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

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Abstract

Objectives—Systemic Juvenile Idiopathic Arthritis (sJIA) is characterized by fevers, rash and arthritis, for which IL1 and IL6 inhibitors appear effective. Pulmonary artery hypertension (PAH), interstitial lung disease (ILD) and alveolar proteinosis (AP) have been recently reported in sJIA patients with increased frequency. Our aim was to characterize and compare these cases to a larger cohort of sJIA patients.

Methods—sJIA patients who developed PAH, ILD and/or AP were identified through an electronic listserv, and their demographic, sJIA and pulmonary disease characteristics, and medication exposure information were collected. These features were compared to a cohort of sJIA patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry.

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Results—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 to have been exposed to an IL-1 inhibitor, tocilizumab, infliximab, corticosteroids, intravenous immunoglobulin, cyclosporine and cyclophosphamide. Eighty% were diagnosed after 2004. Twenty (80%) patients had MAS during their disease course and 15 (60%) had MAS at pulmonary diagnosis. Sixteen patients had PAH, 5 AP and 7 ILD. Seventeen (68%) patients were taking or recently (≤1 month) discontinued a biologic agent at pulmonary symptom onset; 12 (48%) were taking anti-IL1 therapy (primarily anakinra). Seventeen (68%) patients died at a mean of 8.8 months from pulmonary diagnosis.

Conclusions—PAH, AP and ILD are under-recognized complications of sJIA which are frequently fatal. These may be the result of severe uncontrolled systemic disease activity, and may be influenced by medication exposure.

Systemic Juvenile Idiopathic Arthritis (sJIA) is a distinct category of JIA which is characterized by arthritis accompanied by characteristic systemic features (mainly quotidian fevers and evanescent rash, often also organomegaly, lymphadenopathy and serositis). In addition to these features, sJIA patients often have highly abnormal acute phase reactants, anemia and hyperferritinemia. The ILAR criteria are most widely accepted [1] for children under the age of 16. SJIA 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 (HLH) [2, 3, 5–7]. Many sJIA patients with active systemic features are thought to have “sub-clinical” MAS [2–4, 8]. One study of bone marrow biopsies of sJIA 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 poor functional outcomes compared to other forms of JIA [10, 11], sJIA patients have an increased risk of death, with a mortality hazard ratio which 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 sJIA and the discovery of its excellent response to IL1 and IL6 inhibitors have resulted in an improved prognosis for many patients with this difficult to treat disease [13–19].

About 4 years ago, spontaneous reports emerged on an international pediatric rheumatology electronic listserv of unusual pulmonary complications in sJIA patients which were often fatal, especially pulmonary artery hypertension (PAH) [20]. Although pleuritis, along with pericarditis, is a commonly recognized feature of sJIA [11, 21], other pulmonary complications, such as PAH, interstitial lung disease (ILD) and alveolar proteinosis (AP) or lipoid pneumonia, are extremely rare. Only scattered single case reports of PAH, AP, ILD and illnesses that may represent one of these conditions in sJIA and Still’s disease existed in the literature prior to 2008 [22–27], prompting speculation about a possible association between exposure to biologic medications such as IL1 inhibitors and the development of these complications in some patients, because the use of IL1 inhibitors became much more common in sJIA at around this time, when reports of its efficacy in this disease emerged [16,

17]. In this study, we sought to identify and describe sJIA patients with these complications and analyze disease features which might identify characteristics that are specific to these patients.

Patients & Methods

A retrospective chart review was performed of sJIA patients who developed PAH, ILD and/or AP. Cases were solicited through an international pediatric rheumatology electronic listserv managed by McMaster University (Ontario), initially in 2008 and then again in May 2011. Approval was obtained from the Hackensack University Medical Center Institutional Review Board to collect de-identified data for analysis. A questionnaire was designed to collect demographic information, disease characteristics, medication usage, pulmonary disease symptoms, diagnosis and treatment, and laboratory and other diagnostic information. The disease and demographic characteristics, and medication usage history of the study cohort were compared to baseline data of a cross-sectional cohort of sJIA 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.

Results

Demographic and Disease Characteristics

Twenty-five cases were identified from the following countries: United States (N=19), Spain (1), United Kingdom (1), Netherlands (1), Italy (1), and Brazil (2). Twenty-four of the subjects met the ILAR criteria for systemic JIA. The remaining patient met ILAR criteria except that she was 17 years old when sJIA 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 two cohorts. Although the age at diagnosis, race/ethnicity and common disease features were similar in the two cohorts, the study cohort had a significantly larger number 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 (80%) had at least one episode of MAS and 16 (64%) had a serious infection (including sepsis, salmonella gastroenteritis, adenovirus gastroenteritis, pneumonia, Clostridium difficile enteritis, typhlitis and ascariasis) during the course of their disease. Other complications included psychosis (1), myositis (1), transient ischemic attack (1), thrombotic thrombocytopenia purpura (1) and dyslipidemia (1). There were significant differences in decade of disease onset between the two cohorts, with more patients in the CARRA Registry (87%) having onset after 2000 compared to the study cohort (76%).

Medication exposures

Medications ever taken by the study cohort were compared to those of the CARRA registry cohort (Table 2). Significant differences were found, with the study cohort having more exposure to any IL1 inhibitor (also specifically to anakinra and canakinumab), tocilizumab,

infliximab, intravenous immunoglobulin (IVIG), high-dose methylprednisolone pulse treatments, cyclophosphamide and cyclosporine.

Pulmonary Disease Features

Pulmonary disease features in the study cohort are described in Table 3. Dyspnea on exertion and shortness of breath were the most common symptoms. Others included clubbing, cough and chest pain. Two patients had shortness of breath as their only symptom, and 3 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 (80%) after 2004. Sixteen (64%) of the patients had PAH, 5 (20%) AP and 7 (28%) ILD. Six had more than one diagnosis: 2 (PAH and ILD); 2 (PAH and AP); and 2 (AP and ILD). There were no clinical features that distinguished the specific pulmonary diagnoses. The following diagnostic tests were performed: EKG (8 abnormal/19 performed), chest x-ray (15/21), echocardiogram (18/24), chest CT (18/20), pulmonary function tests (13/13), cardiac catheterization (9/10), and lung biopsy (11/12). Seventeen (68%) patients died within a mean of 8.8 ± 11.36 months from diagnosis of their pulmonary disease. Seven of these patients also had a serious infection at around the time of death. The remaining 9 patients have survived for a mean of 56.2 ± 35.3 (range 16–106) months from diagnosis of their pulmonary disease as of June 15, 2012.

Concomitant features of sJIA

Twenty-three (92%) patients had systemic features at the time of pulmonary diagnosis (Table 3), including fever (15 patients), rash (7), serositis (6), lymphadenopathy (6), hepatomegaly (11), and splenomegaly (12). One patient had thrombotic thrombocytopenic purpura. Fifteen (60%) patients had suspected or confirmed MAS at the time of pulmonary disease diagnosis. All fulfilled the Ravelli preliminary criteria for MAS [28]. Five of these patients also had tissue confirmation of MAS: 2 had hemophagocytosis on bone marrow biopsy, 1 on lung biopsy, 1 on myocardial biopsy, and 1 had iron-laden macrophages in the bronchial alveolar 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 time of onset of pulmonary symptoms

Seventeen (68%) patients had been exposed to one or more biologic disease modifying anti-rheumatic drug (DMARD) at the time of pulmonary symptoms onset (Table 4). An IL1 inhibitor (primarily anakinra) was the most common biologic DMARD with 12 (48%) patients either taking an IL1 inhibitor or having recently (<1 month) discontinued it (n=3) at the time pulmonary symptoms developed. The other biologic DMARDs included TNF inhibitors (12%) and tocilizumab (8%). Twenty-one (84%) patients were taking more than one medication 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: one was taking a combination of TNF and IL1 inhibitors and 2 had been exposed to an IL1 and IL6 inhibitor within one month of the other. However, there was no consistent pattern of medication combination exposures among the patients.

Discussion

Although rare isolated case reports of PAH, AP and ILD in sJIA and AOSD have been published [22–27, 29, 30], the findings in this study indicate that these complications may occur more commonly than previously suspected and is fatal in the majority of patients. PAH, ILD and AP are all processes in which inflammation likely has an important role. For example, PAH pathological specimens display 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]. In addition, C-reactive protein has been shown to be increased in patients with PAH and correlates with 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 IL1 beta, IL6 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 morphogenic protein receptor type II (BMPR2); reduced expression of BMPR2 is associated with endothelial cell dysfunction and with the development of PAH [39–41]. IL6, which is increased in sJIA patients with active systemic features [42–44], decreases the expression of BMPR2 in vitro. Therefore, increased IL6 levels characteristic of active sJIA may contribute to the development of PAH in these individuals.

Of interest is the fact that 96% of patients developed these complications after 2000 (and 80% after 2004), since biologic DMARDs (especially IL1 inhibitors) became much more commonly used for sJIA in the mid-2000's. Sixty-eight % of these patients were taking a biologic DMARD (most commonly an IL1 inhibitor) at the time of the development of pulmonary symptoms and had increased likelihood of ever being exposed to biologics, especially IL-1 inhibitors, compared to the CARRA registry cohort. When 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 study cohort's increased exposure to biologics was simply due to these patients having been diagnosed more recently. These facts raise a concern regarding a possible causal relationship between exposure to these medications and the development of these complications.

Although the biologic most frequently used by the study cohort was anakinra, having been used by 80% of patients compared to 43% in the CARRA registry ($p<0.001$), other biologics 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 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 presented on the pediatric rheumatology listserv. Tocilizumab has come into much more common usage since it was approved for use in sJIA by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2011, so the incidence of such events should be closely monitored through systematic post-marketing

studies. Similar surveillance of patients exposed to canakinumab should also be conducted, since this drug is also likely to receive a similar indication by regulatory agencies. Lastly, anakinra is currently the most commonly used biologic for systemic JIA even though it has not been specifically studied in this population and does not have a post-marketing 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 sJIA patients whether or not there is a post-marketing requirement of a specific medication.

It is also clear that most of the study patients had severe systemic disease which likely resulted in increased medication exposures when compared to the CARRA registry cohort, including pulse IV corticosteroids, cyclophosphamide and cyclosporine as well as biologic DMARDs. Many of these patients had active systemic features, including MAS, at the time of pulmonary disease diagnosis, so it seems likely that systemic inflammatory disease severity played an important role in their pathogenesis. In fact, two 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 complications: systemic features in the study cohort appear 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, are also much higher than expected in the study cohort, although adequate comparison is not possible because the frequencies of these features were not collected in the CARRA registry population. Both IL1 inhibitors [13, 14, 17, 45–48] and anti-IL6 antibody (tocilizumab) have been found to be highly effective in sJIA [15, 49, 50]. It remains to be seen whether effective treatments, including IL1 and IL6 inhibition, will reduce the incidence of these complications in these patients, rather than being a possible causative factor.

It will be important to understand the epidemiology and pathophysiology of these adverse events and their relationship to medication exposure as well as disease severity, because sJIA 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 [51]. Traditional single product Phase IV registries will not be useful in understanding whether specific medication exposures lead to these adverse events, because they are rare occurrences in a rare disease. A consolidated disease registry in which all patients with sJIA are enrolled regardless of medication exposure would be the ideal vehicle to capture such information [52]. Such a registry would have the advantage of being able to prospectively identify and follow a large cohort of sJIA patients taking different medications over extended periods of time. In this way, the frequency of these complications in these patients and their association with specific medication exposures could be captured and analyzed efficiently and accurately, taking into account confounders such as disease severity.

Limitations of this study include its retrospective design and possible reporting and recall bias. There is heightened recent awareness of these complications as well as improved ability to diagnose them. Despite this 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. Lastly, the comparator CARRA registry cohort data is a cross-sectional convenience sample of sJIA patients followed at the 52 CARRA registry sites. It is one of the largest contemporary cohorts of JIA patients currently available, but may not reflect an accurate sampling of typical sJIA patients.

Despite recent advances in therapy, sJIA remains a disease with significant morbidity and mortality. This is the first time that a large cohort of sJIA patients who developed PAH, AP and ILD has been described. These are important but under-recognized complications of sJIA which 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 complications. Increased awareness regarding these complications in sJIA is needed, and screening for these complications should be considered in sJIA patients with significant and persistent systemic disease activity.

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Appendix

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Significance and Innovations

- Serious pulmonary complications are being reported with increased frequency in systemic JIA (sJIA) patients and are frequently fatal
- The characteristics of these pulmonary complications, disease features and medication exposures of affected patients need to be studied
- This study uses sJIA patients enrolled in the CARRA Registry as a comparator group, which is the largest known database of JIA patients in the world
- Affected patients have increased severity of systemic disease and more exposure to medications, especially biologic agents

Table 1

Patient demographics and sJIA disease characteristic

	Study Cohort n=25 (%)	CARRA Registry Cohort n=389 (%)**	P Value
Age at sJIA diagnosis Mean ± SD (range)	7.4 ± 5.5 (1.1 – 17.2)	5.8 ± 4.3 (0.2 – 15.9)	NS*
Disease duration (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
Caucasian	17 (68)	302 (78)	
Black	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 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
Hepato/Splenomegaly	20 (80)	102 (31)	<0.001
Serositis	14 (56)	Unknown	NA
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)	

* NS: not significant means P>0.05

** The sum of all frequencies may not be equal to total sample size due to missing values.

At the time of pulmonary diagnosis

NA: Not applicable

Table 2

Medications used during disease course

Medication	Study Cohort n=25 (%)	CARRA Registry Cohort n=389 (%)	P Value
Biologic DMARDs			
Abatacept	2 (8)	19 (6)	NS*
IL1 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
Non-biologic DMARDs		NR	
Mycophenolate	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	

NR = Not reported; IVIG = intravenous immunoglobulin; DMARD = disease modifying anti-rheumatic drug

* NS: not significant with P> 0.05

Table 3

Clinical features at pulmonary disease diagnosis

Total N: 25	
Age at start of pulmonary symptoms (years)*	11.7 ± 5.2 (3.5–18.8)
Disease duration at pulmonary diagnosis (months [mos])*	50.6 ± 44.6 (8–160)
Time between pulmonary symptoms to diagnosis (mos)*	3.1 ± 3.2 (0–10)
Time between pulmonary diagnosis to death (mos) (N=17)*	10.2 ± 13 (0–44)
Disease features at pulmonary disease diagnosis	N (%)
sJIA manifestations	
Any systemic manifestation**	23 (92)
MAS (suspected or confirmed)	15 (60)
Pericarditis/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 artery hypertension	16 (64)
Alveolar proteinosis	5 (20)
Interstitial lung disease	7 (28)

* Mean ± SD (range)

** Includes patients with one or more of the following: fever, rash, lymphadenopathy, hepatomegaly, splenomegaly

Table 4

Medications at time of development of pulmonary symptoms*

Medication	Number of patients	Mean exposure in months ± SD (range)
Corticosteroids	24	47.3 ± 48.2 (3–161)
Cyclosporine	7	6.3 ± 7.3 (1–22)
Etoposide	1	1
Gold	1	53
Methotrexate	13	32.9 ± 38.2 (1–126)
Thalidomide	1	22
IL1 inhibitor (any)	12	15.1 ± 15.0 (3–47)
Anakinra	10	16.9 ± 15.9 (3–47)
Canakinumab	1	6
Rilonacept	1	6
TNF inhibitor (any)	3	17.0 ± 13.1 (2–26)
Adalimumab	2	12.5 ± 14.9 (2–23)
Etanercept	1	26
Tocilizumab	2	6.0 ± 7.1 (1–11)

* Or discontinued within a month prior to symptoms

SD = standard deviation