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American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

Treatment Consistent with Idiopathic Multicentric Castleman Disease Guidelines is Associated with Improved Outcomes

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Sheila Pierson (University of Pennsylvania, United States) Megan Lim (Memorial Sloan Kettering Cancer Center, United States) Gordan Srkalovic (Herbert-Herman Cancer Center, United States) Joshua Brandstadter (University of Pennsylvania, United States) Mateo Sarmiento Bustamante (University of Pennsylvania, United States) Saishravan Shyamsundar (University of Pennsylvania, United States) Natalie Mango (University of Pennsylvania, United States) Criswell Lavery (University of Pennsylvania, United States) Bridget Austin (University of Pennsylvania, United States) Daisy Alapat (UAMS, United States) Mary Jo Lechowicz (Emory University Winship Cancer Institute, United States) Adam Bagg (University of Pennsylvania, United States) Honzhe Li (University of Pennsylvania,) Corey Casper (AAHI, United States) Frits Van Rhee (University of Arkansas for Medical Sciences, United States) David Fajgenbaum (Raymond and Ruth Perelman School of Medicine, University of Pennsylvania, United States)

Abstract:
Idiopathic multicentric Castleman disease (iMCD) is a hematologic disorder with an unknown etiology that is diagnosed in approximately 1000-1200 individuals in the US annually. Clinical presentation is heterogeneous, ranging from mild constitutional symptoms with lymphadenopathy to life-threatening multi-organ dysfunction. International, consensus treatment guidelines were developed in 2018. These guidelines relied upon a limited number of clinical trials and small case series; however, real-world performance of these recommendations has not been subsequently studied. Siltuximab, a monoclonal antibody against interleukin 6 (IL6), is approved for the treatment of iMCD and recommended first-line, and tocilizumab, a monoclonal antibody directed against the IL6 receptor, is recommended when siltuximab is unavailable. Chemotherapy, rituximab, and immunomodulators are recommended as second- and third-line treatments based on limited evidence. Corticosteroid monotherapy is used by clinicians, though not recommended. Here, we draw upon the ACCELERATE Natural History Registry to inventory regimens and evaluate regimen response for 102 expert-confirmed iMCD cases. Siltuximab{plus minus}corticosteroids was associated with a 52% response, while corticosteroid monotherapy was associated with a 3% response. Anti-IL6 directed therapy with siltuximab or tocilizumab demonstrated better response and more durability than was observed with rituximab{plus minus}corticosteroids. Cytotoxic chemotherapy was associated with a 52% response and was predominantly administered in patients with TAFRO (thrombocytopenia, anasarca, fever, renal failure/reticulin, organomegaly) syndrome. Our results provide evidence in support of current recommendations to administer anti-IL6 first-line, to administer cytotoxic chemotherapy in severe, refractory patients, and to limit corticosteroid monotherapy. These results also demonstrate that evidence remains limited for effective agents for anti-IL6-refractory patients.

Conflict of interest: COI declared - see note

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Treatment Consistent with Idiopathic Multicentric Castleman Disease Guidelines is Associated with Improved Outcomes

Short title: Treatment effectiveness patterns in iMCD

Sheila K. Pierson[1], Megan S. Lim[2], Gordan Srkalovic[3], Joshua D. Brandstadter[4], Mateo S. Bustamante[1], Saishravan Shyamsundar[1], Natalie Mango[1], Criswell Lavery[1], Bridget Austin[1], Daisy Alapat[5], Mary Jo Lechowicz[6], Adam Bagg[7], Hongzhe Lee[8], Corey Casper[9,10,11], Frits van Rhee[12], David C. Fajgenbaum[1]*

1 Center for Cytokine Storm Treatment & Laboratory, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA.

2 Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York City, New York, 10065, USA.

3 Sparrow Herbert-Herman Cancer Center, Michigan State University College of Human Medicine, Lansing, MI, 48912, USA.

4 Division of Hematology/Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA.

5 Department of Pathology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, 72205, USA.

6 Department of Hematology and Medical Oncology, Emory University School of Medicine and Winship Cancer Institute, Atlanta, GA, 30322, USA.

7 Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA.

8 Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA.

9 Access to Advanced Health Institute (formerly Infectious Disease Research Institute), Seattle, WA, 98102, USA.

10 Department of Medicine, University of Washington, Seattle, WA, 98195, USA.

11 Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, WA, 98109, USA.

12 Myeloma Center, Winthrop P. Rockefeller Cancer Institute, University of Arkansas for Medical Sciences, Little Rock, AR, 72205, USA.

*Corresponding Author:

David C. Fajgenbaum MD, MBA, MSc

3535 Market Street, Suite 700

Philadelphia, PA 19104

Email: davidfa@pennmedicine.upenn.edu

Phone: 215-614-0935

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Abstract

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Key Points

Fifty two percent of iMCD patients treated with siltuximab±corticosteroids achieved response

Corticosteroids alone are not effective in iMCD symptom management

Introduction

Idiopathic multicentric Castleman disease (iMCD) is a rare cytokine storm-driven inflammatory disorder.[1] Diagnosis is challenging, as it is based on lymph node histopathology review, which has significant inter-pathologist discordance, and there is a heterogeneous clinical presentation that overlaps with closely related disorders.[2,3] Etiology and pathogenesis are yet unknown; however, interleukin-6 (IL6) has been found to drive disease in some patients.[4,5] Some patients experience an aggressive and rapid disease onset that requires urgent intervention. These patients often meet criteria for the thrombocytopenia, anasarca, fever/elevated C reactive protein (CRP), reticulin fibrosis/ renal failure, and organomegaly (TAFRO) subtype.[6] Other patients who do not meet TAFRO criteria tend to experience a more mild disease course that sometimes includes thrombocytosis, hypergammaglobulinemia, and plasmacytosis.[7] These patients are considered not otherwise specified (NOS) and a subset of them are sometimes referred to as the idiopathic plasmacytic lymphadenopathy (IPL) subtype.

Treatment guidelines for iMCD were developed by an international expert panel in 2018 based on review of a limited number of clinical trials and small case series, and recommendations were stratified by disease severity.[3] In both severe and mild/moderate disease, siltuximab, a monoclonal antibody directed against interleukin 6 (IL6) that is the lone medication approved for the treatment of iMCD in the United States and Europe, is recommended first-line. This was based on evidence from its registrational phase II trial, which demonstrated a 34% response,[8] together with data supporting its long-term safety.[9] Adjunctive corticosteroids are recommended as needed.[8] Tocilizumab, which has a similar mechanism of action but targets the IL6 receptor, is recommended as an alternative when siltuximab is not available.[10] The addition of cytotoxic chemotherapy is recommended for patients with severe disease who progress on anti-IL6 therapy. Data is more limited for alternative treatments outside of IL6-directed therapy. For patients with mild/moderate disease who are not responding

to IL6 blockade or do not exhibit cytokine-driven symptomatology, rituximab±immunomodulators is recommended as second-line treatment. Rituximab, a monoclonal antibody that depletes B cells, is highly effective for HHV-8-associated MCD but has never been studied in a clinical trial in iMCD. Corticosteroid monotherapy is not recommended due to limited data in support of its use, anecdotal experience from the expert panel, and historically high rates of complications.[11] A number of immunomodulators are listed as possible second- and third-line treatments, but there are limited available data on use of these drugs to treat iMCD.

Since iMCD is a rare disease, diagnosed in approximately 1000-1200 individuals in the United States annually,[12] it is difficult to conduct additional clinical trials that might inform treatment. Consequently, real-world data, or data collected from patients treated in clinical practice and not on treatment trials, have become increasingly important for understanding the natural history of and effective treatments for a rare disease.[13] While clinical trials are the gold standard, real-world data can contribute to the understanding of treatment effectiveness using clearly defined response criteria.

Herein, we present comprehensive treatment data from a cohort of 102 iMCD patients enrolled into the ACCELERATE Natural History Registry (NCT02817997) and provide a large-scale evaluation of treatment effectiveness in this vulnerable population.

Methods

Patient Cohort

Patients self-enrolled into the ACCELERATE Natural History Registry between October 2016 and August 2022, and eligibility was confirmed upon receipt of a reference pathology report.[14] Comprehensive medical data from disease onset until present time was collected from all treating institutions and abstracted into the study database. A panel of iMCD experts (4 clinicians and 3 hematopathologists) adjudicated each case, including central pathology review,

to confirm a diagnosis with iMCD, resulting in a final cohort of 102 iMCD patients (Supplementary Figure 1). All patients provided informed consent, and the research was approved by the University of Pennsylvania Institutional Review Board.

Regimen and Response Definition

Regimens were standardized as one or more drugs or procedures (treatments) that were initiated within two weeks of the start of another drug or procedure. Treatments initiated more than two weeks after a previous treatment started a distinct, new regimen. This grouping strategy enabled systematic evaluation of treatments given together.

Response was defined according to the change in the proportion of abnormal clinical and laboratory abnormalities (elevated CRP, anemia, thrombocytopenia/thrombocytosis, hypoalbuminemia, renal dysfunction, hypergammaglobulinemia, constitutional symptoms, organomegaly, fluid accumulation, eruptive cherry hemangiomatosis or violaceous papules, lymphocytic interstitial pneumonitis) following regimen initiation.[15] To achieve a response, the proportion of symptoms present at regimen initiation had to decrease by at least 50% after regimen initiation, and a new regimen could not be initiated within one-year. Non-response either did not ever meet 50% reduction in proportion of symptoms or met 50% reduction in symptoms but required a new regimen within one year.

Consistent with the primary endpoint used in the phase II trial of siltuximab,[8] lymph node and symptomatic response (LNSR) in this study required at least a 50% decrease in the short axis measurement(s) of the enlarged lymph node(s) as well as at least a stable best clinical response (i.e., no change in the proportion of clinical and laboratory abnormalities).

Disease severity was defined according to the iMCD treatment guidelines.[8] Specifically, severe disease required at least two of renal failure, fluid accumulation, severe anemia,

pulmonary involvement, or hospitalization. Adverse events were coded and categorized according to Medical Dictionary for Regulatory Activities.

Statistical Analyses

Siltuximab±corticosteroids and tocilizumab±corticosteroids were consolidated into anti-IL6±corticosteroids to compare the effect of anti-IL6±corticosteroids with rituximab±corticosteroids on response. The effect was tested using a generalized linear mixed effects model with severity, age, and sex as covariates; the patient was included as the random intercept to account for the multiple regimens for some patients. The relationship between clinical subtype and severity was also tested by generalized linear mixed effects model with the patient as the random intercept. Cohen's kappa statistic was used to measure interrater reliability between response and LNSR. A linear mixed model was used to test for the effect of regimen on hemoglobin, albumin, and CRP at time of best response; the nearest pre-treatment value was included as a covariate and the patient was included as the random intercept when the model required. Post-hoc comparison adjusted by Tukey method was performed upon finding a global significance. A Cox proportional hazards model adjusted by age category (<35 years vs. ≥35 years), sex, and clinical subtype was used to calculate the effect of treatment regimen on durability of response. The model was stratified by severity to account for different baseline risks and clustered by patient to account for repeated regimens. The Grambsch and Therneau method was used to test for proportional hazards. A likelihood ratio test was used to test the assumption that covariates act similarly on the baseline hazard function within each stratum.

Data Sharing Statement

These data are available upon request by emailing accelerate@pennmedicine.upenn.edu.

Results

Cohort of 102 patients panel-confirmed to meet iMCD diagnosis

In total, 102 iMCD patients were confirmed to have a diagnosis of iMCD by an expert panel of 7 clinicians and pathologists. Forty-four (43.1%) patients identified as female, and nearly two-thirds identified as white/Caucasian. The mean (standard deviation) age is 35.9 (16.4) years, and there are 19 (18.6%) pediatric patients. At the time of analysis, 8 (7.8%) iMCD patients had died from their disease, and over half of the patients (n=61, 59.8%) had the TAFRO subtype. We found high consistency of diagnosis confirmation among patients with the TAFRO subtype – of the 73 patients who met TAFRO criteria and were reviewed by the panel, 60 (82.2%) were confirmed by the panel. Of note, there was considerable inconsistency with regards to confirming Castleman disease (CD) diagnoses among the full cohort of CD cases considered for this study. In fact, 127 of the 328 cases considered for this study were not confirmed for inclusion because there either was missing data or the expert panel determined that they were not consistent clinicopathologically with any subtype of CD. An additional 99 patients were determined to have a subtype of CD other than iMCD (Supplementary Figure 1). Interestingly, of the 74 iMCD cases with paired data available on histopathological subtype from local sites and central panel review, only 36 (48.6%) cases were concordant and 38 (51.4%) were discordant. Patients demonstrated considerable clinical and laboratory abnormalities at the time of diagnosis irrespective of treatment status (Table 1).

High degree of variability in the treatments administered in iMCD

First, we set out to establish an inventory of iMCD treatments and regimens. Drugs were categorized as corticosteroid, antineoplastic, anti-IL6 directed therapy, or other immunomodulator. We found that across the cohort, 93 patients (91%) received at least one corticosteroid, 87 (85%) received anti-IL6 directed therapy, 69 (68%) received at least one other immunomodulator, and 31 (30%) received at least one antineoplastic agent (Figure 1A). Forty-one unique drugs were administered to this cohort, including siltuximab and tocilizumab, 12

antineoplastic agents, six corticosteroids, and 21 immunomodulators. Figure 1B displays the proportion of patients who ever received each drug as part of any regimen. After prednisone, which was administered to 77% of patients, siltuximab was administered to 65% (n=66) as part of various regimens. Among procedures, we identified four used for iMCD treatment, including plasmapheresis/plasma exchange (n=6), radiation therapy (n=3), splenectomy (n=3), and thymus excision (n=2).

We examined the adverse drug reaction profiles of the most commonly administered targeted treatments: siltuximab, tocilizumab, and rituximab. Musculoskeletal and connective tissue disorder events occurred most frequently among rituximab-associated events (24.1%), skin and subcutaneous tissue disorders occurred most frequently among siltuximab-associated events (20.0%), and gastrointestinal disorders occurred most frequently among tocilizumab-associated events (23.1%) (Supplementary Table 1). Rigors was the most frequently observed adverse event with rituximab (n=8 occurrences), rash (n=9 occurrences) with siltuximab, and anaphylactic reaction (n=4 occurrences) with tocilizumab (Supplementary Table 2).

We next cataloged the regimens that represent combinations of these drugs and procedures. A total of 304 regimens were administered and 110 of them were unique combinations of drugs and procedures (Figure 2A, Supplementary Table 3). We categorized these 110 combinations into 13 regimen categories (Supplementary Table 4). Two of the 102 patients received no medical treatment following their diagnostic lymph node excision. Siltuximab±corticosteroids was the most frequently administered regimen; 51 (50.0%) patients received this regimen at least once. Corticosteroid monotherapy was also frequently administered, with 45 (44.1%) patients receiving at least one corticosteroid monotherapy regimen. We examined the timing of regimen initiation with the hypothesis that many of the corticosteroid regimens were administered before iMCD diagnosis was confirmed (Figure 2B). Indeed, we found that 49% of the corticosteroid regimens were administered after symptomatic

presentation but prior to confirmed diagnosis. Overall, these data demonstrate the wide variety of treatments administered to iMCD patients.

Response metrics support current treatment guidelines

Next, we sought to evaluate regimen effectiveness. Of particular interest was the evaluation of regimen categories defined in the 2018 iMCD treatment guidelines, including anti-IL6±corticosteroids, which included siltuximab±corticosteroids and tocilizumab±corticosteroids; rituximab±corticosteroids; and chemotherapy-based regimens. Additionally, we evaluated the performance of corticosteroid monotherapy, which we found to be frequently administered.

We found that 50% (29/58) of patients treated with anti-IL6±corticosteroids ever achieved response. Specifically, 52% (22/43) of patients treated with siltuximab±corticosteroids and 44% (8/18) treated with tocilizumab±corticosteroids ever achieved response. Additionally, 27% (7/26) treated with rituximab±corticosteroids, 52% (13/25) treated with chemotherapy-based regimens, and 3% (1/36) treated with corticosteroid monotherapy ever achieved response (Table 2). Given that rituximab±corticosteroids is recommended as an alternative first-line to anti-IL6±corticosteroids in specific cases, we tested for a differential effect between these regimens. Controlling for severity (β=-0.97, p=0.12), age at regimen initiation (β=-0.10, p=0.70), and sex (β=-0.23, p=0.67), we found that rituximab±corticosteroids is associated with a 1.19 lower log-odds or a 69.3% decrease in the odds of response compared to anti-IL6±corticosteroids (β=-1.18, CI: -2.29, -0.06, p=0.038). This finding supports the recommendation to first utilize anti-IL6 directed therapy; though, the 27% response to rituximab±corticosteroids is evidence that its use is reasonable in mild/moderate cases when anti-IL6 directed therapy is ineffective.

Next, we examined the timing of treatment with anti-IL6±corticosteroids and whether there was a difference in the effectiveness of anti-IL6±corticosteroids between patients who

received it as a first-line therapy (with the exception of corticosteroid monotherapy) or as a subsequent therapeutic approach. Among patients who were diagnosed after the approval of siltuximab for the treatment for iMCD (April 22, 2014) and received anti-IL6±corticosteroids, the median (IQR) time to treatment with anti-IL6±corticosteroids was 22 (0, 70) days and the mean (SD) was 113.4 (224.6) days. We next looked at the effectiveness of patients treated early vs. later in their treatment course. Among the 58 patients who had an evaluable anti-IL6±corticosteroids regimen, 33 (56.9%) received it as first-line therapy and 25 (43.1%) received it subsequent to another therapeutic approach. We found that there was a 48% (16/33) response among patients who received anti-IL6±corticosteroids first-line and a 52% (13/25) response among patients who received ant-IL6±corticosteroids as a subsequent approach. There was no statistical difference (X=0, p-value=1).

Since chemotherapy-based regimens are defined by the inclusion of multiple different antineoplastic/cytotoxic agents and may contain other agents including anti-IL6 directed therapy, immunomodulators, or corticosteroids, we also further interrogated these regimens to identify trends among those that elicited a response. Among the 13 patients who ever achieved a response to a chemotherapy-based regimen, there were 24 chemotherapy-based regimens administered and 15 (62.5%) resulted in response and 9 (38.5%) did not. Comparatively, among the 12 patients who never achieved a response to a chemotherapy-based regimen, there were 16 chemotherapy-based regimens administered (Supplementary Table 5). To investigate the heterogeneity of chemotherapy-based regimens, we categorized the inclusion of each antineoplastic agent among regimens that achieved response compared to those that did not achieve response. We did not identify a trend suggesting superiority of a specific regimen but the sample size was likely underpowered to detect significant differences (Supplementary Table 6).

To evaluate the use of alternatives with unknown efficacy, we examined response to immunomodulator regimens. Among the immunomodulator regimens, we found 17 unique combinations, the most frequent of which was sirolimus±corticosteroids (n=7). Across all immunomodulator±corticosteroid regimens, we observed a relatively low response. Four (19%) patients with an evaluable regimen achieved at least one response (Supplementary Figure 2).

Lastly, we performed a secondary analysis to investigate LNSR, which includes radiologic response and closely matches the primary endpoint in the phase II trial.,[8] Applying that definition, we found comparable response across regimen categories (Supplementary Table 7), and among regimens for which there was corresponding response data, we found substantial agreement (κ=0.64, p=4.0x10^{-14}). The strong concordance of results between our definition of response and LNSR strengthens our findings.

Characterization of response during severe disease and by clinical subtype

As treatment recommendations are stratified by disease severity, we next characterized response by disease severity at the time of regimen initiation (Figure 3A). First, we examined the relationship between severity and regimen received and after accounting for multiple regimens within a given patient, found no significant relationship (X=7.6, p-value=0.18). Within each regimen category, there was a larger number of patients who had ever initiated a regimen during mild/moderate compared to severe disease. Notably, we observed a substantial proportion of patients who achieved a response to siltuximab±corticosteroids during each mild/moderate (57%) and severe (42%) disease. There appeared to be a lower response to tocilizumab±corticosteroids during severe disease compared to mild/moderate (25% vs. 60%), but the number of observations was low and a statistical comparison to evaluate the difference in response between mild/moderate and severe disease within each regimen category was not performed due small number of observations that do not allow for covariate adjustment.

Given the high proportion of TAFRO patients in our cohort (60%) and that TAFRO patients typically demonstrate severe symptoms, we also investigated the relationship between severity and clinical subtype. First, we found strong association between severity and TAFRO status (β=3.14, CI: 2.00, 4.27, p<0.001). The odds of severe disease occurring in a TAFRO patient is approximately 23 times the odds of severe disease occurring in an NOS patient. Among regimens initiated in severe disease, 91.2% occurred in TAFRO patients, whereas regimens initiated in mild/moderate disease equally represent TAFRO (50.3%) and NOS patients (49.7%) (Figure 3B). Response proportions by TAFRO and NOS subtype were similar to those observed in mild/moderate and severe disease (Supplementary Figure 3). Of note, TAFRO patients received the majority of chemotherapy-based regimens, which resulted in a 47.8% response. These data support the recommendation to initiate patients in all stages of disease on anti-IL6 directed therapy and substantiate chemotherapy as an option in severe disease/TAFRO subtype.

Substantial improvement in objective laboratory parameters notable in siltuximab±corticosteroids

As a quantitative assessment of regimen performance, we examined three reliable markers of disease activity (hemoglobin, albumin and CRP), at the time of regimen initiation and time of best response within regimen categories of interest. For each regimen category, mean hemoglobin, albumin, and CRP levels were abnormal (<12.0 g/dL, <3.5 g/dL, and >10 mg/L respectively) at regimen initiation (Figure 4). When controlling for parameter levels prior to treatment initiation, we found that siltuximab±corticosteroids resulted in a substantial and statistically significant increase in hemoglobin compared to both rituximab±corticosteroids (p=0.034) and corticosteroid monotherapy (p<0.001). Chemotherapy-based regimens (p=0.0198) and tocilizumab±corticosteroids (p=0.0448) also each demonstrated a significant increase compared to corticosteroids. Likewise, chemotherapy-based regimens (p<0.001),

siltuximab±corticosteroids (p<0.001), and tocilizumab±corticosteroids (p=0.0232) each resulted in a substantial and statistically significant increase in albumin compared with corticosteroid monotherapy. Corticosteroid monotherapy was the only treatment regimen that did not result in raising mean hemoglobin or albumin levels to the normal range. Siltuximab±corticosteroids was the only regimen to result in a clinically substantial improvement in CRP (within normal limits), though interpretation of CRP data is limited as the smaller number of CRP measurements available prevented detection of differences between regimens. These findings demonstrate additional support for the current treatment recommendations and for limiting the use of corticosteroid monotherapy.

Time-to-event analysis highlights successful durability of siltuximab±corticosteroids

Lastly, as an assessment of regimen durability, we analyzed time to event (disease progression or start of new regimen) for regimens initiated after confirmed diagnosis. Median time-to-event for siltuximab±corticosteroids was 1566 days (95% confidence interval (CI): 546, no upper limit), tocilizumab±corticosteroids was 924 (233, no upper limit), chemotherapy-based regimens was 338 (120, 2734), rituximab±corticosteroids was 214 (119, no upper limit), and corticosteroid monotherapy was 56.5 (27, 98) (Figure 5A). We compared siltuximab±corticosteroids, tocilizumab±corticosteroids, rituximab±corticosteroids, and chemotherapy-based regimens and controlled for age, sex, and clinical subtype in a Cox proportional hazards model stratified by severity. Siltuximab±corticosteroids demonstrated durability over rituximab±corticosteroids (HR: 2.70 95% CI: 1.49-4.90, p=0.001) (Figure 5B). Regimens administered to NOS patients also demonstrated durability over those administered to TAFRO patients (HR: 1.74 95% CI: 1.03-2.96, p=0.04), which may be due to the fact that TAFRO patients typically experience a more intense flare-like disease. These strong and consistent results highlight that first-line therapy is able to induce a durable response.

Discussion

Though treatment guidelines for iMCD were developed in 2018, this is the first systematic assessment of the treatments included in those guidelines. Given the frequency of off-label prescribing for iMCD and limited active clinical trials underway, real-world data collected and abstracted as part of the ACCELERATE Natural History Registry provide an ideal source of information for evaluating treatment outcomes in iMCD.. Increasingly, rare disease researchers are leveraging real-world data to provide valuable clinical insights when clinical trials are not able to be performed. A recent study on immune-mediated thrombotic thrombocytopenic purpura (iTTP) used real-world data to report the current clinical treatment practice and to assess the benefits and risks of caplacizumab, an approved treatment for iTTP, outside of a clinical trial setting.[16] Like in iMCD, where the most severe patients were excluded from the only Phase II clinical trial, iTTP had limited data on the outcomes of severely ill patients and found concordance between real-world data and clinical trial results.

Our evaluation of treatment patterns in 102 confirmed iMCD patients identified 41 unique drugs that have been used in the treatment of iMCD. Our finding that 85% of iMCD patients were treated with siltuximab or tocilizumab conflicts with a recent epidemiologic study that reported treatment with IL6 directed therapy in less than 10% of iMCD patients, based on insurance claims data.[12] This discrepancy might be explained by the fact that this study looked at claims data between 2006 and 2020 and could reflect a gradual adoption of IL6-directed therapy. Alternatively, considering that patients self-enroll into ACCELERATE, it is possible that this represents a bias towards enrollment of patients more likely to be treated with recommended treatment. It is also possible that our strict adjudication process resulted in a cohort of patients more likely to have iMCD than those identified by insurance claims data, which could have included a large number of unicentric Castleman disease and other diseases that could not be removed from the analysis.

Beyond anti-IL6 directed therapies, there is no consensus for optimal second-line therapy. Sirolimus, an mTOR inhibitor identified as a potential iMCD treatment, has been administered to 17% of our cohort. It has previously been found to induce a clinically beneficial response in a small number of patients; a clinical trial is underway to further evaluate its efficacy (NCT03933904).[17–19] Here, we found evidence of response in a small number of patients. Interestingly, other immunomodulators recommended in the 2018 treatment guidelines, including cyclosporine A, anakinra, and thalidomide, which was recently reported along with cyclophosphamide and prednisone to be an effective treatment in a small phase II trial,[20] were only used in a small percentage of patients in this cohort. Bortezomib has also been reported along with thalidomide and dexamethasone to be an effective treatment approach from a single-center phase II trial in relapsed and refractory iMCD patients;[3,21] however, no patients in our cohort received that regimen.

Given the challenges assessing treatment response to individual drugs administered concurrently, we defined regimens according to the timing of administration and developed a response criteria well suited to real-world data.[14] These data reveal a higher response to siltuximab±corticosteroids (52%) than was observed in the phase II clinical trial (34%).[8] Since our response definition differed from the phase II study, we also applied a response criteria that corresponded with the definition used in the trial and showed concordance for all regimen categories. This supports defining response using clinical metrics, which are more aligned with patient-reported challenges. This also suggests that the difference in response observed in this real-world data compared to the phase II trial is less likely to be due to the difference in response variables. In fact, retrospective review of patients enrolled in the phase II trial suggests that some patients may not have had iMCD and that patients who met more criteria had a greater likelihood of response.[15] Patients who did not satisfy the iMCD clinical criteria (n=16) had a 0% response, potentially diluting the signal of efficacy among confirmed iMCD

patients. Given that each case herein was rigorously reviewed, this cohort is highly likely to represent iMCD and the response to siltuximab was similar to that in patients in the phase II study who retrospectively met criteria.[2]

Our study reports on regimens administered during both mild/moderate and severe disease. The phase II siltuximab clinical trial excluded patients with severe disease and therefore siltuximab effectiveness in severe patients was largely unknown and unreported. We found comparable response during both mild/moderate and severe disease. Our results also demonstrate that use of anti-IL6±corticosteroids is associated with a higher response than rituximab±corticosteroids after controlling for severity, supporting the current international guideline recommendations. Notably, we showed that the vast majority of regimens that were initiated during severe disease occurred in TAFRO patients, and stratification of response by clinical subtype was similar to that observed in stratification by severity. A recent study on a large cohort of TAFRO patients reported no significant differences in response to tocilizumab or rituximab between TAFRO and NOS.[22] While TAFRO and NOS patients demonstrate distinct clinical symptomology, it is not yet known whether this is due to different disease mechanisms.

We found improvement in objective laboratory metrics after the initiation of appropriate therapy. Clinical improvement of each hemoglobin, albumin, and CRP was seen in most regimen categories; however, none improved to clinically significant levels on corticosteroid monotherapy, which was associated with a 3% response. CRP, hemoglobin, albumin, and performance status have been combined into a CHAP score and proposed as a marker of disease activity.[23] Hemoglobin was previously identified in a model of laboratory parameters (along with CRP, fibrinogen, and IgG) predictive of response to siltuximab that has not been validated.[24]

There are several limitations to this study. First, to address the inherent limitations to real-world data, we created systematic rules to define a regimen and response as well as

rigorous criteria to ensure that each patient's diagnosis of iMCD was confirmed by central review of extensive clinical, histopathologic, and radiologic data. Real-world data is at risk for missingness, bias due to lack of randomization, lack of objectively defined and systematically evaluated response, etc. Here, response is based on the change in the proportion of abnormal clinical and laboratory criteria after a treatment regimen is initiated, which enables determination of trends in improvement even when data are missing for a specific criterion. Nevertheless, comparative data need to be interpreted with caution given heterogeneity. Second, variability in regimens limited interpretation in some cases. Chemotherapy-based regimens were highly variable and sometimes included anti-IL6-directed agents or other immunomodulators, but always included a cytotoxic agent. Third, limited sample size for some newly identified and potentially promising treatment approaches precluded statistical investigation of response. While there were a high number of unique regimens, certain regimens of interest that have been recently identified, like combination thalidomide-cyclophosphamide-prednisone were not present in this dataset.[20] Likewise, JAK inhibition has been recently identified as a promising possible therapeutic target in iMCD and has been shown to have clinical benefit in some patients[25–27], but our data included too few patients treated with JAK inhibitors to assess. A larger sample size would have improved our ability to detect differences between regimens. Lastly, C-X-C Motif Chemokine Ligand-13 (CXCL13) has been recently identified as an early indicator of response to siltuximab and is under investigation as a possible treatment target, but no drugs targeting CXCL13 or it's receptor, CXCR5, are approved in humans thus precluding clinical investigation.[28] One of the most pressing needs for iMCD patients is the identification of a consensus second-line therapy for anti-IL6-refractory patients, and this study was not powered to make such comparisons. However, the rigor with which our cohort was reviewed and selected likely improved the accuracy of our results. Notably, our sample was biased towards the TAFRO clinical subtype and 65% of our cohort was white, which may not be consistent with

the population of iMCD. Despite these limitations, we assembled a large, expert-confirmed cohort of iMCD patients and obtained extensive clinical and treatment data.

Our study of 102 confirmed iMCD patients demonstrates support for the current treatment guidelines. We found a 50% response to anti-IL6±corticosteroids and showed that objective laboratory metrics and time-to-event data support the use of anti-IL6 directed regimens and limiting corticosteroid 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.

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Authorship Contributions

S.K.P.: Conceptualization, formal analysis, writing – original draft preparation, writing – review and editing, and visualization; M.S.L.: Supervision, writing – review and editing; G.S.: Supervision, writing – review and editing; J.D.B.: Supervision, writing – review and editing;

M.S.B.: Investigation, writing – review and editing; S.S.: Investigation, writing – review and editing; N.M.: Investigation, writing – review and editing; C.L.: Investigation, writing – review and editing; B.A.: Investigation, writing – review and editing; D.A.: Supervision, writing – review and editing; M.J.L.: Supervision, writing – review and editing; A.B.: Supervision, writing – review and editing; H.L.: Supervision, methodology, writing – review and editing; C.C.: Conceptualization, writing – review and editing; F.v.R.: Conceptualization, supervision, writing – review and editing; D.C.F.: Conceptualization, supervision, funding acquisition, writing – review and editing.

Disclosure of Conflicts of Interest

D.C.F. has received research funding for the ACCELERATE registry and consulting fees from EUSA Pharma, study drug with no associated research funding for the clinical trial of sirolimus from Pfizer (NCT03933904), and has two provisional patents pending related to the diagnosis and treatment of iMCD, including one related to CXCL13 as a biomarker in iMCD. G.S. has received Speakers Bureau fees from Takeda, Janssen Pharmaceuticals, Foundation Medicine, and EUSA Pharma. J.D.B. has received consulting fees from EUSA Pharma. F.v.R has received consulting fees from EUSA Pharma, GlaxoSmithKline, Karyopharm, and Takeda and has received research funding from Janssen Pharmaceuticals and Bristol Myers Squibb. All other authors report no conflicts of interest.

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Table 1. Cohort characteristics at the time of diagnosis*

	N=102
Age at diagnosis	
Mean (SD)	35.9 (16.4)
<18, N (%)	19 (18.6)
Deceased, N (%)	8 (7.8)
Sex†, N (%)	
Female	44 (43.1)
Male	58 (56.9)
Race†, N (%)	
American Indian / Alaska Native	1 (1.0)
Asian	14 (13.7)
Black / African American	12 (11.8)
Native Hawaiian / Pacific Islander	1 (1.0)
White / Caucasian	66 (64.7)
Other / Not stated	8 (7.8)
Histopathological subtype, N (%)	
Hyaline vascular	1 (1.0)
Hypervascular	62 (63.9)
Mixed	27 (27.8)
Plasmacytic	7 (7.2)
Unknown	5
Time from diagnostic biopsy to pathologic diagnosis, days	
Median (interquartile range)	4 (2, 8)
Clinical subtype, N (%)	
TAFRO	61 (59.8)
NOS	41 (40.2)
Clinical symptoms, N (% of those assessed)	
Constitutional symptoms	92 (91.1)
Organomegaly	73 (79.3)
Cherry hemangioma/violaceous papules	2 (2.6)
Lymphocytic interstitial pneumonitis	0
Fluid Retention	79 (84.0)
Laboratory Features	
CRP, mg/L	80.0 (22.0, 180.0)
ESR, mm/hr	73.0 (43.0, 107.0)
Platelets, k/uL	134.0 (64.0, 275.8)
Hemoglobin, g/dL	10.0 (8.4, 11.6)
Albumin, g/dL	2.7 (2.3, 3.3)
Creatinine, mg/dL	1.1 (0.9, 1.7)
eGFR, ml/min/1.73m^2, N (%)	
0-20	6 (9.5)
20-40	9 (14.3)
40-60	12 (19.0)
60+	36 (57.1)
Not documented	39
IgG, mg/dL	1150 (780, 1727)
Gammaglobulin, g/dL	1.22 (0.9, 1.8)

Tables

*Data represents closest information to the date of diagnosis within 90 days prior to through 15 days following diagnosis date; labs presented in median (IQR) unless otherwise stated.

†Patient-reported

Table 2. Response by regimen category

	Patients ever achieved a response*		N patients with evaluable regimen
	Yes, N (%)	**No, N (%)**	
Anti-IL6±Corticosteroids[†]	29 (50.0)	29 (50.0)	58
Siltuximab±Corticosteroids	22 (52.4)	20 (47.6)	42
Tocilizumab±Corticosteroids	8 (44.4)	10 (55.6)	18
Rituximab±Corticosteroids	7 (26.9)	19 (73.1)	26
Chemotherapy-based regimen	13 (52.0)	12 (48.0)	25
Immunomodulator±Corticosteroids	4 (19.0)	17 (81.0)	21
Anti-IL6 + Rituximab±Other	5 (41.7)	7 (58.3)	12
Anti-IL6 + Immunomodulator(s)±Corticosteroids	6 (60.0)	4 (40.0)	10
Anti-IL6 + Procedure±Corticosteroids	0	1 (100)	1
Rituximab + Immunomodulator(s)±Corticosteroids	1 (12.5)	7 (87.5)	8
Corticosteroids	1 (2.8)	35 (97.2)	36
Procedure+drug therapy	1 (25.0)	3 (75.0)	4
Procedure	0	2 (100)	2
No Medical Treatment	0	2 (100)	2

*For patients who >1 instance of the same regimen category, they are considered to have achieved response if response was achieved at least one time.

[†]Includes patients ever treated with either Siltuximab±Corticosteroids and/or Tocilizumab±Corticosteroids. Best response among those regimens is included; therefore, the N evaluable for each Siltuximab±Corticosteroids and Tocilizumab±Corticosteroids may not sum to the N evaluable for Anti-IL6±Corticosteroids

Figure Legends

Figure 1. Many treatments across several treatment categories are used in the treatment of iMCD. (A) iMCD patients receive a variety of treatments, including corticosteroids (91%), immunomodulators (68%), antineoplastic agents (30%), and anti-IL6 directed therapy (85%). (B) Forty-one unique drugs have been administered across a cohort of N=102 iMCD patients, and siltuximab, the first-line recommended therapy, has been administered to 65% of the cohort.

Figure 2. Treatment regimen administration in iMCD is highly variable and more generalized regimens are often administered prior to confirmed diagnosis. (A). Thirteen different regimen categories were identified and administered among this cohort. A total of 304 regimens were administered among the 102 iMCD patients. Fifty-one (50%) patients received siltuximab±corticosteroids at least once throughout their treatment course. Plot is sequentially ordered with the earliest enrollees at the bottom and the most recent enrollees at the top. Regimens administered prior to confirmed diagnosis are represented to the left of the vertical bar, and regimens administered on or after diagnosis are represented to the right of the vertical bar. (B). Given variability in presentation and the time until accurate diagnosis, some regimens are administered prior to confirmed diagnosis. In this cohort, 49% of the corticosteroid regimens were administered prior to confirmed diagnosis, while only 1.7% of the siltuximab±corticosteroids regimens were administered prior to confirmed diagnosis. Regimens defined as immunomodulator(s) ±corticosteroids, anti-IL6 therapy + rituximab±other treatments, anti-IL6 therapy + immunomodulator(s) ±corticosteroids, anti-IL6 therapy + procedure±corticosteroids, procedure + drug therapy, procedure, and no medical treatment have been combined into an ‘Other’ category in the above figure. Abbreviations: CS: corticosteroids.

Figure 3. Regimen response by severity and relationship between severity and clinical subtype. (A) Best response by regimen category stratified by disease severity at the start of the regimen.

Each dot represents a given patient within a regimen category and severity status colored by best response (responder status indicated by blue and non-responder status indicated by gold). Within each regimen category, there was a higher number of regimens initiated in mild/moderate compared to severe disease. A comparable proportion of patients achieved a response to siltuximab±corticosteroids during each mild/moderate (57%) and severe (42%) disease. Corticosteroids alone was associated with response in one patient during mild/moderate disease only. (B) Severe disease was strongly associated with TAFRO status (β=3.14, CI: 2.00, 4.27, p<0.001). The majority (91.2%) of regimens initiated in severe disease occurred in TAFRO patients, but regimens initiated in mild/moderate disease occurred equally among TAFRO (50.3%) and NOS (49.7%) patients. Abbreviations: CS: corticosteroids.

Figure 4. Laboratory parameters indicate that some regimen categories outperform others. Mean and standard error of (B) hemoglobin (red) and albumin (blue) and (C) C reactive protein (CRP) at the initiation of a given regimen category (closest value within +/- 7 days) and at the time of best response (closest value within +/- 7 days). Anti-IL6 directed therapies show the most dramatic improvements in laboratory parameters, while corticosteroids shows limited improvement. Slope between timepoints shown; available data points contributing to plots provided below plots. Only statistically significant results are marked, and statistical significance is defined by the number of asterisks: * P ≤ .05; ** P ≤ 0.01; *** P ≤ 0.001; **** P <0.00001. Abbreviations: CS: corticosteroids.

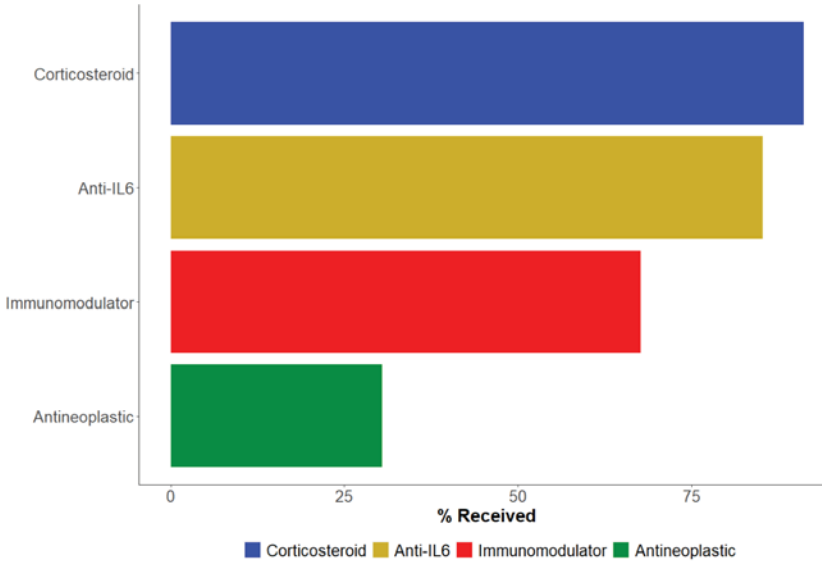
Figure 5. Time-to-event analysis highlights the durability of anti-IL6 directed therapies. (A) Survival curve showing time-to-event by regimen category. Event is defined as disease progression or start of new regimen. (B) Results from a Cox proportional hazards model comparing siltuximab±corticosteroids, tocilizumab±corticosteroids, rituximab±corticosteroids, and chemotherapy-based regimens, stratified by severity and controlled for age, sex, and clinical subtype. Siltuximab±corticosteroids demonstrated stronger durability over

rituximab±corticosteroids (HR: 2.72 95% CI: 1.50-4.91, p=0.001). Abbreviations: CS: corticosteroid

Figures

Figure 1. Treatments administered to iMCD patients

A.



B.

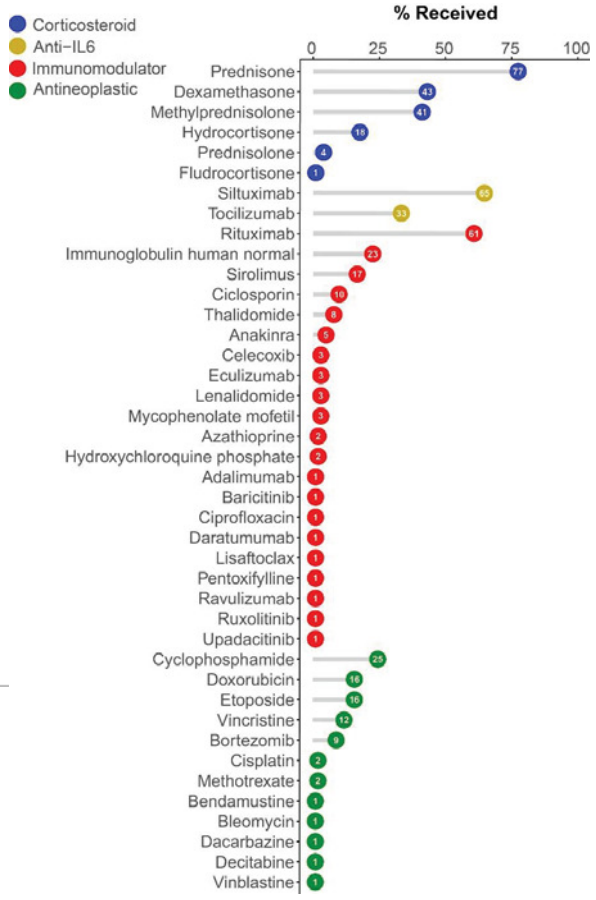


Figure 2. Regimens administered to iMCD patients

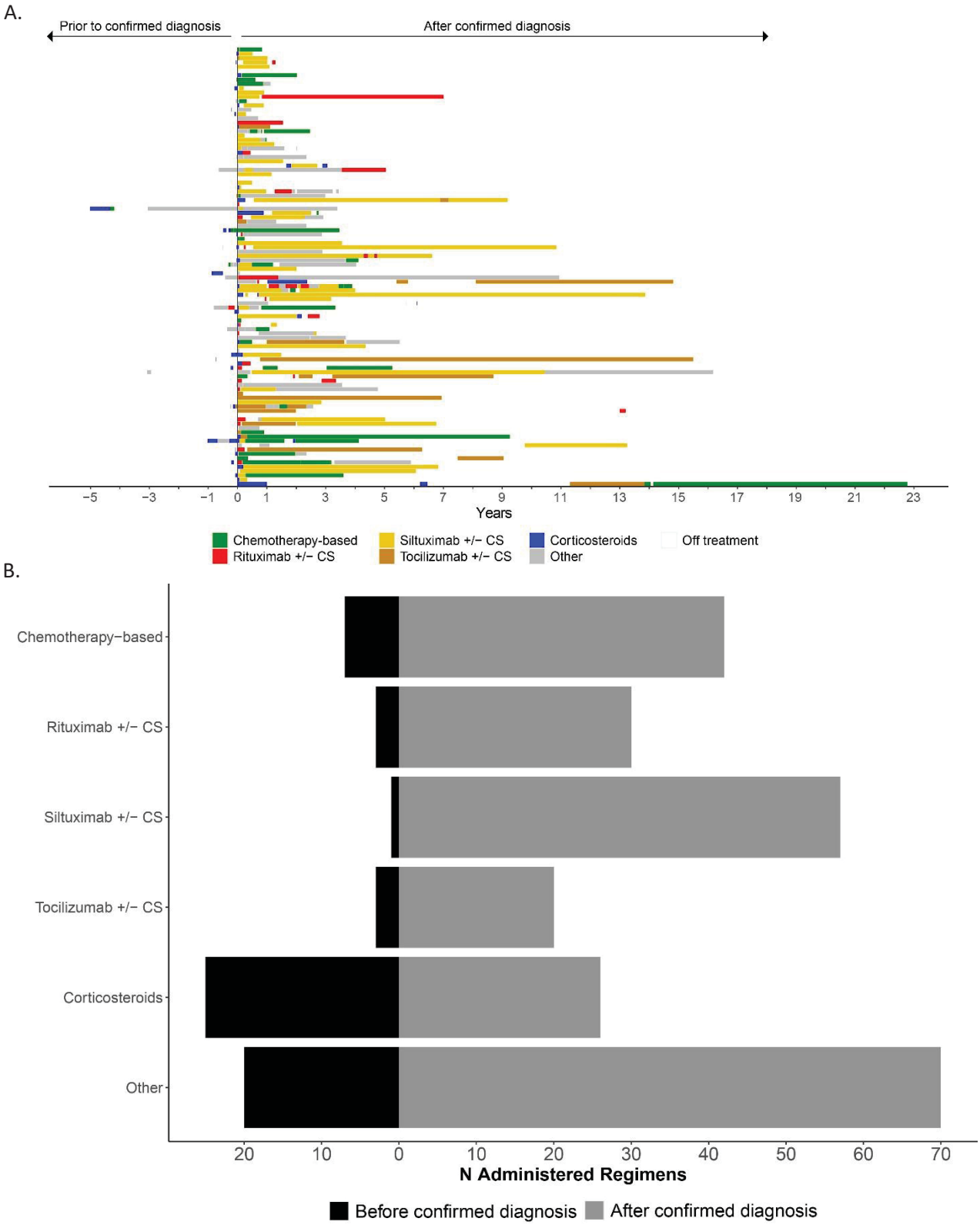


Figure 3. Regimen response by severity and relationship between severity and clinical subtype

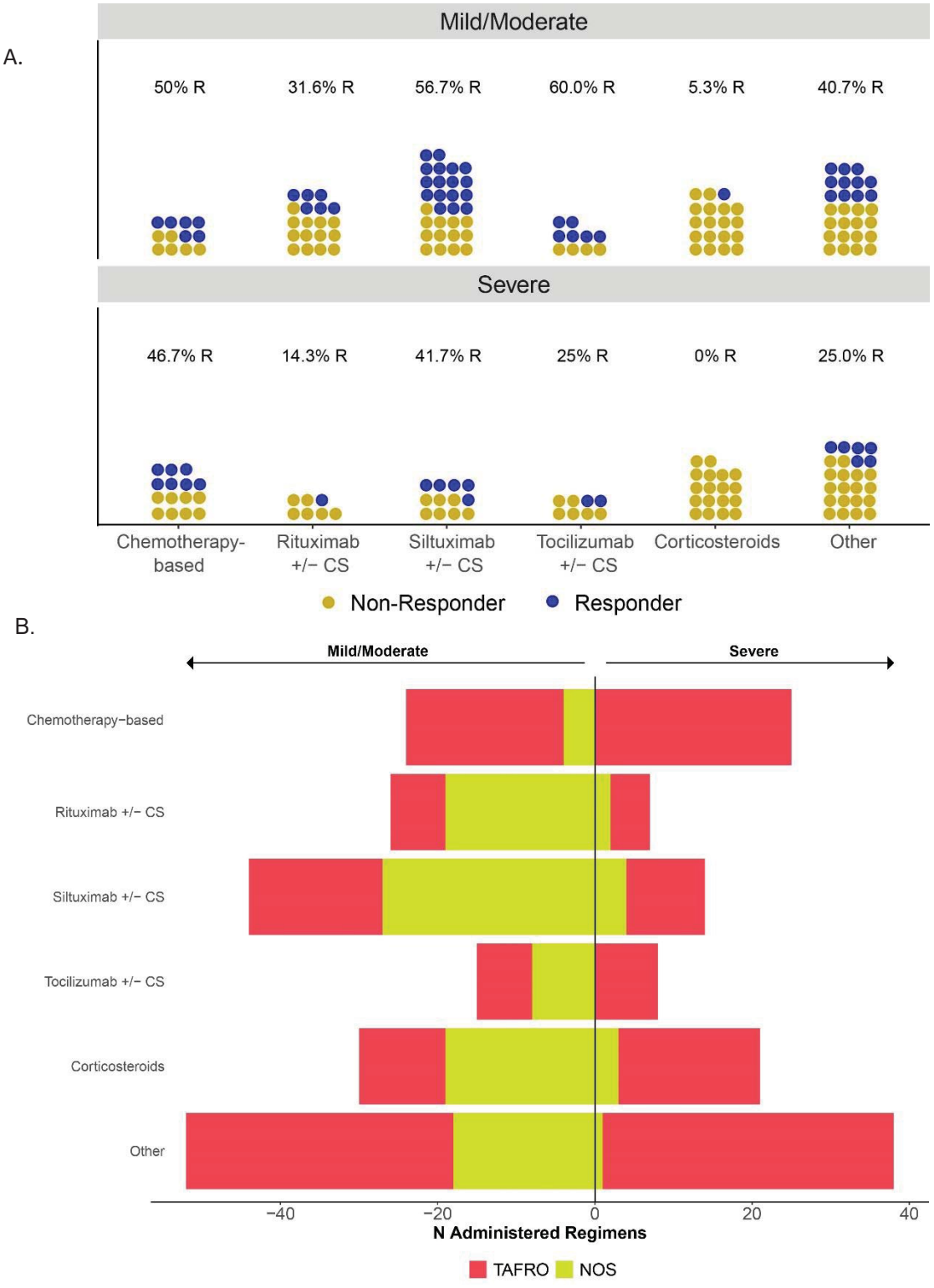
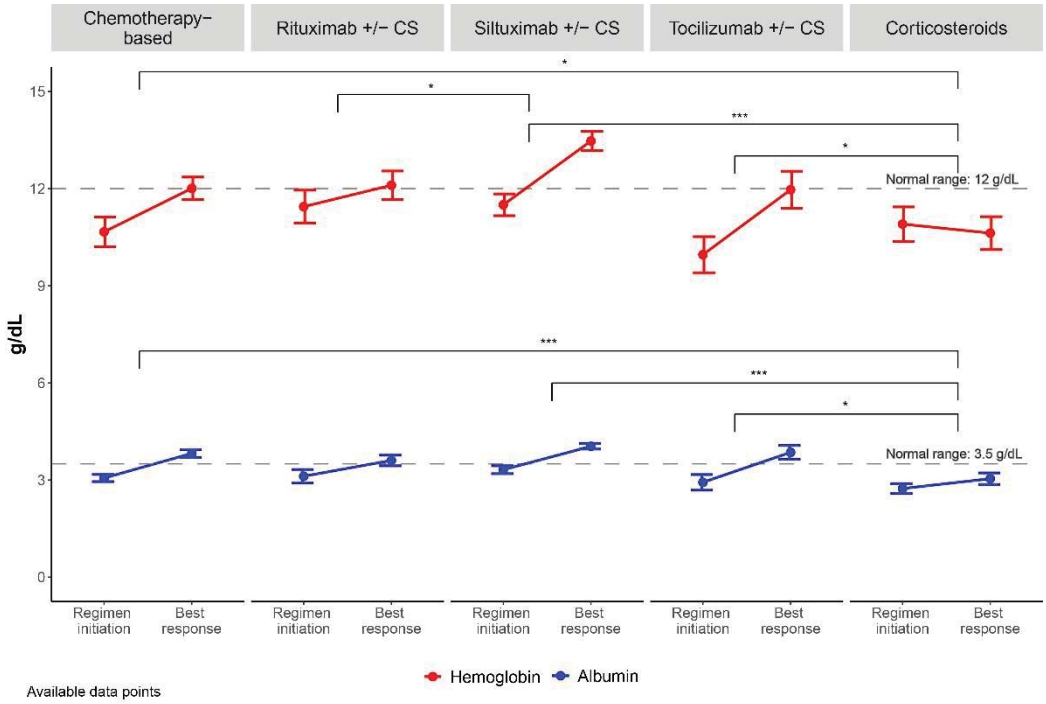


Figure 4. Improvement in laboratory parameters following regimen administration.

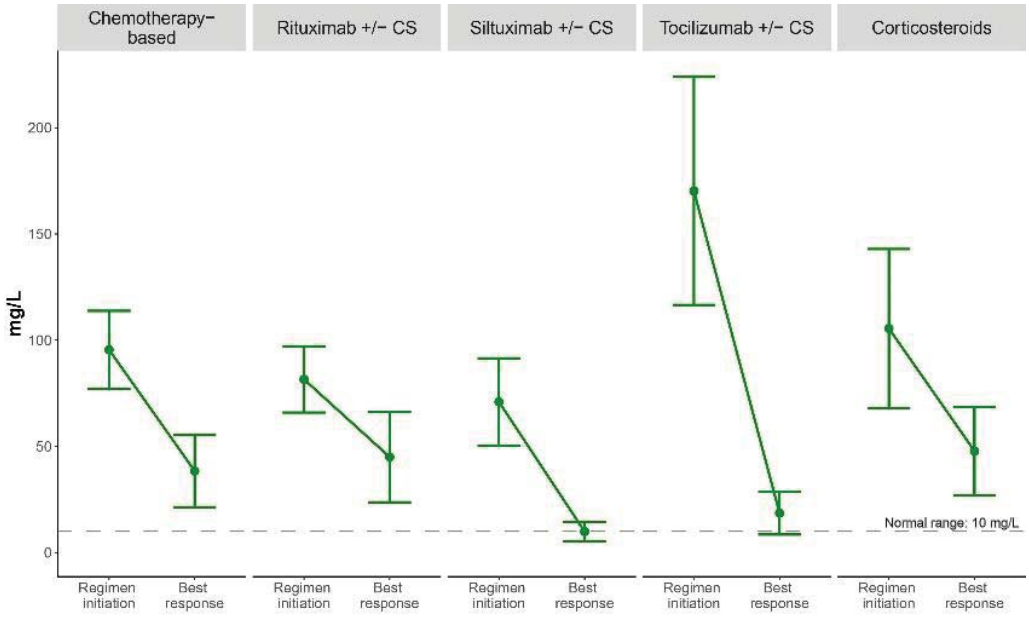
A.



Available data points

●	42	28	49	15	27
●	39	19	39	12	22

B.

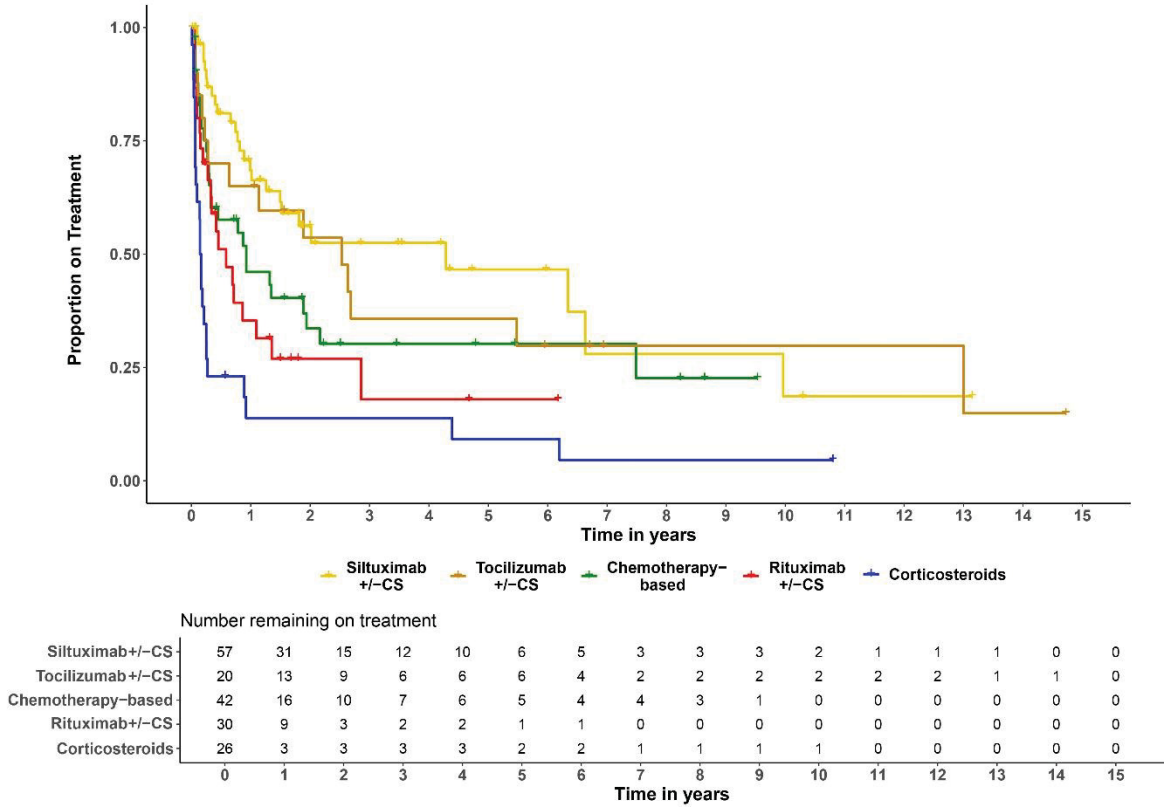


Available data points

●	24	6	18	6	9

Figure 5. Time-to-next treatment

A.



B.