

# Pulmonary Hypertension and Other Potentially Fatal Pulmonary Complications in Systemic Juvenile Idiopathic Arthritis

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**Objective.** Systemic juvenile idiopathic arthritis (JIA) is characterized by fevers, rash, and arthritis, for which interleukin-1 (IL-1) and IL-6 inhibitors appear to be effective treatments. Pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), and alveolar proteinosis (AP) have recently been reported with increased frequency in systemic JIA patients. Our aim was to characterize and compare systemic JIA patients with these complications to a larger cohort of systemic JIA patients.

**Methods.** Systemic JIA patients who developed PAH, ILD, and/or AP were identified through an electronic Listserv and their demographic, systemic JIA, and pulmonary disease characteristics as well as their medication exposure information were collected. Patients with these features were compared to a cohort of systemic JIA patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry.

**Results.** The patients (n = 25) were significantly ( $P < 0.05$ ) more likely than the CARRA registry cohort (n = 389) to be female; have more systemic features; and have been exposed to an IL-1 inhibitor, tocilizumab, corticosteroids, intravenous immunoglobulin, cyclosporine, and cyclophosphamide. Twenty patients (80%) were diagnosed with pulmonary disease after 2004. Twenty patients (80%) had macrophage activation syndrome (MAS) during their disease course and 15 patients (60%) had MAS at pulmonary diagnosis. Sixteen patients had PAH, 5 had AP, and 7 had ILD. Seventeen patients (68%) were taking or recently discontinued (<1 month) a biologic agent at pulmonary symptom onset; 12 patients (48%) were taking anti-IL-1 therapy (primarily anakinra). Seventeen patients (68%) died at a mean of 10.2 months from the diagnosis of pulmonary complications.

**Conclusion.** PAH, AP, and ILD are underrecognized complications of systemic JIA that are frequently fatal. These complications may be the result of severe uncontrolled systemic disease activity and may be influenced by medication exposure.

## INTRODUCTION

Systemic juvenile idiopathic arthritis (JIA) is a distinct category of JIA that is characterized as arthritis accompanied by characteristic systemic features (mainly quotidian

fevers and evanescent rash, but often also organomegaly, lymphadenopathy, and serositis). In addition to these features, systemic JIA patients often have highly abnormal acute-phase reactants, anemia, and hyperferritinemia. The

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## Significance & Innovations

- Serious pulmonary complications are being reported with increased frequency and are frequently fatal in systemic juvenile idiopathic arthritis (JIA) patients.
- The characteristics of these pulmonary complications, disease features, and medication exposures in the affected patients need to be studied.
- This study used systemic JIA patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance registry as a comparator group, which is the largest known database of JIA patients in the world.
- The affected patients had increased severity of systemic disease and more exposure to medications, especially biologic agents.

International League of Associations for Rheumatology (ILAR) criteria are most widely accepted for children under the age of 16 years (1). Systemic JIA patients are susceptible to a potentially fatal complication called macrophage activation syndrome (MAS), which is characterized by unremitting fever, pancytopenia, coagulopathy, and organ dysfunction, commonly of the liver and central nervous system (2–4). Tissue biopsies often show foamy macrophages and active phagocytosis of blood elements (hemophagocytosis). MAS is thought to be an acquired form of hemophagocytic lymphohistiocytosis (2,3,5–7). Many systemic JIA patients with active systemic features are thought to have subclinical MAS (2–4,8). One study of bone marrow biopsies of systemic JIA patients at disease

diagnosis showed the presence of hemophagocytosis even when overt clinical features of MAS were absent (9).

In addition to increased morbidity and poorer functional outcomes when compared with other forms of JIA (10,11), systemic JIA patients have an increased risk of death, with a mortality hazard ratio that can be almost double that of other JIA categories mostly because of complications such as MAS and serious infections (2,4,12). Recently, advances in the understanding of systemic JIA and the discovery of its excellent response to interleukin-1 (IL-1) and IL-6 inhibitors have resulted in an improved prognosis for many patients with this difficult-to-treat disease (13–19).

Nearly 4 years ago, spontaneous reports emerged about an international pediatric rheumatology electronic Listserv of unusual pulmonary complications in systemic JIA patients that were often fatal, especially pulmonary arterial hypertension (PAH) (20). Although pleuritis, along with pericarditis, is a commonly recognized feature of systemic JIA (11,21), other pulmonary complications, such as PAH, interstitial lung disease (ILD), and alveolar proteinosis (AP) or lipoid pneumonia, are extremely rare. Prior to 2008, only scattered single case reports of PAH, AP, ILD, and illnesses that may represent one of these conditions in systemic JIA and Still's disease existed in the literature (22–27), so the number of cases being reported to the Listserv represented an increase. Because IL-1 inhibitors became much more commonly used in systemic JIA in the mid-2000s, there was concern about a possible association between exposure to biologic medications such as IL-1 inhibitors and the development of pulmonary complications in some patients (16,17). In this study, we sought to identify and describe systemic JIA patients with these pulmonary complications and analyze the disease features that might identify characteristics specific to these patients.

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## PATIENTS AND METHODS

A retrospective chart review of patients with systemic JIA who developed PAH, ILD, and/or AP was performed. Cases were solicited initially in 2008 and then again in May 2011 through an international pediatric rheumatology electronic Listserv managed by McMaster University (Ontario). Approval was obtained from the Hackensack University Medical Center Institutional Review Board to collect deidentified data for analysis. A questionnaire was designed to collect information on demographics, disease characteristics, medication usage, pulmonary disease symptoms, diagnosis and treatment, and laboratory and other diagnostic data. The disease and demographic characteristics and medication history of the study cohort were compared to baseline data of a cross-sectional cohort of systemic JIA patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) pediatric rheumatic diseases registry. Statistical analysis was performed using frequencies and the data set variables were compared using Fisher's exact test to determine a *P* value.

**Table 1. Patient demographics and systemic JIA disease characteristics\***

	Study cohort (n = 25)	CARRA registry cohort (n = 389)†	P
Age at systemic JIA diagnosis, mean ± SD (range) years	7.4 ± 5.5 (1.1–17.2)	5.8 ± 4.3 (0.2–15.9)	NS
Disease duration, mean ± SD (range) months	51.6 ± 48.8 (8–173)‡	61.9 ± 51 (0.6–219.5)	0.012
Female	19 (76)	213 (55)	0.040
Race			NS
White	17 (68)	302 (78)	
African American	7 (28)	45 (12)	
Asian	1 (4)	20 (5)	
Other/unknown	0 (0)	20 (5)	
Ethnicity			NS
Hispanic	5 (20)	50 (13)	
Non-Hispanic	20 (80)	337 (87)	
JIA symptoms (ever had during disease course)			
Fever	25 (100)	352 (93)	NS
Rash	23 (92)	326 (87)	NS
Arthritis	25 (100)	378 (100)	NS
Lymphadenopathy	19 (76)	157 (46)	< 0.001
Hepatomegaly or splenomegaly	20 (80)	102 (31)	< 0.001
Serositis	14 (56)	Unknown	N/A
Decade of disease onset			0.0068
1980s	1 (4)	0	
1990s	5 (20)	35 (9)	
2000 and later	19 (76)	335 (87)	
Unknown	0	16 (4)	

\* Values are the number (percentage) unless otherwise indicated. JIA = juvenile idiopathic arthritis; CARRA = Childhood Arthritis and Rheumatology Research Alliance; NS = not significant ( $P > 0.05$ ); N/A = not applicable.  
† Sum of all frequencies may not be equal to the total sample size because of missing values.  
‡ At the time of pulmonary complication diagnosis.

## RESULTS

**Demographic and disease characteristics.** Twenty-five cases were identified from the US (n = 19), Spain (n = 1), the UK (n = 1), The Netherlands (n = 1), Italy (n = 1), and Brazil (n = 2). Twenty-four of the subjects met the ILAR criteria for systemic JIA. The 1 remaining patient met the ILAR criteria, except that she was 17 years old when her systemic JIA symptoms began. The CARRA registry cohort consisted of 389 patients at the time of the data cut (April 30, 2012). Table 1 shows the disease and demographic characteristics of the 2 cohorts. Although age at diagnosis, race/ethnicity, and common disease features were similar between the 2 cohorts, the study cohort had a significantly larger proportion of female patients and patients with lymphadenopathy and organomegaly (splenomegaly and/or hepatomegaly). Disease or treatment complications in the study cohort included growth failure (40%), osteoporosis (40%), pathologic fractures (8%), cataracts (24%), avascular necrosis (12%), and amyloidosis (4%). Twenty patients (80%) had at least 1 episode of MAS and 16 patients (64%) had a serious infection (including sepsis, salmonella gastroenteritis, adenovirus gastroenteritis, pneumonia, *Clostridium difficile* enteritis, typhilitis, and ascariasis) during the course of their disease. Other complications included psychosis (1 patient), myositis (1 patient), transient ischemic attack (1 patient), thrombotic thrombocytopenia purpura (1 patient), and dyslipidemia (1 patient). There were significant differences in the de-

cade of disease onset between the 2 cohorts, with more patients in the CARRA registry (87%) having onset after 2000 compared to the study cohort (76%).

**Medication exposures.** Medications that the study cohort had ever taken were compared to those of the CARRA registry cohort (Table 2). Significant differences were found, with the study cohort having more exposure to any IL-1 inhibitor (also specifically to anakinra and canakinumab), tocilizumab, intravenous immunoglobulin (IVIG), high-dose methylprednisolone pulse treatments, cyclophosphamide, and cyclosporine.

**Pulmonary disease features.** The pulmonary disease features in the study cohort are shown in Table 3. Dyspnea on exertion and shortness of breath were the most common symptoms; the other symptoms included clubbing, cough, and chest pain. Two patients had shortness of breath as their only symptom and 3 patients had only clubbing. One patient was diagnosed at autopsy and did not have any known prior pulmonary symptoms. Twenty-four patients (96%) developed pulmonary disease after 2000, and 20 patients (80%) developed pulmonary disease after 2004. Sixteen patients (64%) had PAH, 5 patients (20%) had AP and/or lipid pneumonia, and 7 patients (28%) had ILD. Six patients had >1 diagnosis; 2 patients had PAH and ILD, 2 patients had PAH and AP, and 2 patients had AP and ILD. There were no clinical features that distinguished the specific pulmonary diagnoses. The following diagnos-

Table 2. Medications used during disease course\*

	Study cohort (n = 25)	CARRA registry cohort (n = 389)	P
Biologic DMARDs			
Abatacept	2 (8)	19 (6)	NS
IL-1 inhibitor (any)	20 (80)	168 (43)	< 0.001
Anakinra	20 (80)	156 (40)	< 0.001
Canakinumab	3 (12)	7 (2)	0.018
Rilonacept	4 (16)	27 (7)	NS
IVIG	7 (28)	24 (6)	0.001
Rituximab	0 (0)	7 (2)	NS
Tocilizumab	5 (20)	29 (8)	0.044
TNF inhibitor (any)	15 (60)	174 (45)	NS
Adalimumab	5 (20)	48 (12)	NS
Certolizumab	0 (0)	2 (1)	NS
Etanercept	12 (48)	140 (36)	NS
Golimumab	0 (0)	2 (1)	NS
Infliximab	6 (24)	54 (14)	NS
Glucocorticoids			
Methylprednisolone pulses	23 (92)	122 (31)	< 0.001
Prednisone	25 (100)	336 (86)	NS
Nonbiologic DMARDs			
		NR	
Mycophenolate mofetil	3 (12)	12 (3)	NS
Cyclophosphamide	5 (20)	7 (2)	0.001
Cyclosporine	14 (56)	45 (12)	< 0.001
Etoposide	5 (20)	NR	
Gold	1 (4)	NR	
Methotrexate	22 (88)	232 (78)	NS
Penicillamine	1 (4)	NR	
Tacrolimus	2 (8)	8 (2)	NS
Thalidomide	4 (16)	NR	

\* Values are the number (percentage). CARRA = Childhood Arthritis and Rheumatology Research Alliance; DMARD = disease-modifying antirheumatic drug; NS = not significant ( $P > 0.05$ ); IL-1 = interleukin-1; IVIG = intravenous immunoglobulin; TNF = tumor necrosis factor; NR = not reported.

tic tests were performed: electrocardiogram (8 of 19 abnormal), chest radiographs (15 of 21 abnormal), echocardiogram (18 of 24 abnormal), chest computed tomography scan (18 of 20 abnormal), pulmonary function tests (13 of 13 abnormal), cardiac catheterization (9 of 10 abnormal), and lung biopsy (11 of 12 abnormal). Seventeen patients (68%) died within a mean  $\pm$  SD time of  $10.2 \pm 13$  months from the diagnosis of their pulmonary disease. Seven of these patients also had a serious infection near the time of death. The remaining 8 patients survived for a mean  $\pm$  SD time of  $56.2 \pm 35.3$  months (range 16–106 months) from the time of pulmonary disease diagnosis (as of June 15, 2012).

**Concomitant features of systemic JIA.** Twenty-three patients (92%) had systemic features at the time of pulmonary disease diagnosis (Table 3), including fever (15 patients), rash (7 patients), serositis (6 patients), lymphadenopathy (6 patients), hepatomegaly (11 patients), and splenomegaly (12 patients). One patient had thrombotic thrombocytopenic purpura. Fifteen patients (60%) had MAS (suspected or confirmed) at the time of the pulmonary disease diagnosis. All 15 patients fulfilled the Ravelli preliminary criteria for MAS (28). Five of these patients also had tissue confirmation of MAS; 2 patients had he-

mophagocytosis on bone marrow biopsy, 1 on lung biopsy, 1 on myocardial biopsy, and 1 patient had iron-laden macrophages in the bronchoalveolar lavage fluid. A sixteenth patient who did not fulfill the Ravelli criteria at the time of diagnosis had a rapidly deteriorating course and died 5 months later; the autopsy showed multiple organs with evidence of hemophagocytosis.

#### Medication exposures at onset of pulmonary symptoms.

Seventeen patients (68%) had been exposed to  $\geq 1$  biologic disease-modifying antirheumatic drug (DMARD) at the onset of pulmonary symptoms (Table 4). An IL-1 inhibitor (primarily anakinra) was the most common biologic DMARD taken, with 12 patients (48%) either taking an IL-1 inhibitor or having recently ( $< 1$  month) discontinued it at the time their pulmonary symptoms developed ( $n = 3$ ). The other biologic DMARDs included tumor necrosis factor (TNF) inhibitors (12%) and tocilizumab (8%). Twenty-one patients (84%) were taking  $> 1$  medications at the time of symptom onset and 13 were taking combinations of DMARDs. Three patients had been exposed to a combination of biologic DMARDs within a month of symptom onset; 1 was taking a combination of TNF and IL-1 inhibitors and 2 had been exposed to an IL-1 and IL-6 inhibitor within 1 month of the other. However, there was

**Table 3. Clinical features at pulmonary disease diagnosis (n = 25)\***

	Value
Age at start of pulmonary symptoms, mean $\pm$ SD (range) years	11.7 $\pm$ 5.2 (3.5–18.8)
Disease duration at pulmonary diagnosis, mean $\pm$ SD (range) months	50.6 $\pm$ 44.6 (8–160)
Time between pulmonary symptoms to diagnosis, mean $\pm$ SD (range) months	3.1 $\pm$ 3.2 (0–10)
Time between pulmonary diagnosis to death (n = 17), mean $\pm$ SD (range) months	10.2 $\pm$ 13 (0–44)
Disease features at pulmonary disease diagnosis	
Systemic JIA manifestations	
Any systemic manifestation†	23 (92)
MAS (suspected or confirmed)	15 (60)
Pericarditis or serositis	11 (44)
Thrombotic thrombocytopenic purpura	1 (4)
Arthritis	16 (64)
Pulmonary symptoms	
Shortness of breath	16 (64)
Dyspnea on exertion	18 (72)
Cough	11 (44)
Clubbing	10 (40)
Chest pain	5 (20)
Pulmonary diagnosis	
Pulmonary arterial hypertension	16 (64)
Alveolar proteinosis	5 (20)
Interstitial lung disease	7 (28)

\* Values are the number (percentage) unless otherwise indicated. JIA = juvenile idiopathic arthritis; MAS = macrophage activation syndrome.  
† Includes patients with one or more of the following: fever, rash, lymphadenopathy, hepatomegaly, and splenomegaly.

no consistent pattern of medication combination exposures among the patients.

## DISCUSSION

Although isolated case reports of PAH, AP, and ILD in systemic JIA and adult-onset Still's disease have been pub-

lished (22–27,29,30), the findings in this study indicate that these complications may occur more commonly than previously suspected and are fatal in the majority of patients. PAH, ILD, and AP are all processes in which inflammation likely has an important role; for example, pathologic PAH specimens show an increased inflammatory perivascular infiltrate, including macrophages, dendritic cells, lymphocytes, and mast cells (31–33). In AP, there is an accumulation of lipoproteinaceous material in the airways due to macrophage dysfunction and ineffective clearance in the alveoli as well as the presence of foamy macrophages (29,34). AP can coexist with lipoid pneumonia, in which cholesterol clefts and an inflammatory infiltrate can be seen. In addition, C-reactive protein levels have been shown to be increased in patients with PAH and correlated with the severity of disease (35). Infections, toxins, and drugs have long been hypothesized as having a primary or secondary role in triggering PAH. Increased levels of cytokines, especially IL-1 $\beta$ , IL-6, and TNF $\alpha$ , have been found in the serum and tissue of patients with PAH (36–38). In addition, hereditary PAH and a minority of sporadic PAH cases are associated with heterozygous mutations in bone morphogenetic protein receptor type II (BMPRII); reduced expression of BMPRII is associated with endothelial cell dysfunction and the development of PAH (39–41). IL-6, which is increased in systemic JIA patients with active systemic features (42–44), decreases the expression of BMPRII in vitro. Therefore, increased IL-6 levels characteristic of active systemic

**Table 4. Medications being taken at the time of development of pulmonary symptoms or discontinued within a month prior to symptoms\***

Medication	No. patients	Exposure, months
Corticosteroids	24	47.3 $\pm$ 48.2 (3–161)
Cyclosporine	7	6.3 $\pm$ 7.3 (1–22)
Etoposide	1	1
Gold	1	53
Methotrexate	13	32.9 $\pm$ 38.2 (1–126)
Thalidomide	1	22
IL-1 inhibitor (any)	12	15.1 $\pm$ 15.0 (3–47)
Anakinra	10	16.9 $\pm$ 15.9 (3–47)
Canakinumab	1	6
Rilonacept	1	6
TNF inhibitor (any)	3	17.0 $\pm$ 13.1 (2–26)
Adalimumab	2	12.5 $\pm$ 14.9 (2–23)
Etanercept	1	26
Tocilizumab	2	6.0 $\pm$ 7.1 (1–11)

\* Values are the mean  $\pm$  SD (range). IL-1 = interleukin-1; TNF = tumor necrosis factor.

JIA may contribute to the development of PAH in these individuals.

Of interest is the fact that 96% of the patients developed these pulmonary complications after 2000 (and 80% after 2004) because biologic DMARDs (especially IL-1 inhibitors) became much more commonly used for systemic JIA in the mid-2000s. Of all the patients, 68% were taking a biologic DMARD (most commonly an IL-1 inhibitor) at the time of the development of pulmonary symptoms and had an increased likelihood of ever being exposed to biologic agents, especially IL-1 inhibitors, compared to the CARRA registry cohort. When the decade of disease onset was examined, the study cohort was significantly less likely to have been diagnosed after the year 2000 compared to the CARRA registry cohort, making it unlikely that the reason for the increased exposure to biologic agents in the study cohort was simply due to these patients having been diagnosed more recently. These facts raise the concern of a possible causal relationship between exposure to these medications and the development of pulmonary complications.

Although the biologic agent most frequently taken by the study cohort was anakinra, which was taken by 80% of the study patients compared to 40% of the CARRA registry cohort ( $P < 0.001$ ), other biologic agents with significantly increased exposure included canakinumab, tocilizumab, and IVIG (Table 2). Of note, the patient who developed PAH while taking canakinumab had also been exposed to tocilizumab (which was discontinued 4 months prior to the onset of pulmonary symptoms) and 2 additional patients who developed PAH were also taking tocilizumab. An additional patient not included in the study cohort who developed AP while taking tocilizumab was recently included in the pediatric rheumatology Listserv. Tocilizumab has been used much more frequently since it was approved for use in systemic JIA by the US Food and Drug Administration and the European Medicines Agency in 2011; therefore, the incidence of pulmonary events should be closely monitored through systematic postmarketing studies. A similar surveillance of patients exposed to canakinumab should also be conducted because this drug is also likely to receive a similar indication by regulatory agencies. Anakinra is currently the most commonly used biologic agent for systemic JIA even though it has not been specifically studied in this population and does not have a postmarketing commitment or requirement. However, the majority of the patients in the study cohort were exposed to this medication, underlining the importance of performing systematic prospective monitoring of all systemic JIA patients whether or not there is a postmarketing requirement of a specific medication.

It is also clear that most of the study patients had severe systemic diseases that likely resulted in increased medication exposures when compared with the CARRA registry cohort, including IV pulse corticosteroids, cyclophosphamide, and cyclosporine as well as biologic DMARDs. Many of these patients had active systemic features (including MAS) at the time of the pulmonary disease diagnosis; thus, it seems likely that systemic inflammatory disease severity played an important role in the pathogenesis of PAH, ILD, and AP. In fact, 2 of the patients had

evidence of hemophagocytosis in non–bone marrow tissue specimens (lung and myocardium). Disease severity itself is therefore likely to play an important role in the pathogenesis of these pulmonary complications; systemic features in the study cohort appeared to be significantly increased compared to the CARRA registry cohort, specifically hepatosplenomegaly and lymphadenopathy (both  $P < 0.001$ ) (Table 1). The frequencies of serositis (56%) and MAS (80%), both markers of systemic disease severity, were also much higher than expected in the study cohort, although an adequate comparison was not possible because the frequencies of these features were not collected in the CARRA registry population. Both IL-1 inhibitors (13,14,17,19,45–47) and anti-IL-6 antibodies (tocilizumab) have been found to be highly effective in systemic JIA (15,48,49). It remains to be seen whether effective treatments, including IL-1 and IL-6 inhibition, will reduce the incidence of pulmonary complications in patients with systemic JIA rather than being a possible causative factor.

It will be important to understand the epidemiology and pathophysiology of adverse events such as PAH, AP, and ILD, and their relationship to medication exposure as well as disease severity, because while biologic DMARDs are being used with increased frequency, systemic JIA itself is associated with significantly increased morbidity and mortality compared to other categories of JIA (10–12,21) and because biologic DMARDs are now being used with increased frequency (50). Traditional single-product phase IV registries will not be useful for understanding whether specific medication exposures lead to these adverse events because PAH, AP, and ILD are rare occurrences in a rare disease like systemic JIA. A consolidated disease registry in which all patients with systemic JIA are enrolled regardless of medication exposure would be the ideal vehicle to capture such information (51). This registry would have the advantage of being able to prospectively identify and follow a large cohort of systemic JIA patients taking different medications over extended periods of time. In this way, the frequency of pulmonary complications in patients with systemic JIA and their association with specific medication exposures could be captured and analyzed efficiently and accurately, while taking into account confounders such as disease severity.

The limitations of this study include its retrospective design and possible reporting and recall bias. There is a recent heightened awareness of pulmonary complications in patients with systemic JIA as well as an improved ability to diagnose them. Despite this study being the largest reported cohort of patients with these severe pulmonary complications, there were not enough patients with each pulmonary diagnosis to be able to discern differences in clinical presentation. Last, the comparator CARRA registry cohort data are from a cross-sectional convenience sample of systemic JIA patients followed at the 52 CARRA registry sites. The registry is one of the largest contemporary cohorts of JIA patients currently available but may not reflect an accurate sampling of typical systemic JIA patients.

Despite recent advances in therapy, systemic JIA remains a disease with significant morbidity and mortality. This study marks the first time that a large cohort of sys-

temic JIA patients who developed PAH, AP, and ILD has been described. PAH, AP, and ILD are important but underrecognized complications of systemic JIA that are likely to be the result of severe uncontrolled systemic disease activity and inflammation but may be influenced by exposure to certain medications. Further prospective studies are needed to determine the factors associated with the development of these pulmonary complications. Increased awareness regarding these pulmonary complications in systemic JIA is needed and screening for these complications should be considered in systemic JIA patients with significant and persistent systemic disease activity.

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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. Dr. Kimura had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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#### APPENDIX A: CONTRIBUTING CHILDHOOD ARTHRITIS AND RHEUMATOLOGY RESEARCH ALLIANCE CARRANET INVESTIGATORS

The contributing Childhood Arthritis and Rheumatology Research Alliance CARRANet investigators are as follows: Leslie Abramson, Timothy Beukelman, James Birmingham, Suzanne Bowyer, Elizabeth Chalom, Fatma Dedeoglu, Polly Ferguson, Donald Goldsmith, Beth Gottlieb, Thomas Graham, J. Roger Hollister, Anna Huttenlocher, Norman Ilowite, Lisa Imundo, Christi Inman, Rita Jerath, Lawrence Jung, Philip Kahn, Daniel Kingsbury, Marisa Klein-Gitelman, Thomas Lehman, Carol Lindsley, Deborah McCurdy, Nandini Moorthy, Barry Myones, Andrew Lasky, Jorge Lopez-Benitez, Judyann Olson, Kathleen O'Neil, Kabita Nanda, Karin Peterson, Sampath Prahalad, Ana Quintero, Ann Reed, Sarah Ringold, Deborah Rothman, Natasha Ruth, Christy Sandborg, Kenneth Schikler, David Sherry, Nora Singer, Steven Spalding, Reema Syed, Kathryn Torok, Richard Vehe, Emily von Scheven, Andrew White, Ali Yalcindag, and Lawrence Zemel.