Pediatric Idiopathic Multicentric Castleman Disease Is Often Severe and Responds to Siltuximab

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Introduction

- Idiopathic multicentric Castleman disease (iMCD) is a potentially fatal hematologic disorder marked by widespread lymphadenopathy and inflammation.
- Siltuximab, an interleukin-6 (IL-6) inhibitor, is the only FDA-approved treatment, but not for pediatric patients where there is limited data on its use in this population
- We systematically characterized pediatric iMCD and treatment efficacy.

Methods

- 30 pediatric and 96 adult patients enrolled in the ACCELERATE Natural History registry where diagnoses were confirmed by an expert panel of physicians and pathologists.
- Disease severity was assessed with a modified CHA score [C-reactive protein (CRP), hemoglobin, albumin] within 90 days of diagnosis.
- Regimens were defined as treatments started within 2 weeks of each other and categorized into six groups: siltuximab ± corticosteroids (CS), tocilizumab ± CS, immunomodulator(s)±CS, anti-IL-6+immunomodulator±CS, chemotherapy ± other treatments, or CS monotherapy.
- Clinical response (≥50% decrease in the proportion of abnormal symptoms and laboratory measures after regimen initiation) and durable response (a clinical response where no new regimens were started within one year of the index regimen) were compared between pediatric and adult patients.

Table 1. Demographic Characteristics

	Pediatrics (n=30)	Adults (n=96)
Age at Symptom Onset, Years		
Median [Range]	15 [1-18]	40 [20-74]
Sex, n (%)		
Male	20 (67)	51 (53)
Race, n (%)		
White	24 (80)	58 (60)
Black/African American	3 (10)	12 (13)
Asian Indian	1 (4)	1 (1)
Asian	0	8 (8)
American Indian/Alaska Native	0	1 (1)
Pacific Islander	0	2 (2)
Other/Refused to Answer	2 (7)	9 (9)

Results

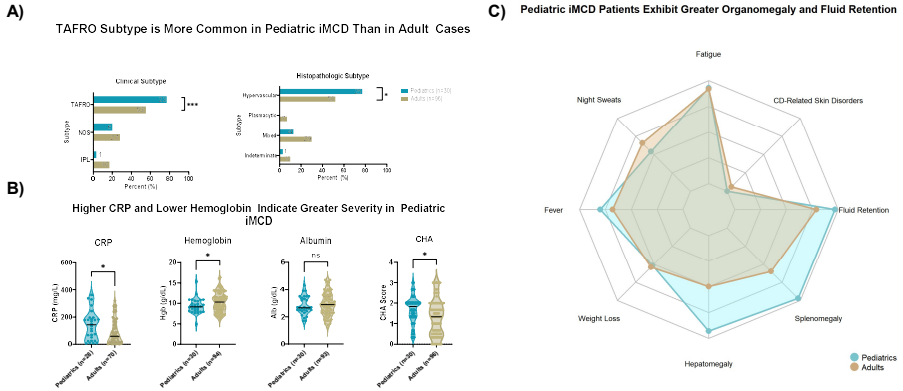

Figure 1. Pediatric iMCD Patients Experience More Severe Disease. A) The severe TAFRO subtype of iMCD (thrombocytopenia, anasarca, fever, renal dysfunction/reticulin fibrosis, organomegaly) was more prevalent in children (77% vs 55%, p<0.001). Hypervascular lymph node histology was more common in children compared to adults (83% vs 52%, p<0.05). B) Pediatric patients had higher CHA scores at diagnosis (1.67 vs 1.31, p<0.05), indicating greater disease severity, due to worse anemia (Hgb 9.3 vs 10.2 g/dL, p<0.05) and higher CRP (138.3 vs 89.1 mg/L, p<0.05). C) Pediatric patients had higher rates of organomegaly (hepatomegaly: 93% vs 50%,p<0.001 , and splenomegaly: 97% vs 60%, p<0.001) and fluid retention (97% vs 79%, p<0.05) compared to adults.

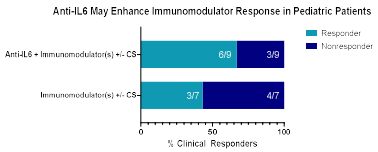

Figure 3. The Addition of IL6 Blockade May Improve Response in Pediatric patients. A higher proportion of pediatric patients achieving clinical response was observed in those treated with the combination of anti-IL6 and immunomodulator compared with immunomodulator monotherapy.

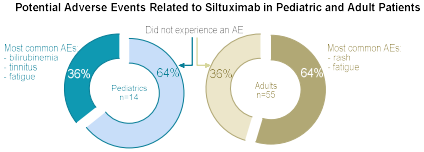

Figure 4. Adults have a higher rate of potentially medication-associated adverse events with siltuximab.

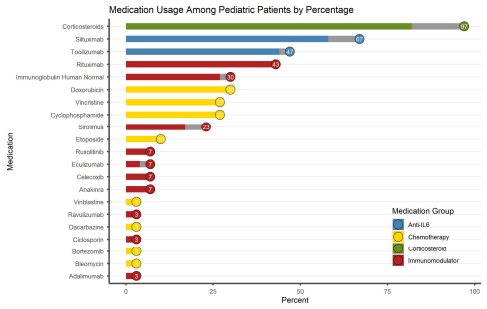

Figure 2. Pediatric iMCD Patients Try a Variety of Medications. Pediatric iMCD is treated with a variety of medications, including anti-IL6 therapies, chemotherapy, corticosteroids, and immunomodulators (sirolimus, ruxolitinib, anakinra, lenalidomide, eculizumab, etc.). Patients could have received more than one therapy (concomitant or sequential) during the observation period. Proportion of monotherapy regimens displayed in gray.

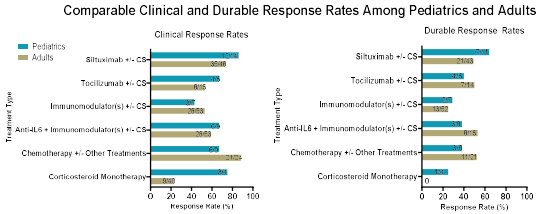

Figure 5. Pediatric iMCD Patients Respond Similarly to iMCD Therapies. Both clinical response rates and durable clinical response rates were similar between children and adults across all treatments, with no significant differences, indicating that pediatric patients respond to iMCD therapies similarly as adults. However, we did observe trends of improved response rates to anti-IL6 therapies and worse response rates with corticosteroid monotherapy.

Discussion

- In the largest pediatric iMCD analysis to date, we found pediatric patients to have more severe disease with higher CHA scores and more TAFRO cases than in adults.
- We observed similar high response rates to siltuximab in children compared with adults.
- Since the phase 2 siltuximab trial excluded children and had few TAFRO cases, these results are reassuring with no new safety concerns.
- Despite being the largest, best-validated pediatric iMCD cohort to date, findings should be interpreted with caution due to the registry's observational, non-randomized, non-controlled design, and small sample size in some subsets.
- No new safety concerns were identified.
- Further investigation and longer follow up is needed on a larger cohort of pediatric iMCD patients.

Acknowledgements

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