Longitudinal, real-world data reveal treatment effectiveness in idiopathic multicentric Castleman disease and support current treatment guidelines

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Introduction

- Idiopathic multicentric Castleman disease (iMCD) is an immunologic disorder with unknown etiology that is diagnosed in approximately 1200 individuals in the US annually.[1]
- Presentation is heterogeneous – ranging from mild/moderate constitutional symptoms to severe multi-organ dysfunction.
- Treatment guidelines were developed by an international expert panel in 2018 based on the review of a limited number of clinical trials and small case series.[2]
- Siltuximab, a monoclonal antibody against interleukin-6 (IL6) approved for the treatment of iMCD, is recommended first-line based on evidence from its phase II trial.[3]
- High-dose steroids and cytotoxic chemotherapy are recommended for patients with severe disease who progress on anti-IL6 therapy.
- For patients with mild/moderate disease not responding to IL6 blockade, rituximab +/- immunomodulators is recommended.
- While concurrent steroids are recommended in some cases, steroid monotherapy is discouraged.

Objective

- Limited real-world data exist on treatment patterns and effectiveness of therapies used to treat iMCD.
- Herein, we evaluate treatment regimens administered to a cohort of 88 iMCD patients with longitudinal treatment and response data.

Methods

- A panel of experts reviewed and confirmed the diagnosis for 88 iMCD patients enrolled in the ACCELERATE natural history registry.
- Real-world data, including longitudinal treatment and response data, were abstracted from patient medical records.
- Treatment regimen was defined as a single treatment or a combination of treatments initiated ≤2 weeks of one another.
- Durable treatment response was defined as the best response according to the change in the proportion of abnormal clinical/ laboratory criteria and no change in treatment for at least 1 year.
- Severity at the time of treatment initiation was defined as at least 2 of the following: renal failure, fluid accumulation, severe anemia, pulmonary involvement, or hospitalization.
- Time-to-next-treatment was used as a proxy for treatment failure. A survival analysis was performed on siltuximab +/- corticosteroids (CS), tocilizumab +/- CS, rituximab +/- CS, chemotherapy +/- maintenance, and steroid monotherapy.
- Log rank test was used to determine differences across treatment regimens, and pairwise comparisons were Bonferroni corrected.

Results

- Cohort demographics are summarized in Table 1.
- A total of 278 regimens were administered across the cohort (Fig. 1).

Figure 1: Regimen timeline presented for each respective patient.

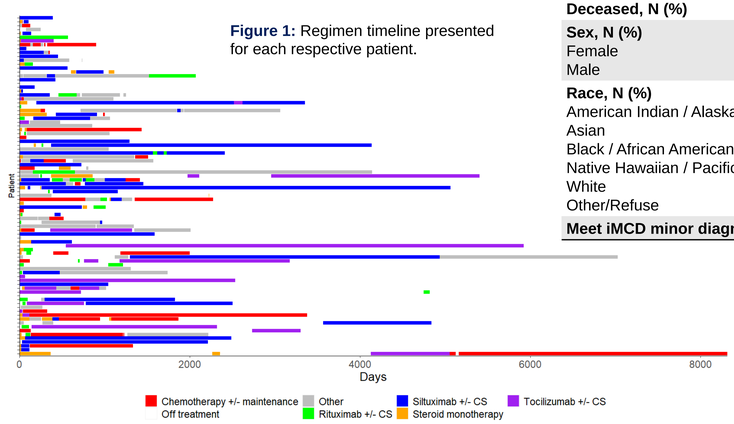

Table 1.	N=88
Age at diagnosis	
Mean (SD)	36.0 (16.1)
<18, N (%)	15 (17.0)
Deceased, N (%)	8 (9.1)
Sex, N (%)	
Female	42 (47.7)
Male	46 (52.3)
Race, N (%)	
American Indian / Alaska Native	1 (1.1)
Asian	10 (11.4)
Black / African American	10 (11.4)
Native Hawaiian / Pacific Islander	1 (1.1)
White	58 (65.9)
Other/Refuse	8 (9.1)
Meet iMCD minor diagnostic criteria, N (%)	84 (95.0)

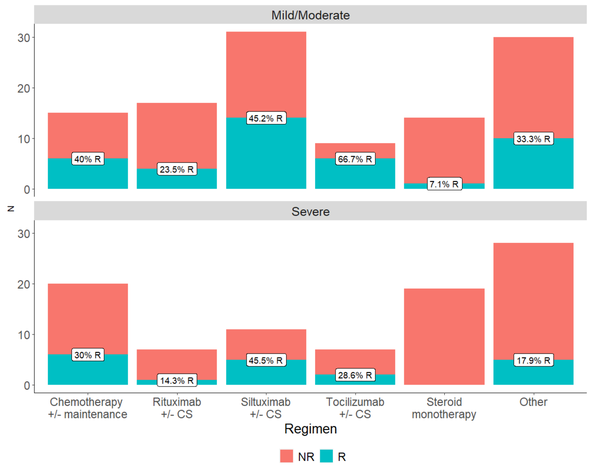

Figure 2: Durable response by patient stratified by severity. Includes regimens with evaluable severity and response data.

- 55% (22/40) of patients who received siltuximab +/-CS and had an evaluable response achieved durable response (Table 2).
- Steroid monotherapy was significantly less likely to induce a durable response than siltuximab +/- CS (p=0.02).
- Response rates on a per patient level are no different when regimen is started in severe disease (p=0.08) (Fig. 2).
- We also found that the treatment regimen significantly predicts time-to-next-treatment (p<0.0001, Fig. 3).

Table 2.	Responded / Evaluable (%)
Siltuximab +/- CS	22/40 (55%)
Tocilizumab +/- CS	8/17 (47%)
Rituximab +/- CS	6/24 (25%)
Chemotherapy +/- maintenance	11/21 (52%)
Steroid monotherapy	1/33 (3%)

- Siltuximab +/-CS, tocilizumab +/-CS, and chemotherapy +/- maintenance each have a significantly longer time-to-next-treatment compared with steroids (p<0.05).
- Siltuximab +/- CS also had a significantly longer time-to-next-treatment than rituximab +/- CS (p=0.02).
- There were no other differences between regimens.

Figure 3: Survival plot stratified by treatment regimen category. Time-to-next-treatment is significantly affected by treatment category.

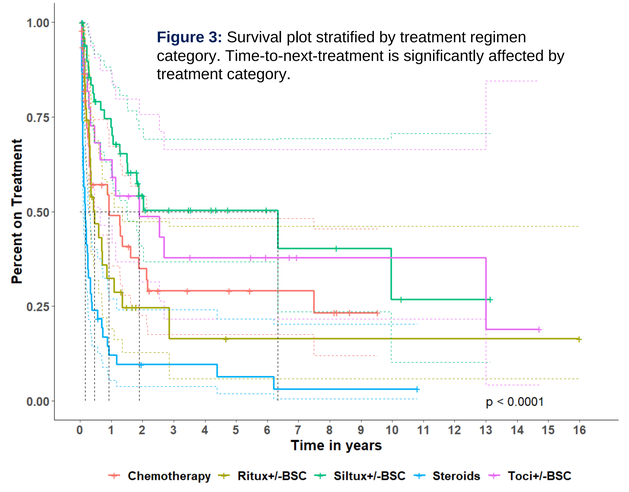

Table 3	Median Time-to-next-treatment, days [95% CI]
Siltuximab +/- CS	2316 [554, No Upper Limit]
Tocilizumab +/- CS	689 [234, No Upper Limit]
Rituximab +/- CS	166 [116, 495]
Chemotherapy +/- maintenance	338 [110, 791]
Steroid monotherapy	61.5 [36, 98]

Conclusions

- This is the first systematic assessment of iMCD treatment regimens since the 2018 published guidelines.
- We found differences in durable response rates and in time-to-next-treatment between regimen approaches.
- This cohort includes the largest reported proportion of siltuximab-treated patients with severe disease. Patients in mild/moderate disease and severe disease demonstrated a similar response to siltuximab.
- Our results support current recommendations to administer siltuximab first-line and limit steroid monotherapy.
- These results also demonstrate that additional agents are needed for refractory patients, who have few options and are at risk of death due to progression.

References

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