month column in table 1. The chances that a child stopping antirheumatic treatment will be inactive for the subsequent 12 months are the reciprocal of the values in the 12-month column in table 2. However, this calculation only approximates probabilities of 'remission off medication' as defined by Wallace *et al*,[11 21] given the above differences in definitions of inactive disease.

The course of JIA may have multiple periods of disease quiescence and relapses.[23–25] However, focusing on first flares produces robust probability estimates as it avoids bias due to few patients contributing many flares. We emphasise Kaplan–Meier estimates for the first 2 years after attaining inactive disease and the first year after discontinuation of treatment because the number of subjects in some JIA categories is small afterwards.

The Juvenile Arthritis Disease Activity Score, a well-validated composite measure including active joint count, PGA and parent global assessment with or without the sedimentation rate,[26] could also be used as a basis for defining flare, but this option was not feasible in our study since the ReACCh-Out protocol did not include parent global assessment at interim visits.

Lastly, the reported probabilities of flare may relate to variables inherent to a patient's biology[27] as well as to the treatments received,[1] and our results may not fully apply to children treated in a substantially different way.

CONCLUSIONS

In this prospective JIA inception cohort, the probability of flare within a year of attaining a state of inactive disease was 42.5%, with a lower probability for children with systemic JIA and a higher probability for those with RF-positive polyarthritis. Children with a severe disease course or positive ANA had an increased risk of flare. Flares often consisted of a few swollen joints for an average of 6 months, and 40% were not associated with intensification of treatment. Overall, the probability of a flare requiring reinitiation of treatment was 25% within a year after treatment discontinuation; but only 3% for children with systemic JIA.

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REFERENCES

1 Guzman J, Oen K, Tucker LB, *et al*, for the ReACCh-Out investigators. The outcomes of juvenile idiopathic arthritis in children managed with contemporary treatments: results from the ReACCh-Out cohort. *Ann Rheum Dis* 2014. Published Online First: 19 May 2014. doi:10.1136/annrheumdis-2014-205372
2 Guzman J, Gómez-Ramírez O, Jurencak R, *et al*. What matters most for patients, parents, and clinicians in the course of juvenile idiopathic arthritis? A qualitative study. *J Rheumatol* 2014;41:2260–9.
3 Petty RE, Southwood TR, Manners P, *et al*. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;31:390–2.
4 Lanni S, Bertamino M, Consolaro A, *et al*. Outcome and predicting factors of single and multiple intra-articular corticosteroid injections in children with juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2011;50:1627–34.
5 Papadopoulou C, Kostik M, Gonzalez-Fernandez MI, *et al*. Delineating the role of multiple intraarticular corticosteroid injections in the management of juvenile idiopathic arthritis in the biologic era. *Arthritis Care Res (Hoboken)* 2013;65:1112–20.
6 Foell D, Wulffraat N, Wedderburn LR, *et al*, Paediatric Rheumatology International Trials Organization (PRINTO). Methotrexate withdrawal at 6 vs 12 months in juvenile idiopathic arthritis in remission: a randomized clinical trial. *JAMA* 2010;303:1266–73.
7 Lovell DJ, Giannini EH, Reiff A, *et al*. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med* 2000;342:763–9.
8 Brunner HI, Lovell DJ, Finck BK, *et al*. Preliminary definition of disease flare in juvenile rheumatoid arthritis. *J Rheumatol* 2002;29:1058–64.
9 Oen K, Tucker L, Huber AM, *et al*. Predictors of early inactive disease in a juvenile idiopathic arthritis cohort: results of a Canadian multicenter, prospective inception cohort study. *Arthritis Rheum* 2009;61:1077–86.
10 Giannini EH, Ruperto N, Ravelli A, *et al*. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997;40:1202–9.
11 Wallace CA, Ruperto N, Giannini EH, for the CARRA, PRINTO and PRCSG. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol* 2004;31:2290–4.
12 Bingham CO 3rd, Pohl C, Woodworth TG, *et al*. Developing a standardized definition for disease "flare" in rheumatoid arthritis (OMERACT 9 Special Interest Group). *J Rheumatol* 2009;36:2335–41.
13 Oen K. Long-term outcomes and predictors of outcomes for patients with juvenile idiopathic arthritis. *Best Pract Res Clin Rheumatol* 2002;16:347–60.
14 Ravelli A, Martini A. Early predictors of outcome in juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2003;21(5 Suppl 31):S89–93.

15 Adib N, Silman A, Thomson W. Outcome following onset of juvenile idiopathic inflammatory arthritis: II. Predictors of outcome in juvenile arthritis. *Rheumatology (Oxford)* 2005;44:1002–7.
16 Beukelman T, Patkar NM, Saag KG, *et al*. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res* 2011;63:465–82.
17 Singh-Grewal D, Schneider R, Bayer N, *et al*. Predictors of disease course and remission in systemic juvenile idiopathic arthritis: significance of early clinical and laboratory features. *Arthritis Rheum* 2006;54:1595–601.
18 Lovell DJ, Ruperto N, Goodman S, *et al*, Pediatric Rheumatology Collaborative Study Group; Pediatric Rheumatology International Trials Organisation. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008;359:810–20.
19 Ruperto N, Lovell DJ, Quartier P, *et al*, Paediatric Rheumatology International Trials Organization; Pediatric Rheumatology Collaborative Study Group. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet* 2008;372:383–91.
20 Ravelli A, Varnier GC, Oliveira S, *et al*. Antinuclear antibody-positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis. *Arthritis Rheum* 2011;63:267–75.
21 Wallace CA, Giannini EH, Huang B, *et al*. American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)* 2011;63:929–36.
22 Ruperto N, Lovell DJ, Quartier P, *et al*. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. *Arthritis Rheum* 2010;62:1792–802.
23 Ringold S, Seidel KD, Koepsell TD, *et al*. Inactive disease in polyarticular juvenile idiopathic arthritis: current patterns and associations. *Rheumatology (Oxford)* 2009;48:972–7.
24 Wallace CA, Huang B, Bandeira M, *et al*. Patterns of clinical remission in select categories of juvenile idiopathic arthritis. *Arthritis Rheum* 2005;52:3554–62.
25 Berard RA, Tomlinson G, Li X, *et al*. Description of active joint count trajectories in juvenile idiopathic arthritis. *J Rheumatol* 2014;41:2466–73.
26 Consolaro A, Negro G, Chiara Gallo M, *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.
27 Eng SW, Duong TT, Rosenberg AM, *et al*, on behalf of the REACCH OUT and BBOP Research Consortia. The biological basis for clinical heterogeneity in childhood arthritis. *Arthritis Rheumatol* 2014;66:3463–75.