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.

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.](image)

Table 1

| Table 1. | N=88
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Age at diagnosis</td>
<td>Mean (SD) 36.0 (16.1)</td>
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<tr>
<td>&lt;18, N (%)</td>
<td>15 (17.0)</td>
</tr>
<tr>
<td>Decreased, N (%)</td>
<td>6 (7.1)</td>
</tr>
<tr>
<td>Sex, N (%)</td>
<td>Female 42 (47.7) Male 46 (52.3)</td>
</tr>
<tr>
<td>Race, N (%)</td>
<td>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 Race 1 (1.1) Missing 11 (12.6)</td>
</tr>
<tr>
<td>Meet IMCD minor diagnostic criteria, N (%)</td>
<td>84 (95.5)</td>
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![Figure 2: Durable response by patient stratified by severity. Includes regimens with evaluable severity and response data.](image)

• 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 per patient level are not 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).

![Figure 3: Survival plot stratified by treatment regimen category. Time-to-next-treatment is significantly affected by treatment category.](image)

Table 2

<table>
<thead>
<tr>
<th>Table 2</th>
<th>N=88</th>
<th>Median Time to next treatment, days [95% CI]</th>
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<tr>
<td>Siltuximab +/-/CS</td>
<td>239 (157, 324)</td>
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<tr>
<td>Tocilizumab +/-/CS</td>
<td>689 (234, No Upper Limit)</td>
<td></td>
</tr>
<tr>
<td>Rituximab +/-/CS</td>
<td>338 (110, 791)</td>
<td></td>
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<tr>
<td>Steroid monotherapy</td>
<td>61.3 [36, 98]</td>
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</table>

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

4. Contact: Sheila.Pierson@pennmedicine.upenn.edu This study was funded by EUSA-RECORDATI.