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Predictors of response to anti-IL6 monoclonal antibody therapy (siltuximab) in idiopathic multicentric Castleman disease: secondary analyses of phase II clinical trial data

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Summary

Siltuximab is the only US Food and Drug Administration-approved treatment for idiopathic multicentric Castleman disease (iMCD), a rare haematological disorder associated with substantial morbidity and mortality. Although siltuximab induces a response in a significant proportion of iMCD patients via interleukin 6 (IL6) neutralization, it is not universally effective. To develop a predictive model of response, we performed an in-depth analysis of 38 baseline laboratory parameters in iMCD patients from the phase II siltuximab trial who met criteria for treatment response or treatment failure. Univariate analyses identified eight baseline laboratory parameters that were significantly different between responders and treatment failures: albumin, immunoglobulin G (IgG), immunoglobulin A, C reactive protein (CRP), fibrinogen, haemoglobin, sodium and triglycerides. Stepwise logistic regression analysis of these candidate parameters identified a top performing model that included fibrinogen, IgG, haemoglobin and CRP. Based on cross-validation of the final multivariate logistic regression model, the model accurately discriminated responders from those who failed treatment (area under the receiver operator characteristic curve 0·86, 95% confidence interval: 0·73–0·95). All four laboratory parameters associated with response to siltuximab have biological relationships with IL6 and acute inflammation. Our model suggests that iMCD patients with laboratory evidence of an inflammatory syndrome are the best candidates for siltuximab therapy.

Keywords: idiopathic multicentric Castleman disease, siltuximab, interleukin-6.

Human herpesvirus (HHV) 8-negative, idiopathic multicentric Castleman disease (iMCD) is a rare haematological disease characterized by multiple regions of enlarged lymph nodes that demonstrate a spectrum of characteristic histopathological features. The hyaline vascular/hypervascular histopathological subtype features prominent atrophic germinal centres with increased vascularity, whereas the plasmacytic histopathological subtype includes hyperplastic germinal centres with plasmacytosis; 'mixed' includes features of both (Fajgenbaum *et al*, 2017). Patients also display heterogeneous clinical and laboratory abnormalities, including constitutional symptoms, anasarca, organomegaly, renal failure, anaemia, hypergammaglobulinaemia, hypoalbuminaemia, thrombocytopenia or thrombocytosis, and elevated C reactive protein (CRP), due to elevated levels of inflammatory cytokines (Iwaki *et al*, 2016; Srkalovic *et al*, 2017). Some patients present with mild symptoms that do not require hospitalization while others present with acute episodes of multi-organ dysfunction requiring intensive care. The diagnosis of iMCD is challenging as its clinical and histopathological features overlap with other diseases, which must be excluded prior to making a definitive diagnosis (Fajgenbaum *et al*, 2017).

The aetiology of iMCD is unknown, and multiple mechanisms probably contribute to its associated hypercytokinaemia. Excessive interleukin 6 (IL6) signalling is the established mechanism in a subset of cases (Fajgenbaum *et al*, 2014). Yoshizaki *et al* (1989) identified a clinical correlation between serum IL6 and iMCD symptoms. Subsequent work found that overexpression of IL6 in mice recapitulates many iMCD features, including anaemia, hypoalbuminaemia,

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hypergammaglobulinaemia and lymphadenopathy (Brandt *et al*, 1990; Screpanti *et al*, 1995; Katsume *et al*, 2002). IL6 is known to induce B cell and plasma cell maturation, acute inflammation, secretion of vascular endothelial growth factor (VEGF), and autoimmune manifestations characteristic of iMCD (van Rhee *et al*, 2010a,b, 2014). As a result, monoclonal antibodies directed at the IL6 receptor (tocilizumab) and IL6 (siltuximab) were developed as iMCD therapies.

An open-label study of tocilizumab demonstrated its efficacy to decrease acute-phase reactants, such as CRP and fibrinogen, alleviate anaemia and shrink enlarged lymph nodes in a large proportion of iMCD patients, leading to its regulatory approval in Japan (Nishimoto *et al*, 2005). However, tocilizumab was not approved by the United States Food and Drug Administration (US FDA) for the treatment of iMCD because it never underwent a randomized controlled trial. Siltuximab received US FDA approval for iMCD following a randomized controlled trial that achieved its primary endpoint (van Rhee *et al*, 2010a). In the trial, 34% of patients who received siltuximab achieved partial or complete response compared with 0% of those who received placebo (van Rhee *et al*, 2014). However, a significant proportion of patients did not respond to siltuximab, and it is not known why these patients did not respond. A recent retrospective study (Fajgenbaum *et al*, 2017) found that patients in the siltuximab phase II clinical trial who demonstrated greater numbers of iMCD minor criteria, as defined by the iMCD diagnostic criteria (Fajgenbaum *et al*, 2017), had higher response rates. This study did not explore predictive baseline laboratory parameters.

Considering that iMCD patients can present with acute and life-threatening multi-organ failure, timely intervention with siltuximab is essential for those individuals who will demonstrate dramatic improvement. For those patients who will not respond, timely administration of second-line treatment options – corticosteroids, rituximab, cytotoxic chemotherapy or immunomodulatory agents – is needed to prevent disease progression and death. Therefore, identification of siltuximab response predictors may lead to faster administration of appropriate therapies and, potentially, improve patient outcomes. Herein, we performed an in-depth characterization of the siltuximab phase II randomized controlled trial patients who either met response criteria or failed treatment. Using baseline biomarkers, we developed a model to predict treatment response.

Methods

Siltuximab phase II study design and patient population

We performed secondary analyses of data obtained from the phase II randomized, double-blind, placebo-controlled trial of siltuximab (NCT01024036) (van Rhee *et al*, 2014), the details of which have been previously described (van Rhee *et al*, 2014). Briefly, subjects aged ≥18 years with symptomatic, human immunodeficiency virus-negative, and HHV-8-negative iMCD (as confirmed by central pathology review), baseline laboratory values within specified ranges (absolute neutrophil count $\geq 1{\cdot}0 \times 10^9$/l; platelet count $\geq 75 \times 10^9$/l; alanine aminotransferase, total bilirubin and alkaline phosphatase liver fraction within 2·5 times the upper limit of normal (ULN); serum creatinine ≤265 μmol/l), and an Eastern Cooperative Oncology Group (ECOG) Performance Status 0–2 were eligible for inclusion. Subjects were randomized to receive siltuximab or placebo every 3 weeks along with best supportive care, which could include up to 1 mg/kg/day of prednisone or equivalent, until treatment failure, discontinuation of treatment, withdrawal from the study or 48 weeks after the last subject started treatment (van Rhee *et al*, 2014). Subjects who met treatment failure criteria were unblinded and, if randomized to placebo, able to crossover to siltuximab. Response was defined as durable tumour (lymph node) and symptomatic response lasting ≥18 weeks. Complete response was defined as the complete disappearance of all measurable and evaluable disease and resolution of baseline symptoms attributed to iMCD, according to 34 investigator-graded disease-related signs and symptoms, whereas partial response was defined as a ≥50% decrease in sum of the product of the diameters of index lymph node lesion(s), no worsening of the 34 signs and symptoms, and absence of treatment failure. Treatment failure was defined as any of the following: (i) a sustained increase from baseline in disease-related symptoms ≥Grade 2 persisting for at least 3 weeks; (ii) onset of any new disease-related symptoms (Grade 3 or higher); (iii) sustained (i.e., at least 3 weeks) deterioration in performance status (≥2 point increase from baseline in ECOG Performance Status); (iv) radiological progression, as measured by modified Cheson criteria (Cheson *et al*, 2007); or (v) initiation of any other therapy intended to treat iMCD (i.e., prohibited treatments) (van Rhee *et al*, 2014).

Of the 79 subjects who met inclusion criteria, 53 were randomized to receive siltuximab and 26 were randomized to receive placebo. Thirteen subjects (50%) in the placebo arm crossed over to receive siltuximab. In total, 66 patients received siltuximab either by intent-to-treat or by cross-over (Fig 1) (van Rhee *et al*, 2014). To better characterize response predictors, subjects who neither achieved response nor treatment failure during the study period (i.e. stable disease) ($N = 26$) were removed from our analyses. Subsequent analyses included only siltuximab-treated subjects who achieved either partial or complete response ($N = 18$) (treatment response group) or who failed treatment ($N = 22$) (treatment failure group).

Statistical analyses

Descriptive analyses were performed on demographic, clinical and laboratory data at baseline, defined as prior to the first infusion of siltuximab on cycle 1 day 1. When unavailable,

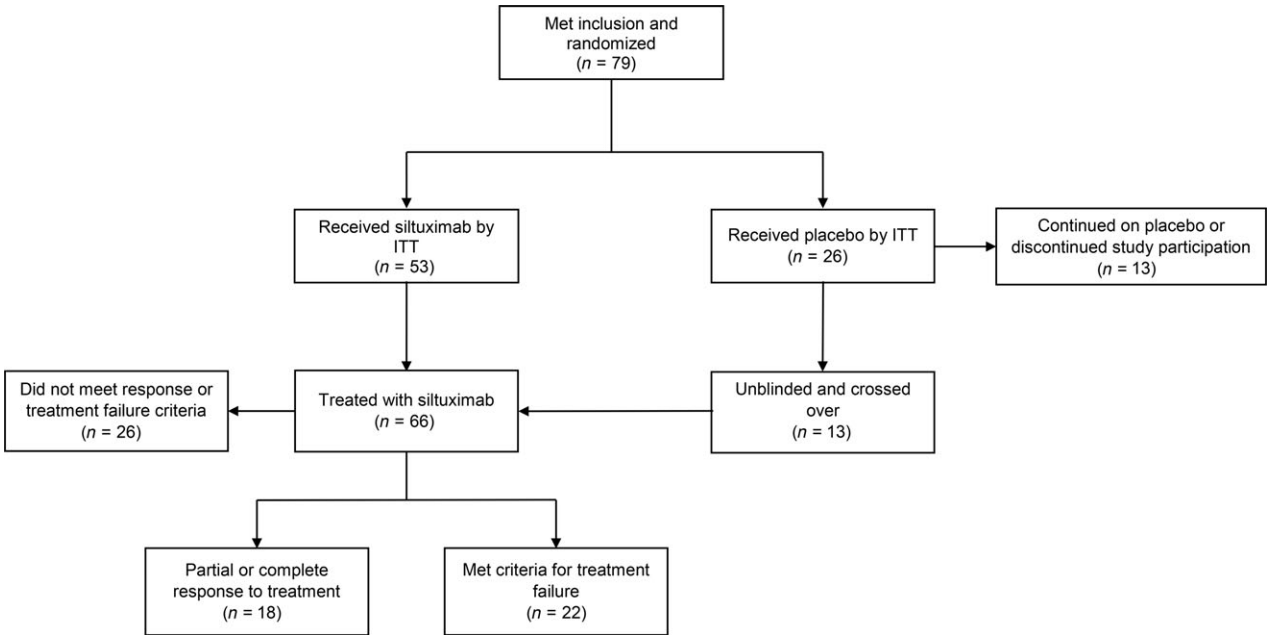

Fig 1. Flow of patients from the phase II randomized, double-blind, placebo-controlled trial of siltuximab (NCT01024036). ITT, intention-to-treat.

screening data (collected within 28 days prior to cycle 1 day 1) were used. Pearson correlation coefficients and *P*-values were computed for comparisons.

Using all baseline laboratory parameters, a principal component analysis (PCA) was performed to determine if treatment response and treatment failure groups cluster. As neither the first nor second principal component separated patients by response status, we developed a logistic regression model to identify predictive parameters.

To develop the predictive model, univariate analysis was performed on all 38 baseline variables. *P*-values were computed using the Mann–Whitney *U* test for continuous non-normal variables and chi-square test (or Fisher exact test) for categorical variables. After false discovery rate (FDR) correction, variables with $P < 0{\cdot}10$ were selected as possible candidate variables for logistic regression. Candidate variables were examined against their clinically normal range and excluded from logistic regression if the median value for both the treatment response and treatment failure groups were in the clinically normal range. Multicollinearity was assessed, and variables were retained if their variance inflation factor (VIF) was <5.

Laboratory variables were $\log_{10}$ transformed prior to regression analysis. A stepwise logistic model was performed with the candidate variables using a forward-backward approach, which selects the best predictors based on the lowest Akaike Information Criterion (AIC) (Akaike, 2011). The final logistic regression model was computed using the predictors identified from the stepwise selection method. Four-fold cross-validation was performed to assess the accuracy of the model and the area under the receiver operator curve (AUC) was determined (Robin *et al*, 2011). All analyses were completed using R computing software (version 3.4.3) (R Core Team, 2018). Unless otherwise noted, an alpha value of 0·05 was considered statistically significant.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Cohort baseline characteristics

Of the 40 subjects in the phase II siltuximab clinical trial who achieved either partial or complete response (treatment response group, $N = 18$) or who failed treatment (treatment failure group, $N = 22$), 16 were female (40%) and the median age was 48 years (interquartile range: 39–55). Univariate analysis of baseline characteristics compared by treatment response found no significant differences in demographic characteristics (Table I) or clinical abnormalities (Table II). There was a trend towards the presence of a palpably enlarged liver ($P = 0{\cdot}053$) and spleen ($P = 0{\cdot}114$) in the treatment failure group. Lymph node histopathological subtype was significantly different between the groups ($P = 0{\cdot}003$). All 12 subjects identified as hyaline vascular/hypervascular histopathological subtype were in the treatment

Table I. Demographic and disease characteristics of the treatment failure and treatment response groups.

	Treatment failure (N = 22)	Treatment response (N = 18)	P-value (FDR corrected)
Demographic characteristics			
Age (years)	48·5 [46·3; 55·0]	45·0 [37·0; 55·8]	0·793
Female	9 (40·9)	7 (38·9)	1·000
Race			0·665
Asian	11 (50·0)	12 (66·7)	
Black/African American	1 (4·6)	2 (11·1)	
Native Hawaiian/other Pacific Islander	0 (0)	1 (5·6)	
Not reported	1 (4·6)	0 (0)	
Other	1 (4·6)	0 (0)	
White	8 (36·4)	3 (16·7)	
Disease characteristics			
Histopathology			0·003
Hyaline vascular	12 (54·6)	0 (0)	
Mixed	9 (40·9)	11 (61·1)	
Plasmacytic	1 (4·6)	7 (38·9)	
Corticosteroid use at baseline	9 (40·9)	5 (27·8)	0·793
Years since diagnosis	0·6 [0·4; 1·7]	0·6 [0·4; 2·7]	0·883

Data are presented as median [interquartile range] for continuous variables as computed by Mann–Whitney U test and applied false discovery rate (FDR) correction.
Data are presented as count (%) for categorical variables as computed by Chi-square or Fisher exact test and applied FDR correction.

failure group. As expected, significant correlations were identified between laboratory parameters, with correlations ≥ the absolute value of 0·80 observed between white blood cell and neutrophil counts (r = 0·9); the inflammatory markers, CRP and fibrinogen (r = 0·8); liver enzymes, alanine aminotransferase and aspartate aminotransferase (r = 0·8); iron levels and transferrin saturation (r = 0·8); total cholesterol and low-density lipoprotein cholesterol levels (r = 0·9); hepcidin and ferritin (r = 0·8); immunoglobulin G (IgG) and total blood protein levels (r = 0·9); and the coagulation parameters, prothrombin international normalized ratio and prothrombin time (r = 0·8) (Figure S1). Less strong correlations were identified for other laboratory tests.

Development of a stepwise predictive model of response to treatment

As PCA analysis (Fig 2) did not demonstrate clear separation by response status, we began model development to identify a limited number of laboratory parameters that could accurately predict treatment response. To do this, we performed univariate analyses of baseline laboratory parameters between the two groups, which identified eight laboratory tests with significant differences (P < 0·10) between the treatment failure and response groups (Tables III and SI, Fig 3). We then examined each group's median laboratory test value against the test's normal range. The median values were outside of the normal range for six of eight parameters for the treatment response group and within the normal range for all parameters for the treatment failure group. Sodium and triglycerides had median values within the normal range for both groups and were therefore excluded as potential candidate parameters for model generation. Further, to limit redundancy of strongly correlated variables in our model, multicollinearity was examined and the VIFs of all remaining variables were confirmed to be within a predefined range of <5. This analysis pipeline identified six baseline laboratory parameters (albumin, CRP, fibrinogen, haemoglobin, immunoglobulin A [IgA] and IgG) as candidates for generating a stepwise model.

To develop the model for predicting treatment response or failure, we employed a stepwise selection to find the best combination of parameters using the fewest number of variables. The model with the lowest AIC value included CRP, fibrinogen, haemoglobin and IgG. According to this model, when all other variables are kept equal, an increase in levels of fibrinogen or IgG increases the log odds of response to siltuximab, whereas an increase in levels of haemoglobin or CRP decreases the log odds of response to treatment. The values of the coefficients, which are related to the contribution of each variable to the logistic regression model, are provided in Table IV. The model explains 57% (corrected R^2) of the variance in treatment response, and all four variables are significantly associated with treatment response in the final regression model. A receiver operator characteristic (ROC) curve was calculated to examine the performance of the model at classifying patients into treatment response or treatment failure groups over a range of sensitivity and (1 − specificity) values (Fig 4). Based on four-fold cross-validation, the observed smoothed AUC was 0·86 [95% confidence interval: 0·73–0·95]. The predicted probability of response for each patient is shown in Fig 5.

Table II. Baseline clinical abnormalities of the treatment failure and treatment response groups.

	Count (%)		
	Treatment failure (N = 22)	Treatment response (N = 17)	P-value
Autoimmune phenomena	0 (0)	1 (5·9)	0·436
Fluid retention	9 (40·9)	5 (29·4)	0·685
MCD other symptoms (e.g., fever, fatigue, weight loss)	4 (18·2)	3 (17·7)	1·000
Neuropathy	10 (45·5)	5 (29·4)	0·491
Skin disorders	10 (45·5)	8 (47·1)	1·000
Spleen, palpable by physical examination	4 (18·2)	0 (0)	0·114
Liver, palpable by physical examination	5 (22·7)	0 (0)	0·053

One patient in the response group did not have clinical features assessed at baseline.
MCD, multicentric Castleman disease.

Discussion

Siltuximab is the only US FDA-approved treatment for iMCD based upon its ability to induce a response in a significant proportion of patients. However, it is not universally effective (van Rhee *et al*, 2014; Fajgenbaum *et al*, 2017). In a previous analysis of data obtained from the phase II siltuximab clinical trial, Casper *et al* (2015) investigated the association between select baseline laboratory parameters, including CRP and IL6, and treatment response in the siltuximab arm of the phase II clinical trial. Their analysis did not find a significant association between baseline levels of IL6 or CRP and treatment response; however, they did observe a trend towards higher CRP and IL6 levels in the treatment response group (Casper *et al*, 2015).

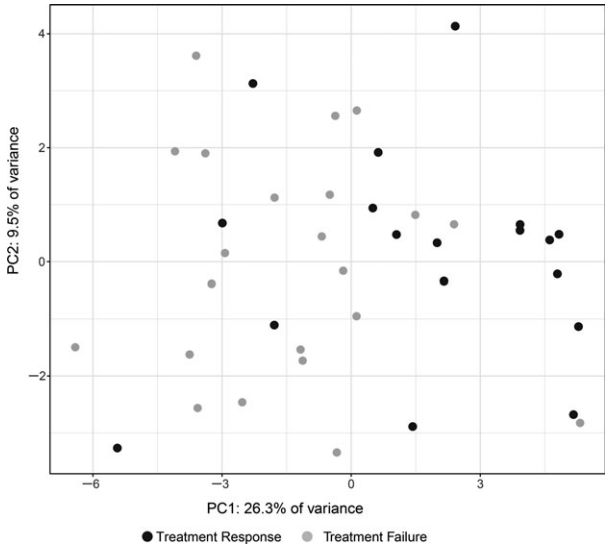

Fig 2. Principal component analysis of treatment failure (N = 22) and treatment response (N = 18) groups using baseline laboratory values. Neither principal component (PC) 1 nor PC2 separated patients by response status.

We performed a secondary analysis of the phase II siltuximab clinical trial to identify baseline laboratory parameters associated with treatment response and treatment failure. In contrast to the study reported by Casper *et al* (2015), we removed patients with ambiguous outcomes that did not meet treatment response or failure criteria because it is unclear if 'stable disease' is meaningful relative to the natural history of iMCD. Additionally, we included patients who crossed-over from placebo to siltuximab in our analyses. The overall purpose was to have two separate cohorts comprising patients demonstrating clear treatment response or failure. Our analyses of all 38 baseline laboratory parameters identified eight that were significantly different between the treatment response and treatment failure groups, six of which (albumin, CRP,

Table III. Significantly different baseline laboratory parameters between the treatment failure and treatment response groups.

	Treatment failure (N = 22)	Treatment response (N = 18)	P-value (FDR corrected)
Albumin (g/l)	38·0 [34·2; 41·9]	30·5 [24·3; 35·7]	0·038
C reactive protein (mg/l)	6·8 [2·6; 25·9]	38·0 [25·6; 107·8]	0·065
Fibrinogen (g/l)	4·0 [3·5; 5·6]	7·6 [5·5; 8·7]	0·010
Haemoglobin (g/l)	135·5 [114·3; 141·8]	99·0 [89·6; 112·3]	0·003
Immunoglobulin A (g/l)	2·5 [1·9; 3·7]	4·8 [3·4; 5·8]	0·033
Immunoglobulin G (g/l)	14·3 [11·6; 15·7]	36·5 [26·8; 60·2]	0·003
Sodium (mmol/l)	140·0 [138·2; 141·7]	136·5 [135·0; 138·0]	0·032
Triglycerides (mmol/l)	1·5 [1·0; 1·6]	0·7 [0·5; 1·0]	0·004

Data are presented as median [interquartile range] as computed by Mann–Whitney U test and applied false discovery rate (FDR) correction.

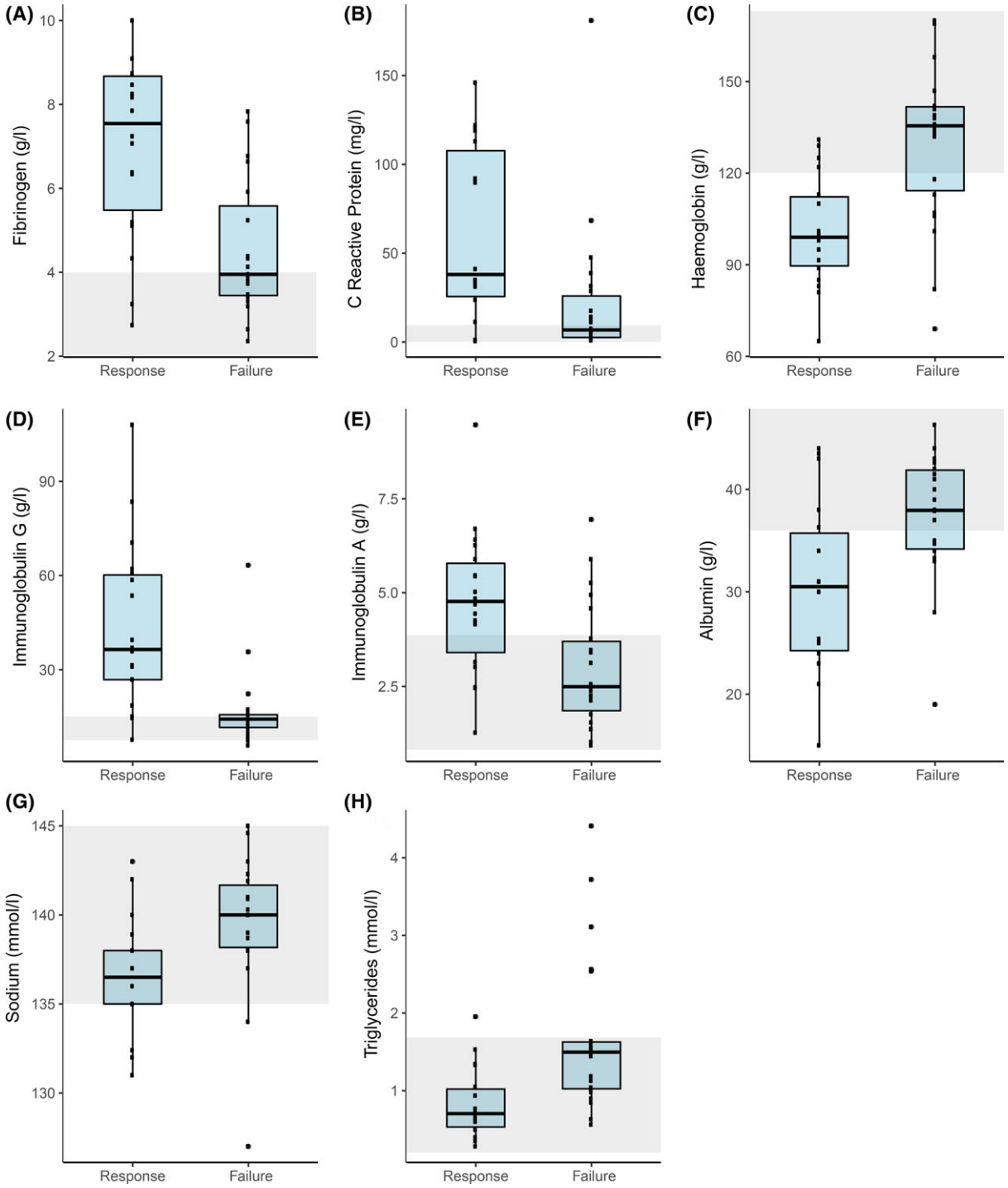

Fig 3. Univariate analysis of baseline laboratory values of treatment failure ($N = 22$) and treatment response ($N = 18$) group individuals who received siltuximab. Box plots of baseline (A) fibrinogen, (B) C reactive protein, (C) haemoglobin, (D) immunoglobulin G, (E) immunoglobulin A, (F) albumin, (G) sodium and (H) triglycerides show medians, lower quartile, upper quartile, range and outliers. Each box represents the range from the first quartile (Q1) to the third quartile (Q3). The median is indicated by the bold horizontal line. The vertical whiskers extend respectively from Q1 and Q3 to the minimum and maximum data points, excluding outliers. Outliers are represented as points beyond 1·5 times the interquartile range. The normal range of each parameter is depicted by the shaded region. [Colour figure can be viewed at wileyonlinelibrary.com]

fibrinogen, haemoglobin, IgA, IgG) were outside of the normal ranges. A stepwise logistic regression analysis performed with the six candidate biomarkers, whose median values were abnormal for either the treatment response or treatment failure group, identified a model that differentiated response status with high accuracy.

	Coefficient (β)	Standard error	*Z* values	*P*-value
Intercept	8·985	13·753	0·653	0·514
Haemoglobin (g/l)	−13·429	6·697	−2·005	0·045
Immunoglobulin G (g/l)	6·505	2·647	2·458	0·014
C reactive protein (mg/l)	−3·216	1·502	−2·141	0·032
Fibrinogen (g/l)	11·125	5·474	2·032	0·042

Table IV. Logistic regression results of the model predicting response to siltuximab.

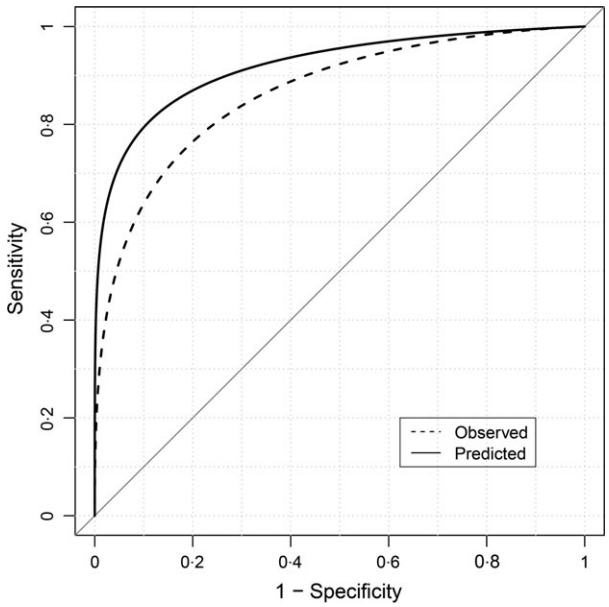

Fig 4. Receiver operator characteristic (ROC) curve of the predictive model of response to siltuximab computed by 4-fold cross-validation. The variables included in the model include: C reactive protein (CRP), fibrinogen, haemoglobin and immunoglobulin G (IgG). The predicted area under the curve (AUC) (solid curve) is 0·92 [95% confidence interval (CI): 0·79–0·96] and the observed AUC (dashed curve) is 0·86 (95% CI: 0·73–0·95).

The final model included four laboratory parameters: haemoglobin, fibrinogen, CRP, and IgG. The AUC of the model was 0·86, which means that the model has an 86% predictive ability to accurately distinguish individuals into the treatment response group or the treatment failure group. Regarding the ROC curves, a perfect predictive model assigns a probability of 1 to all patients who demonstrate the predicted outcome and a probability of 0 to patients who do not (Fawcett, 2006). In our model, 15 of 18 (83%) patients in the treatment response group had a >50% predicted probability of response, whereas 19 of 22 (86%) patients in the treatment failure group had a <50% predicted probability of response.

Interestingly, the univariate and multivariate analyses produced seemingly conflicting results regarding the association of CRP with response to siltuximab. By univariate analysis, increased CRP values were positively associated with likelihood of response; yet, by multivariate logistic regression analysis, increased CRP values were negatively associated with likelihood of response. This apparent discrepancy is probably the result of many factors, including collinearity and relative strength of association, which affect the magnitude of each coefficient within a logistic regression model. Further, the coefficient for each covariate can only be considered in the context of the other covariates included in the model. Of note, the magnitude of the negative CRP coefficient (3·216) was smaller than the magnitudes of the other covariates. The positive coefficient for fibrinogen (11·125), another acute-phase reactant, is over three times greater in magnitude. Thus, despite the negative CRP coefficient, a patient exhibiting an inflammatory phenotype on multiple serum markers would probably be predicted to achieve a positive response by our model.

Though IL6 itself was not significantly different between the two groups, the eight laboratory parameters identified all have important relationships with IL6 and acute inflammation. IL6, produced by antigen-presenting cells and non-haematopoietic cells following external stimuli, is an important mediator of the inflammatory response and the major regulator of hepatic production of acute phase proteins, such as fibrinogen, CRP and hepcidin (Castell *et al*, 1989; Xing *et al*, 1998; Wong *et al*, 2007; Dienz *et al*, 2009). Hepcidin is a master regulator of iron metabolism, and excess levels cause reduced iron availability and decreased haemoglobin (D'Angelo, 2013). Albumin is a negative acute phase reactant whose synthesis is decreased by the liver during acute inflammation (Moshage *et al*, 1987). IL6 is also a potent growth factor for B cells and inducer of plasma cell differentiation and antibody production, including both IgG and IgA (Castell *et al*, 1989). Furthermore, sodium is bound by IgG, resulting in artificially low observed levels in patients with elevated IgG in the setting of monoclonal gammopathies (Yu *et al*, 2005). Lastly, excess IL6 causes a decrease in circulating triglycerides (Fernandez-Real *et al*, 2000; Hashizume *et al*, 2010). Our results demonstrate that IL6 blockade with siltuximab is more likely to be effective for iMCD patients who have greater abnormalities in laboratory parameters associated with IL6-mediated processes. For those patients who failed treatment, pathological mechanisms other than IL6 signalling are probably driving iMCD. Additional work is needed to uncover alternative therapeutic targets for patients who do not benefit from siltuximab.

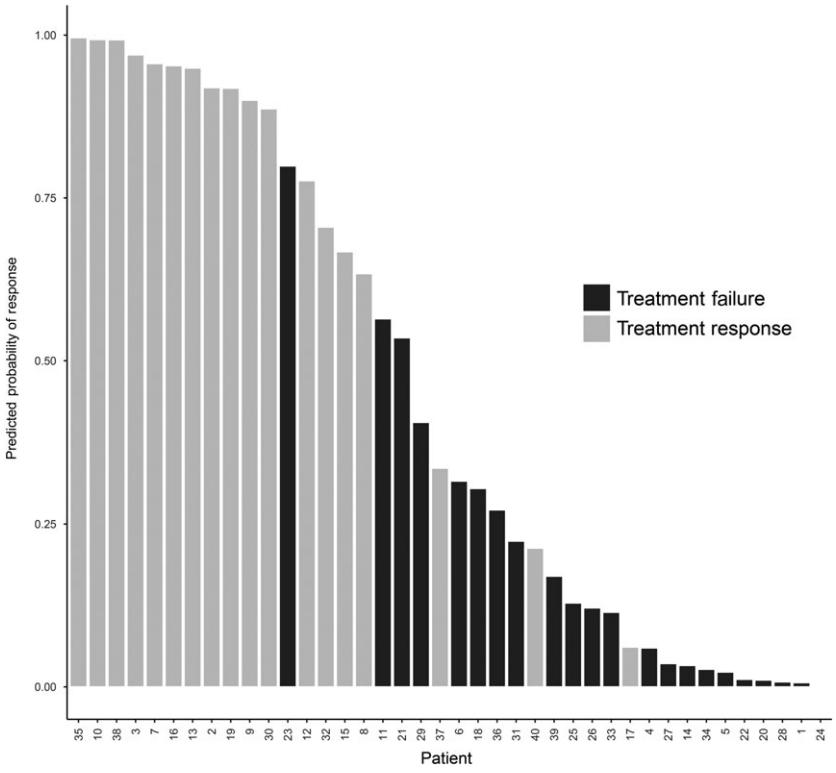

Fig 5. Bar chart depicting the predicted probability of response for each patient who responded ($N = 18$) or failed treatment ($N = 22$).

It is also important to note that none of the iMCD patients with hyaline vascular/hypervascular histopathology met the threshold of response defined by the clinical trial. However, these patients may still benefit from treatment with siltuximab, as iMCD patients with hyaline vascular/hypervascular histopathology did benefit according to secondary endpoints and investigator assessment of response in this trial (van Rhee *et al*, 2014). Additionally, some patients with the hyaline vascular/hypervascular histopathology did meet response criteria in the phase I study of siltuximab (van Rhee *et al*, 2010a).

In summary, iMCD patients exhibiting a clear constellation of abnormal inflammatory parameters, including CRP, fibrinogen, IgG and haemoglobin, are the best candidates for siltuximab therapy. For those iMCD patients who do not have these abnormal laboratory parameters, clinicians should still consider siltuximab as a first-line therapy as this model is not 100% sensitive or specific, it has not been validated in a second cohort, and siltuximab is currently the only FDA-approved treatment for iMCD. However, clinicians should have an increased index of suspicion that siltuximab may not work for these patients and be prepared to initiate alternative second-line therapies more quickly. It is also important for the treating clinician to be aware that patients with these abnormal inflammatory parameters may still fail treatment with siltuximab. For example, six of the 20 patients with CRP greater than two times the upper limit of normal failed to respond to siltuximab.

There are several limitations to this study that must be considered. While the dataset came from the largest clinical trial of iMCD to date, the sample size was limited. The phase II study included 79 patients across 19 countries, reflecting the challenge of collecting data on large samples of iMCD patients and the strict nature of the inclusion/exclusion criteria. The sample size for our analysis was further limited by exclusion of patients who did not demonstrate a clear response or failure on treatment. Given the small sample size, we limited the number of predictors used in the model to reduce overfitting. Due to the strict eligibility criteria, this trial may not have been representative of the full spectrum of iMCD. Specifically, baseline laboratory values within specified ranges and an ECOG Performance Status of 0–2 were required. Therefore, hospitalized patients and those with more significant disease severity were excluded (Oken *et al*, 1982; van Rhee *et al*, 2014). Patients with the recently described clinical subtype of iMCD characterized by thrombocytopenia, anasarca, fibrosis of bone marrow, renal dysfunction and organomegaly (TAFRO) would have probably also been excluded based on platelet count $<75 \times 10^9$/l or disease severity. Interestingly, iMCD-TAFRO patients demonstrate some features consistent with the treatment failure group in our study, such as normal IgG levels and hyaline vascular/hypervascular histopathology. On the other hand, TAFRO patients typically have elevated CRP, anaemia and low albumin, and siltuximab has been reported to be effective in some iMCD-TAFRO cases (Hawkins & Pillai, 2015; Behnia *et al*, 2017). Future studies including patients with iMCD-TAFRO are needed to determine if the proposed predictive model would apply. Lastly, although IL6/IL6 receptor

signalling is interrupted by both siltuximab (anti-IL6) and tocilizumab (anti-IL6 receptor), our findings are only relevant to siltuximab and further investigation of their implications for tocilizumab are needed.

Further research is needed to validate the predictors identified in this study. ACCELERATE (www.CDCN.org/ACCELERATE) is a global natural history registry of iMCD launched in 2016 that allows patients to directly enrol online. When adequate patient accrual has occurred, data in ACCELERATE may be utilized to test our predictive model and provide further clarity as to which iMCD patients are most likely to derive therapeutic benefit from siltuximab.

In summary, our data suggest that iMCD patients with several abnormal laboratory parameters indicative of an inflammatory state are the best candidates for siltuximab therapy. Given that iMCD may have a sudden and severe onset, timely treatment is necessary to save lives. A greater understanding of the parameters that increase or decrease the likelihood that patients will respond to siltuximab may improve clinician decision making, ultimately improving patient outcomes.

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Author contributions

DEM, SKP, DS, FvR and DCF developed the study methodology. DEM and SKP performed the analysis. DEM, SKP, DS, SN, CA, MG, CT, FvR and DCF interpreted the data. DEM, SKP, DS, SN, CA, MG, CT, FvR and DCF wrote and revised the manuscript.

Declaration of interests

SN, CA, MG and CT have been employed by Janssen Research & Development and own stock in Johnson & Johnson. DCF has received research funding from Janssen Research & Development. The other authors have no conflicts of interest to disclose.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Pearson correlation plot of baseline laboratory parameters.

Table S1. Additional baseline laboratory parameters of the treatment response and treatment failure groups.

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