Sinha *et al. Pediatric Rheumatology* 2023, **21**(Suppl 1):91
https://doi.org/10.1186/s12969-023-00863-2

Pediatric Rheumatology

INTRODUCTION **Open Access**

Proceedings from the 4th NextGen Therapies for SJIA and MAS virtual symposium held February 13–14, 2022

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From 4th NextGen Therapies for SJIA and MAS virtual symposium
Virtual. 16-18 February 2022. https://www.systemicjia.org/nextgen22/

Introduction

Refractory Systemic Juvenile Idiopathic Arthritis (SJIA) remains a major source of morbidity and mortality in children with pediatric rheumatic disease [1, 2]. Although several potential therapeutic targets have been recently identified, only few patients have been enrolled in ongoing clinical trials. The 4th"NextGen Therapies for SJIA and MAS" virtual symposium organized by the "SJIA Foundation" and held February 13–14, 2022, brought together SJIA families, leading researchers, clinicians and representatives from Pharma and FDA with the main goals to identify barriers to clinical research in this area and develop new strategies to advance it.

Systemic Idiopathic Arthritis (SJIA; estimated U.S. prevalence of 1:10,000 children) is the most severe subtype of chronic childhood arthropathy, notable for marked systemic immune activation with features of autoinflammation, and development of severe joint damage [2–6]. The licensing of IL-1 and IL-6-blocking monoclonal antibodies in 2012 resulted in superior control of SJIA-associated arthritis and systemic manifestations [7–11]. However, despite the use of these biologic disease modifying antirheumatic medications (b-DMARDs) about 15% of patients with SJIA develop macrophage activation syndrome (MAS), i.e. potentially fatal episodes of systemic hyperinflammation that are associated with hemophagocytosis [5, 6, 12, 13]. Furthermore, since the licensing of these b-DMARDs, children with SJIA (~5% in 2020) have increasingly been diagnosed with life-threatening chronic parenchymal lung disease (SJIA-LD) [14–16]. This has prompted speculations that drugs blocking IL-1 and/or IL-6 might contribute to the development of SJIA-LD [16]. Given high mortality and frequent need for hospitalization, there is an urgent need for life-saving treatments for SJIA-LD and MAS.

Translational research identified IFN-γ as the pivotal cytokine in MAS [6, 17–19] and Phase II clinical trials are in progress [20]. In contrast, the nature of the SJIA-associated lung disease remains elusive, and potential therapeutic targets in this disease still need to be defined. The typical histopathology of SJIA-LD includes (a) extensive lymphoplasmacytic inflammatory infiltrates in the lung interstitial tissue; (b) organizing pneumonia; (c) pleural and interlobular septal collagenous fibrosis; (d) vasculopathy associated with muscular mural thickening of the pulmonary arteries; and (e) alveolar inflammation with accumulation of foamy *alveolar macrophages* with some features of pulmonary alveolar proteinosis (PAP) [15, 16].

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Features of PAP typically result from dysfunction of *alveolar macrophages* leading to accumulation of pulmonary surfactant in alveolar space, and it has been suggested that there may be acquired *alveolar macrophages* dysfunction in SJIA-LD.

Recent studies suggested potential risk factors for SJIA-LD: (a) SJIA onset under age 2 years with predominantly systemic features and limited arthritis, (b) recurrent MAS episodes, (c) anaphylaxis-like reactions to b-DMARDs, (d) highly pruritic rash associated with peripheral eosinophilia, (e) highly elevated serum IL-18 levels, and (f) and HLA DRB1*15 alleles [15, 16]. Gene expression profiling in SJIA-LD lung tissue revealed strong IFN-induced signature and numerous markers of T cell activation (predominantly Th1) [15]. Further, murine experiments showed that T-cell restricted overexpression of T-bet, a master transcription factor that drives production of the hallmark Th1 cytokine IFN- γ induces dysfunction of bone marrow macrophages, resulting in erythrophagocytosis locally, and *alveolar macrophages* dysfunction with the development of PAP-like lung pathology [21]. Together this suggests that either MAS alone or when combined with IL-1 or IL-6 blocking b-DMARDs contribute to the development of SJIA-LD. Alternative possibilities include environmental factors like infections that could be favored by inhibition of IL-1 and IL-6 with biologics. Marked differences in the prevalence of SJIA-LD in different geographic areas with similar patterns of utilization of b-DMARDS as well as large numbers of SJIA-LD cases reported in areas where b-DMARDs are not commonly used (China, India) support this hypothesis. Alternatively, high rate of anaphylaxis-like reactions as well as pruritic rash and peripheral eosinophilia observed in SJIA-LD patients point to the possibility of a delayed type hypersensitivity (DTH) reaction. The recently reported strong association between LD in SJIA and HLA DRB1*15 alleles, supports this hypothesis [22]. DTH may be driven by IFN- γ in response to either the monoclonal antibody (b-DMARD) itself or to the common excipient shared by these drugs (e.g., polysorbate). These possibilities create much apprehension among pediatric rheumatologists and families of children with SJIA worldwide whether anti-IL-1 and IL-6 b-DMARDs are truly safe for use in SJIA.

Further advancement of clinical studies focused on this patient population, however, has been hampered by the lack of agreement on whether SJIA patients with the lung disease should be classified as a separate diagnostic entity. In part, this is because arthritis is often absent in these patients while the systemic component of the disease seems more prominent compared to what has been historically seen in SJIA. As of now, the absence of arthritis in many of these patients precludes the definitive diagnosis of SJIA rendering them ineligible for existing clinical trials in this disease. Furthermore, the existing outcome measures typically used in clinical trials in SJIA are focused mainly on arthritis and do not fully capture the systemic component, specifically the lung disease.

Discussions around this topic at the 4th "NextGen Therapies for SJIA and MAS" virtual symposium are captured by Nigrovic, et al. in Part 1 of the Proceedings. Furthermore, the existing outcome measures typically used in clinical trials in JIA are focused mainly on arthritis and do not fully capture the systemic component, particularly the lung disease.

In Part 2, Drs. Grom and Schulert summarized further discussions that defined emerging distinct clinical patterns of refractory SJIA. Considering the life-threatening nature of MAS and SJIA-LD, traditional placebo controlled/withdrawal design clinical trials may not be ethically acceptable in these patient populations.

In Part 3, Dr. Fabrizio de Benedetti summarized discussions focused on alternative designs that could be acceptable to clinicians, parents, and regulatory authorities.

Since strikingly high of serum IL-18 levels appear to be a unifying feature of various subgroups of refractory SJIA, Dr. Canna and colleagues explored the possibility of incorporation this biomarker as an inclusion criterion and measure of treatment response to a drug candidate (Part 4).

In the meantime, the patients with refractory SJIA continue to experience not only high mortality but also profound disease- and medication-related morbidities that lead to permanent tissue damage, with long lasting detrimental effects on all aspects of the child's quality of life. The degree of immunosuppression needed in most of these patients is unlikely to be sustainable in the long term due to increased risk of infection and malignancy. As the optimal drug management of SJIA-LD remains elusive, hematopoietic stem cell transplantation (HSCT) has emerged as a potential alternative strategy in the interim. In Part 5, Dr. Silva and colleagues reviewed the growing experience with HSCT specifically for patients with SJIA and summarized the discussion about the technical aspects, optimal timing and preliminary outcomes for several patients who underwent HSCT. This description includes patients who have not been previously reported.

Abbreviations

b-DMARDs	Biologic disease-modifying anti-rheumatic drug
DTH	Delayed type hypersensitivity
HSCT	Hematopoietic stem cell transplantation
IFN-γ	Interferon Gamma
IL	Interleukin
LD	Lung disease
MAS	Macrophage activation syndrome

PAP Pulmonary alveolar proteinosis
SJIA Systemic Juvenile Idiopathic Arthritis

Acknowledgements
Not applicable.

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About this supplement
This article has been published as part of *Pediatric Rheumatology Volume 21 Supplement 1, 2023: Proceedings from the 4th NextGen Therapies for SJIA and MAS virtual symposium*. The full contents of the supplement are available online at https://ped-rheum.biomedcentral.com/articles/supplements/volume-21-supplement-1.

Authors' contributions
All authors participated in the meetings' discussions and were involved in the preparation of the manuscript. The final version was reviewed by all authors.

Funding
Funding for the symposium was provided by the SJIA Foundation. Publication costs have been covered by the SJIA Foundation. The SJIA Foundation did not have any direct influence on the research and results being presented.

Availability of data and materials
All the data discussed during the meeting have now been published and appropriately referenced at the end of the manuscript.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors have reviewed the manuscript and provided their consent to publish. All the patients mentioned in the manuscript gave their permissions to use full names.

Competing interests
RS has no conflicts of interest or competing interests to declare. FDB has received research grants from SOBI, Novartis, Roche, Sanofi, consultancies from Sobi, Novartis, Roche. AAG received research grants from Novartis and SOBI; consulting fees from Novartis and SOBI; royalties from UpToDate Inc. and payment for development of CME slide presentation on MAS from Clinical Viewpoints.

Accepted: 26 July 2023
Published: 5 January 2024

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