Clinical Characteristics and Treatment Outcomes of Idiopathic Multicentric Castleman Disease: Data from a Pediatric Cohort

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Introduction

- Idiopathic multicentric Castleman disease (iMCD) is a rare, atypical lymphoproliferative disorder that involves diffuse lymphadenopathy and systemic inflammation leading to multi-organ dysfunction.
- Clinical presentation is heterogeneous – varying from mild/moderate (iMCD-NOS) to severe (iMCD-TAFRO), with Thrombocytopenia, Anasarca, Fever/Elevated C-Reactive Protein, Renal Dysfunction, Organomegaly.
- Though etiology remains unknown, the pro-inflammatory cytokine, interleukin-6 (IL-6), is a known driver of disease pathogenesis for many patients.
- Consensus guidelines to diagnose and treat iMCD have been established for this rare disease.
- Siltuximab, a monoclonal antibody antagonizing IL-6, is the only FDA-approved treatment for iMCD.
- The pediatric patient experience with iMCD has not been previously systematically investigated and siltuximab clinical trial excluded patients < 18 years.

Objectives

- Leverage real-world data from a longitudinal Castleman disease medical registry with external curation to better characterize pediatric iMCD.
- Identify treatments given to pediatric patients and assess the efficacy of siltuximab and various other iMCD therapies administered.

Methods

- We utilized ACCELERATE, a longitudinal Castleman Disease medical registry to identify patients <18 years at diagnosis.
- Complete medical history and lymph node biopsy slides were collected and extracted, and each case was adjudicated on the likelihood of iMCD diagnosis by a panel of experienced CD clinicians and hematopathologists.
- Demographic, clinical, and laboratory characteristics (±90 days from pathological diagnosis) were aggregated.
- Treatment history was inventoried, and responses were determined:
  - Clinical response was defined as at least 50% reduction in abnormal clinical and laboratory criteria.
  - Durable response was defined as a positive clinical response lasting ≥365 days with no intervening CD treatments.

Results

Most pediatric iMCD patients (84%) presented with the TAFRO clinical subtype with high disease burden

Table 1. Cohort characteristics

Sex, n (%)			
Males		14 (73.7)	
Females		5 (26.3)	
Age at diagnosis			
Mean (SD)		13.6 (4.3)	
Range		1.8 - 17.9	
Race, n (%)			
White		15 (78.9)	
Black/African American		2 (10.5)	
Asian		1 (5.3)	
Native Hawaiian/Pacific Islander		0 (0.0)	
American Indian/Alaska Native		0 (0.0)	
Other/Refused to Answer		1 (5.3)	
Histopathological subtype, n (%)			
Hyaline Vascular		0 (0.0)	
Hypervascular		17 (89.5)	
Mixed		2 (10.5)	
Plasmacytic		0 (0.0)	
Clinical subtype, n (%)			
iMCD-TAFRO		16 (84.2)	
iMCD-NOS		3 (15.8)	
Deceased, n (%)			
iMCD		2 (10.5)	
Clinical Minor Criteria	**Yes, n (%)**	**No, n (%)**	**NA**
Constitutional Symptoms	18 (94.7)	1 (5.3)	0
Fatigue	18 (94.7)	1 (5.3)	0
Night Sweats	11 (64.7)	6 (35.3)	2
Fever	18 (94.7)	1 (5.3)	0
Weight Loss	9 (47.4)	10 (52.6)	0
Organomegaly	19 (100.0)	0 (0.0)	0
Hepatomegaly	18 (94.7)	1 (5.3)	0
Splenomegaly	19 (100.0)	0 (0.0)	0
CD Skin Disorder	0 (0.0)	17 (100.0)	2
LIP	0 (0.0)	16 (100.0)	3
Fluid Retention	19 (100.0)	0 (0.0)	0
Proteinuria	10 (58.8)	7 (41.2)	2
Lab Minor Criteria, Mean (SD)			
CRP mg/L		166.5 (134.4)	
ESR mm/h		78.9 (49.5)	
Hemoglobin g/dL		9.1 (3.3)	
Platelets $10^3/\mu L$		124.2 (117.5)	
Albumin g/dL		2.6 (1.0)	
Creatinine mg/dL		1.5 (1.4)	
IgG mg/dL		967.7 (318.5)	
Gammaglobulin g/dL		0.7 (0.3)	

Most pediatric iMCD patients (83%) achieved a clinical response to the recommended first-line iMCD therapy, siltuximab ± corticosteroids

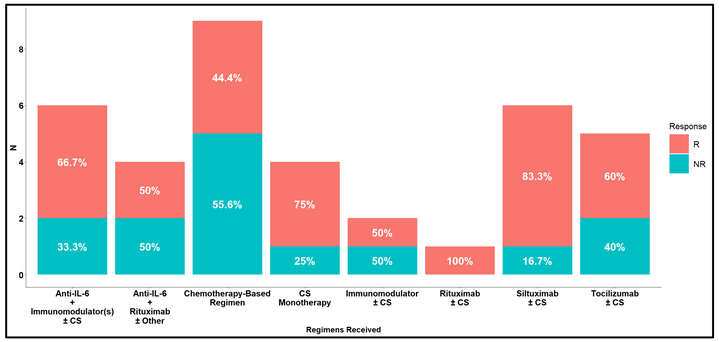

Figure 1. Regimens received and clinical response with assessable data for 19 pediatric iMCD patients.

Nine pediatric iMCD patients received siltuximab-inclusive regimens and six patients received siltuximab ± corticosteroids

Table 2. Siltuximab-inclusive regimens received by cohort

Siltuximab-inclusive regimens	n
Siltuximab +/- CS	
Siltuximab monotherapy	1
Siltuximab + CS	5
Siltuximab + Rituximab +/- Other	
Siltuximab + Rituximab + Sirolimus	1
Siltuximab + Rituximab + Sirolimus + Eculizumab + IVIg + CS	1
Siltuximab + Immunomodulator(s) +/- CS	
Siltuximab + Sirolimus	1
Siltuximab + Ravulizumab + CS	1
Siltuximab + Eculizumab + CS	1
Siltuximab + Eculizumab + IVIg + CS	1

60% of patients who received siltuximab ± corticosteroids achieved a durable response

Table 3. All regimens received and durable response assessment for patients in this cohort.

Regimens Received	Durable Response Yes, N (%)
Siltuximab ± CS	3/5 (60.0)
Tocilizumab ± CS	1/3 (33.3)
Rituximab ± CS	1/1 (100.0)
Chemotherapy-Based Regimen	2/4 (50.0)
Immunomodulator ± CS	1/1 (100.0)
Anti-IL-6 + Rituximab ± Other	1/2 (50.0)
Anti-IL-6 + Immunomodulator(s) ± CS	2/4 (50.0)
CS Monotherapy	1/3 (33.3)

Observable improvement in laboratory markers after siltuximab initiation in a pediatric iMCD patient

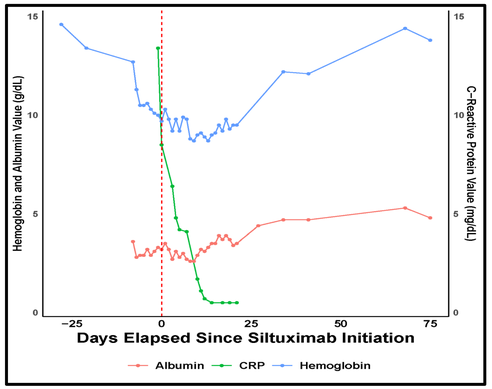

Figure 2. Laboratory markers evaluated around time of siltuximab initiation for a pediatric iMCD patient. Dashed vertical red line (t=0) indicates the start of siltuximab.

Conclusions

- A high disease burden was found within this population.
- A notable degree of TAFRO was observed with clinical manifestations and laboratory abnormalities commonly observed in adult iMCD also present within this cohort.
- A high response rate to siltuximab ± corticosteroids was observed in this cohort.
- Low numbers of patients limited generalizability of findings.
- Further research to investigate the effectiveness of siltuximab in a larger pediatric cohort is needed to identify optimal treatment approaches.

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