Quantitative Changes in Serum Proteins Including CXCL13 Are Early Indicators of Response to Anti-IL6 Therapy in Idiopathic Multicentric Castleman Disease

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INTRODUCTION

- Idiopathic multicentric Castleman disease (iMCD) is a rare hematological disorder.
- Siltuximab, an interleukin (IL)-6 blockade, is the only FDA-approved treatment.
- In the Phase II study of siltuximab (NCT01024036), two-thirds of patients did not meet response criteria[1], and there are no early indicators of treatment response.
- Clinical onset involves polyclonal lymphoproliferation, constitutional symptoms, systemic inflammation and life-threatening cytokine storm-driven multi-organ failure.
- Chemokine (C-X-C motif) ligand 13 (CXCL13), a key regulator of lymph node germinal center development, was recently found to be the most elevated cytokine in iMCD flare, but the clinical significance of this is not yet clear.
- Early indicators of response to siltuximab are urgently needed to inform clinicians about the likelihood of patient response to therapy, adjust treatments if needed, and identify novel therapeutic targets for siltuximab non-responders.

OBJECTIVE

To detect whether kinetic changes in protein expression during early weeks of treatment are associated with anti-IL6 response using clinical and proteomic data

METHODS

- As part of the Phase II study of siltuximab (NCT01024036), clinical data and serum samples were collected from 52 subjects treated with siltuximab and 26 patients in the placebo arm at day 1, day 8, and day 64, as well as 44 healthy controls at a single time point.
- We analyzed 1,178 serum protein analytes quantified by SomaLogic SOMAscan.
- Linear mixed effects models were used to detect whether kinetic changes in protein expression were associated with siltuximab response in treated patients.
- Model Structure:
  *Expr. ~ Time * Treatment Response + (1/Patient ID) + Clinical Covariates*
- Clinical covariates include age, sex (plus interaction with time), and disease activity at baseline (using a modified CHAP- *CRP, Hemoglobin, Albumin, Performance Status*- score)
- A separate model was fitted using each protein, and significance of the interaction between time point and response (based on Benjamini-Hochberg False Discovery Rates, alpha = 0.05) was used to test for differences between responders and non-responders.

OVERALL RESULTS

- Demographic characteristics for 52 patients treated with siltuximab and 26 placebo arm patients are presented in Table 1.

Table 1. Demographic Information

		Siltuximab-treated		Placebo
		Responder	Non-responder	
N		**18**	**34**	**26**
Sex, N (%)	Female	8 (44.4)	14 (41.2)	4 (15.4)
	Male	10 (55.6)	20 (58.8)	22 (84.6)
Age	Mean (SD)	52.2 (15.0)	52.1 (12.7)	53.8 (13.8)
	Missing	0	5	2
Baseline CHAP Score	Mean (SD)	3.7 (2.5)	1.5 (2.4)	1.3 (1.6)
	Missing	1	1	2

- At day 8, 9 proteins were significantly different in responders compared to non-responders. (Table 2)
- At day 64, the number of significantly different proteins increased to 121, including 8 of the 9 proteins from day 8. (Fig. 1)

Table 2. Significant Proteins

Nine Proteins Significant at Day 8	Ten Most Significant Proteins at Day 64	Largest fold change at Day 64
IgA*	IgA*	Myokinase, human
NPS-PLA2	CD36 ANTIGEN	IL-6
CD5L*	IL-6	PPAC
CXCL13*	Growth hormone receptor	UBE2N
b2-Microglobulin*	FCG2B	Aflatoxin B1 aldehyde reductase
ART*	CRDL1	41
IL-18 BPa*	IGFBP-2	WNK3
NRP1*	C7	I-TAC
BCMA*	NovH	Midkine
----	IL-4	CXCL13*

*Significant at both time points
**Green shading indicated positive effect, red shading indicated negative effect

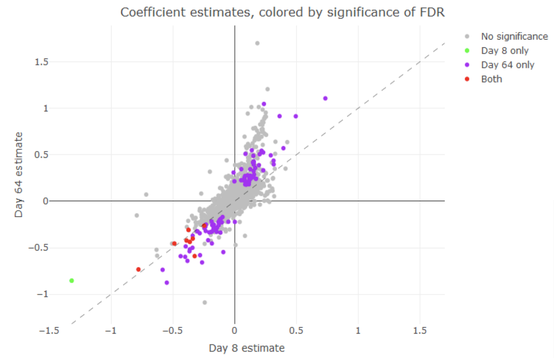

Figure 1. Coefficient estimates at day 8 plotted against those at day 64. Eight proteins were significantly decreased in responders compared to non-responders at both time points.

CXCL13 RESULTS

- The early and significant decline of CXCL13 in responders versus non-responders was highly notable (Day 8: FDR=0.02; Day 64: FDR=0.005). (Fig. 3 A,B)
- Prior to treatment, CXCL13 was significantly higher in this iMCD cohort compared to a group of age-matched healthy donors (p <0.0001).

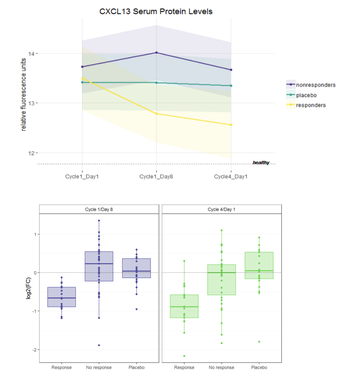

Figure 3.
Expression levels of CXCL13 over time presented by (A) relative expression levels and (B) log2(fold-change) over baseline

CONCLUSIONS

- This analysis represents the first use of high-quality serum proteomics data to study early indicators of response to treatment in iMCD.
- Proteins that change significantly in responders but remain abnormal in non-responders warrant further investigation as candidate therapeutic targets
- CXCL13, along with several other proteins that demonstrated significant decline by day 8, can be routinely measured and could serve as a panel that indicates the likelihood of response soon after commencing therapy, if validated in a separate cohort.
- These proteins could also provide a more continuous scale of response than traditional outcome measures.
- Given that iMCD may have a sudden and severe onset, early indicators of response to anti-IL6 therapy are critical for timely treatment administration.

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