Exploring the development and long-term outcomes of SJIA-related lung disease in pediatric patients

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Introduction

Overview of Systemic Juvenile Idiopathic Arthritis (SJIA)

- Chronic autoinflammatory disease of childhood onset, representing 10-15% of the total juvenile idiopathic arthritis (JIA) population
- Characterized as arthritis accompanied by daily spiking fevers, a fleeting erythematous rash, and various extraarticular features
- Standard treatment utilizes a combination of NSAIDS, corticosteroids, immunosuppressants (i.e. methotrexate), and more recently, biologics targeted at the neutralization of key inflammatory cytokines interleukin-1 (anakinra and canakinumab) and interleukin-6 (tocilizumab) elevated in SJIA

Complications of SJIA

Macrophage Activation Syndrome (MAS)

- A serious episode of hyperinflammation, developing in approximately 10-15% of SJIA patients, that can lead to widespread hemophagocytosis, cytokine overproduction (including IFNγ), liver dysfunction, and coagulopathy

Chronic interstitial lung disease (SJIA-LD)

- Previously uncharacterized inflammatory LD with distinct clinical and immunologic features, whose development has only recently been recognized in association with SJIA
- Incidence has increased markedly in parallel with the widespread use of cytokine-directed biologic therapy
- Disease course, currently affecting as many as 1 in 20 SJIA patients, exhibits high morbidity and mortality

Objectives

This study aims to look at the following:

- Treatment/management strategies for SJIA patients after lung disease diagnosis
- Prognostic predictors for SJIA-LD patients who exhibit poor outcomes
- Long-term outcomes for SJIA-LD patients in terms of morbidity and mortality

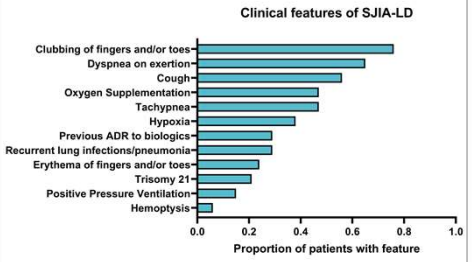
Study population and design

- Prospective cohort study of 34 patients were identified based on the following criteria:
  - **Suspected SJIA-LD**: either of the following, not due to lung disease that preexisted SJIA diagnosis, infection, or other identifiable cause: (1) *objective findings on clinical exam* (including but not limited to tachypnea, cough, or clubbing); (2) *diffuse abnormalities on chest imaging*
  - **Probable SJIA-LD**: *both clinical findings and chest imaging findings* as above; OR *pulmonary hypertension* as measured by echocardiogram
  - **Definite SJIA-LD**: *tissue biopsy* consistent with interstitial lung disease, pulmonary alveolar proteinosis/endogenous lipoid pneumonia, and/or pulmonary artery hypertension
- Clinical data were abstracted from patient medical records
- Study was approved by CCHMC IRB, and written informed consent was obtained from all patients and/or their legal guardians

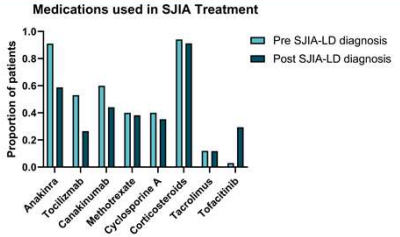
Clinical Findings and Features of SJIA-LD

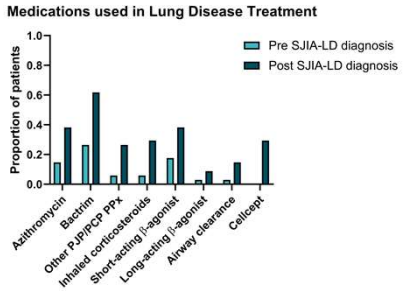
Median age at SJIA diagnosis	Median age at SJIA-LD diagnosis
1.7 years	3.6 years

Number of patients with:		
Suspected SJIA-LD	Probable SJIA-LD	Definite SJIA-LD
6	16	13



Use of SJIA and Lung Disease Medications





Chest CT Findings

Features on Baseline Chest CT	Proportion of total patients	Proportion requiring O_2 supplementation
Pleural thickening	0.353	0.33
Septal thickening	0.647	0.45
Bronchial/peri-bronchovascular thickening	0.382	0.46
Tree-in-bud opacities	0.118	0.50
Ground-glass opacities	0.382	0.62
Peripheral consolidation	0.235	0.38
Lymphadenopathy	0.412	0.43
Pulmonary artery enlargement	0.059	0.50
Average # of features per patient	3	

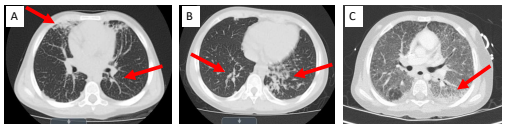


Figure 1. High resolution chest computed tomography images of the lungs of children with systemic juvenile idiopathic arthritis with lung disease. **A**, Focal areas of pleural thickening with associated interlobular septal thickening. **B**, Bronchovascular centric tree in bud opacities. **C**, Ground glass opacities with superimposed interlobular septal thickening resulting in "crazy paving" pattern and peripheral areas of consolidation. **Arrows** indicated affected areas.

Overall Survival and Survival Free of Supplemental O_2

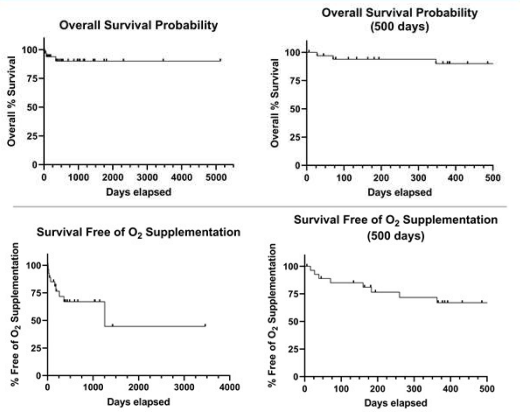


Figure 2. Kaplan-Meier curves of overall survival and O_2 suppl. free survival for total elapsed time and for first 500 days. For both curves, the start date was recorded as date of first abnormal chest CT suspected for lung disease. For overall survival, the end date was recorded as date of last known follow-up or date of death. For O_2 suppl. free survival, the end date was recorded as the date suppl. O_2 was initiated after the first abnormal CT suspected for lung disease or date of last known follow-up for patients who have never required supp. O_2.

Conclusions

- Median age at SJIA diagnosis is 1.7 years and median age at SJIA-LD diagnosis is 3.6 years.
- Most predominant clinical features of SJIA patients at lung disease diagnosis are clubbing, dyspnea, cough, tachypnea, and supplemental oxygen requirement.
- Overall use of the three main biologics for SJIA treatment (ANA, TCZ, CAN) decreased post SJIA-LD diagnosis, while use of the JAK inhibitor tofacitinib increased post SJIA-LD diagnosis. Use of methotrexate, cyclosporine A, corticosteroids, and tacrolimus post SJIA-LD remained comparable to use prior to lung disease diagnosis
- Usage of medications primarily used in the treatment of lung disease increased post SJIA-LD diagnosis.
- Most common feature seen on baseline chest CT for patients diagnosed with SJIA-LD is septal thickening. However, the features with the greatest proportion of patients requiring O2 supplementation are ground-glass opacities, tree-in-bud, and PA enlargement.
- While overall survival is ~90%, there is a steady increase in the proportion of patients requiring home oxygen in the first 500 days. In total,15 out of the 34 patients required supplemental oxygen, with all but 1 patient requiring supplemental oxygen within the first 500 days.

Future Directions

- To track long-term disease outcomes by sending out periodic follow-up surveys for patients who were referred to CCHMC for consultation or secondary opinion and are regularly followed by an outside primary rheumatologist and/or pulmonologist.
- To elucidate the underlying biological mechanism and pathogenesis of SJIA-LD. Previous studies showing differences in the cytokine profile of children with SJIA-LD compared to those without lung disease, such as elevated IL-18, IFNγ pathway activation, and T cell function, suggest that there exist distinct activated cell subsets and cell states associated with SJIA-LD.
- Further characterization of the specific activated immune subsets in patients with SJIA-LD will help better define patients at risk for this LD as well as establish strategies to screen for early onset.

Acknowledgements

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