Published in final edited form as:

Leuk Lymphoma. 2015 May ; 56(5): 1335–1341. doi:10.3109/10428194.2014.956313.

Longitudinal Analysis of Patient-Reported Symptoms Post-AuSCT and their Relationship to Inflammation in Patients with Multiple Myeloma

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Abstract

After autologous stem cell transplant (AuSCT), patients with multiple myeloma (MM) may receive lenalidomide maintenance therapy. This longitudinal study examined patient-reported symptom burden during the 3–9 months post-AuSCT and its association with maintenance therapy and circulating inflammatory markers. Fifty-one MM patients rated symptom severity weekly using the MD Anderson Symptom Inventory MM module. When possible, blood for inflammatory marker assay was drawn at enrollment. Trajectory analysis identified clusters of patients who consistently reported higher or lower symptom severity. Although disease was relatively stable 3–9 months post-AuSCT, patients were not symptom-free: 35% were in the high-symptom group. Fatigue, pain, numbness/tingling, bone aches, and muscle weakness were the most-severe symptoms. Controlled for clinical variables, elevated baseline TNF- α predicted high-symptom group membership ($p = 0.014$). Maintenance therapy and tumor response were not related to high symptom burden. Associations between Inflammation and symptom burden in this exploratory study warrant further confirmatory study.

Clinicaltrials.gov #NCT00688168.

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POTENTIAL CONFLICTS OF INTEREST

None.

Keywords

symptom; inflammation; patient-reported outcome (PRO); maintenance therapy; MD Anderson Symptom Inventory (MDASI); multiple myeloma

INTRODUCTION

High-dose therapy with autologous hematopoietic stem cell transplant (AuSCT) improves both overall and progression-free survival rates in patients with multiple myeloma (MM) [1–3]. Posttransplantation, patients are expected to enjoy relatively low disease burden before they ultimately relapse. Approximately 3 months post-AuSCT, patients with MM are often evaluated for possible initiation of maintenance therapy with an agent such as lenalidomide [1,2]. Clinical studies of low-dose oral lenalidomide post-AuSCT have shown improved progression-free survival [1,2] and demonstrated that lenalidomide is well tolerated by patients with MM in general and is especially preferred for patients with preexisting neuropathy [3,4], despite the possibility of hematological and nonhematological toxic effects.

The textbook description of complications from symptomatic MM includes asthenia, anorexia, and severe bone pain [5]. Although significant inflammation-related symptom development has been observed around white blood cell (WBC) nadir post-AuSCT [6], little is known about how patients feel, what characterizes patients who remain symptomatic, or how symptom burden differs during the 3–9 months post-AuSCT, when patients should have recovered from their transplant and are eligible to receive maintenance therapy. Further, whether systematic inflammation and residual disease play a role in producing high symptom burden is unknown. Characterizing post-AuSCT symptom burden and identifying its source should help both patients and clinicians to understand the symptom course.

Multiple symptoms can be driven by disease, prior or current treatment, or low-grade inflammation. The current study used the psychometrically validated multiple myeloma module of the MD Anderson Symptom Inventory (MDASI-MM) [7] to longitudinally track and identify the major symptoms reported by patients with MM who were either under observational follow-up or receiving maintenance therapy in the 3–9 months post-AuSCT. We examined patient and clinical factors as well as inflammatory markers that might be predictive of high symptom burden during this posttransplant period. Because interleukin (IL)-6 and tumor necrosis factor (TNF)- α are known to be necessary growth factors for the expansion and maintenance of MM cells [8], and because circulating levels of TNF- α are roughly proportionate to the total MM tumor mass in animals [9,10], we hypothesized that MM-driven inflammatory markers, most prominently TNF- α and/or IL-6, would be positively associated with higher symptom levels.

MATERIALS AND METHODS

Patients

Patients were recruited from 2008–2011 in the Department of Lymphoma/Myeloma outpatient clinic at The University of Texas MD Anderson Cancer Center in Houston,

Texas. Patients had a confirmed pathological diagnosis of MM, were at least 18 years old, had undergone induction therapy and their first AuSCT, and were scheduled for either lenalidomide maintenance therapy or observational follow-up. Patient characteristics and clinical parameters (age, sex, race, cancer stage, Charlson comorbidity score [11], induction and AuSCT treatment history, current maintenance-therapy status, body mass index [BMI]), blood counts (hemoglobin [Hgb], WBC, platelets) and other clinical values (β_2 microglobulin [β_2 M], albumin, calcium, creatinine) were recorded at the time of enrollment. Tumor response was recorded at 3 and 9 months post-AuSCT.

The study was approved by the MD Anderson Institutional Review Board and is registered at Clinicaltrials.gov, #NCT00688168. All participants gave written informed consent.

Multisymptom Assessment

The MDASI-MM is a patient-reported outcomes measure that assesses the severity of 13 common cancer-related symptoms [12] (pain, fatigue, nausea, vomiting, dry mouth, shortness of breath, lack of appetite, difficulty remembering, drowsiness, disturbed sleep, sadness, distress, and numbness/tingling) plus seven MM-specific items (bone aches, muscle weakness, sore mouth/throat, rash, difficulty concentrating, constipation, and diarrhea) [7]. Patients rate symptom severity over the previous 24 hours on a 0–10 scale ranging from “not present” to “as bad as you can imagine.”

MDASI-MM assessments were conducted approximately 3 months post-AuSCT (baseline) and then weekly for up to 6 months. When the patient was away from the clinic, the assessments were completed via phone interview.

Inflammatory Marker Assay

We assessed inflammatory markers that have been identified as potentially relevant to symptoms in animal and human studies [6,13–15]. Blood sampling was scheduled for the morning on the day of the patient’s routine clinic visit approximately 3 months post-AuSCT, concurrent with the patient’s baseline MDASI-MM assessment. After serum isolation by centrifugation, samples were stored at -80°C for batch analysis. All serum proteins were measured in 25 μL of serum using MILLIPLEX map assays (EMD Millipore Corporation, Billerica, MA, USA) and acquired using a Luminex 100 Analyzer (Luminex Corporation, Austin, TX, USA) [16]. The Millipore nonmagnetic Human Soluble Cytokine Receptor Panel was used to measure soluble IL-1 receptors 1 (sIL-1R1) and 2 (sIL-1R2), soluble IL-2 receptor antagonist (sIL-2RA), soluble IL-6 receptor (sIL-6R), and soluble TNF- α receptors 1 (sTNF-R1) and 2 (sTNF-R2). C-reactive protein (CRP), a byproduct of inflammation, was measured in 1:27,000 diluted serum sample prior to analysis using the Millipore Human Cardiovascular Disease Panel 2. IL-1 receptor antagonist (IL-1RA) was measured in 100 μL of serum by enzyme-linked immunosorbent assay (R&D Systems, Inc., Minneapolis, MN, USA).

Statistical Analysis

The symptom outcome measure was the mean component score for the five most-severe MDASI-MM symptoms over the 6-month study period. We used this component score and

group-based trajectory modeling (GBTM), a statistical approach designed to group longitudinal observations into interrelated subgroups, to construct symptom trends over time and to investigate how many subgroups based on symptom severity would emerge [17,18]. Prevalence (percentages) of patients per symptom-severity subgroup were reported. Trends in symptom reduction or worsening over time were examined for each symptom-severity subgroup using quadratic models. We examined individual symptoms using the same strategy.

Descriptive analysis was used to present patient characteristics, laboratory results, and mean serum inflammatory marker levels. Alpha was set at $p = 0.05$. Significance testing was performed according to patients' maintenance-therapy status (lenalidomide versus none) and by symptom-severity group. Inflammatory markers that were undetectable in more than 10% of the samples were excluded from analysis; for each marker retained for analysis, individual samples with undetectable values were imputed to have one-half the lowest nonzero value from the samples with detectable values for that marker.

The Wilcoxon rank sum test was used to identify markers that were significantly related to high-symptom group membership, as candidates for the final logistic regression analysis. Adjustment for multiple comparisons was not applied for screening purposes but was used in the final modeling for each marker, wherein significance was set at $p = 0.033$ (0.05/6 symptom outcomes). The candidate markers in the final logistic regression analysis were transformed into natural log scale. The final logistic regression modeling employed stepwise selection to examine the predictive value of patient, clinical, and inflammatory factors on symptom-severity group membership. Time-independent variables included in all models were age, sex, stage, BMI, and maintenance-therapy status. The component score and the individual's symptom-severity group membership were the primary outcomes. Patients who contributed both serum samples and symptom data were included in this analysis.

Role of the Funding Source

This study was supported by grants from the National Cancer Institute (NCI) of the National Institutes of Health. Neither the NCI nor the National Institutes of Health had any role in the study design, data collection, analysis, interpretation, or preparation of the report.

RESULTS

Fifty-one patients who had undergone induction therapy and AuSCT were recruited to the study. Table I presents demographic and clinical characteristics of the 51 participants. There were no significant differences in any variable between patients who were receiving maintenance therapy ($n = 22$) and those who were not ($n = 29$). Of those receiving lenalidomide, 73% remained on therapy during the 6-month study. Four participants (8%) experienced disease progression or relapse during the study.

Symptoms, Trajectory Groups, and Disease Markers

All 51 patients were included in the symptom and baseline variable analyses. Regardless of maintenance-therapy status, the highest mean symptom ratings during the 6-month study were for fatigue, pain, numbness/tingling, bone aches, and muscle weakness. There were no

significant differences in the severity of the component score by age (younger or older than 65 years) or by sex.

Based on the five-symptom component score, trajectory analysis identified two groups: patients who consistently reported higher symptom severity (35%) (rated 4 on the MDASI-MM's 0–10 scale, indicating a moderate to severe level), and patients who consistently reported lower symptom severity (65%) (Table II). Patient factors (age, BMI, sex, race, cancer stage, comorbidities) and post-AuSCT tumor response did not differ significantly by symptom-severity group; see Table I.

Figure 1 presents the component-score trajectory for each group. Symptom severity remained stable across the 6-month study for both groups, by both linear and quadratic modeling (Table II). Table II also shows that presence or absence of lenalidomide maintenance therapy and post-AuSCT symptom severity were not associated with group membership. Additionally, no pre-AuSCT symptom was predictive of high-symptom group membership in the 3–9 months post-AuSCT.

Among the examined baseline blood counts (Hgb, WBC, platelets) and other biological test results (β 2M, albumin, calcium, creatinine), we observed higher β 2M levels (mean $\pm$ standard deviation [SD]) in the high-symptom group than in the low-symptom group (2.96 ± 1.26 mg/L versus 2.05 ± 0.58 mg/L, $p = 0.021$). In a logistic analysis of the 40 patients whose β 2M was measured, controlled for age, sex, BMI, race, MM stage, comorbidities, and maintenance-therapy status, higher β 2M at 3 months post-AuSCT was related to high-symptom group membership (estimate = 1.63, $p = 0.014$, odds ratio [OR] = 5.099, 95% confidence interval [CI] = 1.39–18.65).

Serum Inflammatory Markers

Of the 51 patients enrolled, 33 contributed serum samples. The 13 included markers (ie, those detectable in at least 90% of the samples) were IL-1RA, sIL-1R2, sIL-2RA, IL-6, sIL-6R, IL-8, IL-10, TNF- α , sTNF-R1, sTNF-R2, CRP, MIP-1 α and MCP-1.

Table III presents the mean concentration levels for all 13 inflammatory markers examined, by symptom-severity group. Wilcoxon rank sum test results indicated that IL-6 ($p = 0.002$) and TNF- α ($p = 0.007$) levels were significantly higher in the high-symptom group, whereas sIL-1R2 ($p = 0.001$) and sIL-2RA ($p = 0.045$) levels were significantly lower in the high-symptom group. There was no significant difference in TNF- α concentration levels between patients who were undergoing lenalidomide maintenance therapy and those who were not.

Figure 2 presents serum TNF- α concentrations by high-symptom versus low-symptom group membership. Wilcoxon rank sum test results indicated a significant difference in TNF- α levels by membership for the component score of the five most-severe symptoms and the individual symptoms fatigue, muscle weakness, and bone aches. No significant difference was observed in TNF- α levels between groups for pain.

Association between Inflammatory Factors and High-Symptom Group Membership

Each candidate marker (IL-6, sIL-1R2, sIL-2RA, and TNF- α) was examined by stepwise regression analysis for the five-symptom component score and the five symptoms individually, controlled for covariates (Table IV). Elevated TNF- α was the single marker significantly predictive of high-symptom group membership for five-symptom component ($p = 0.014$), as well as for fatigue ($p = 0.014$), muscle weakness ($p = 0.012$), and bone aches ($p = 0.011$). Elevated IL-6 was related to more-severe numbness/tingling ($p = 0.046$; not significant after adjustment for multiple comparisons). No significant results were found for the pain model.

DISCUSSION

In this longitudinal study of MM patients during the 3–9 months post-AuSCT, five symptoms (fatigue, pain, numbness/tingling, bone aches, and muscle weakness) measured quantitatively by MDASI-MM were the most severe, whether or not the patients received maintenance therapy. Based on the mean component score of these five most-severe symptoms, trajectory analysis indicated that approximately 35% (18/51) of patients clustered into a group with persistently higher symptoms. There was no difference in high-symptom group membership based on presence or absence of lenalidomide maintenance therapy, on tumor response, or on other patient or clinical factors. However, a higher baseline level of TNF- α was predictive of high-symptom group membership. Our results suggest that major symptom burden may be driven by low-level inflammation, as well as by neuropathy (numbness/tingling) related to bortezomib induction therapy. We observed that the severity of the five symptoms for each group was stable across the 6-month period.

A history of AuSCT and maintenance therapy were not likely to be significant sources of high symptom burden for these patients, for several reasons. (1) Most transplant-related symptoms would have resolved by 3 months post-AuSCT, when this study commenced [6]. (2) No differences were found in the proportion of patients in the high-symptom group by maintenance-therapy status. (3) The major symptom burden during the first 100 days post-AuSCT described in a previous study [6] differs from that reported during the 3–9 months post-AuSCT in this study. Not unexpectedly, the most-severe symptom was fatigue, which corroborates with another large, multiple-symptom oncology study [19]. Pain, muscle weakness, and bone aches are also relevant to MM patients, even though they may often be ignored. Although we did not see statistically significant relationships between tumor response and these symptoms, given the limited sample and the fact that a third of patients were not in complete response or very good partial response, an effect from low-grade residual and ongoing myeloma disease post-AuSCT cannot be ruled out. Low-level tumor burden (such as osteolytic bone disease accompanying cytokine overproduction that can dysregulate the bone marrow microenvironment) can persist and induce pain and bone aches. Numbness is likely due to prolonged neuropathic side effects from bortezomib-based induction therapy [20].

Pain may represent a mixed effect of disease-related and treatment-related bone pain [21]. Additional mixed modeling analysis indicated that, controlled for covariates, any 1 unit of change in bone pain resulted in 0.43 unit of change in pain score (estimate = 0.43, $p <$

0.001);) and 1 unit of change in neuropathic pain from bortezomib-based induction therapy resulted in 0.13 unit of change in pain score (estimate = 0.13, $p < 0.001$). In exploratory analysis of the role of inflammatory markers in producing high symptom burden, we observed that elevated serum TNF- α was significantly associated with high-symptom group membership in patients with MM, whether or not they received maintenance therapy. This result held true for the composite score of the five most-severe symptoms and individually for fatigue, muscle weakness, and bone aches.

TNF- α is a phylogenetically conserved signaling molecule synthesized by most of the cells of the body and by MM cells [8]. TNF- α plays an important pathogenic role in MM [22], and clinical evidence suggests that the circulating levels of TNF- α reflect and are roughly proportionate to total MM tumor mass [10]. To our knowledge, our study is the first to demonstrate that TNF- α may indicate MM disease-driven symptom burden post-AuSCT. We also examined two outer-cell-membrane receptors for TNF [13] (sTNF-R1 and sTNF-R2), but neither was relevant to symptom group membership. We cannot rule out a possible impact on TNF- α from maintenance therapy, as lenalidomide is a complex immunomodulatory drug [23]; however, we did not observe a significant difference in TNF- α by maintenance-therapy status.

IL-6 is a known growth factor for MM disease [24]. We observed an association between IL-6 and membership in the high-symptom group in univariate analysis ($p = 0.002$) that remained significant after adjusting for multiple comparisons but lost its significance in multivariate analysis when competing with TNF- α , sIL-1R2, and sIL-2RA. Perhaps IL-6 is more relevant to the development of a cluster of severe symptoms during aggressive cancer therapy, such as at WBC nadir of stem cell transplant or during concurrent chemoradiation therapy [6,14,15], which fits the sickness-behavior model. In the relatively calm post-AuSCT period of lenalidomide maintenance therapy or observational follow-up, IL-6 was not as strongly associated with persistent symptom burden as was TNF- α . Dexamethasone, which is often added upon occurrence of progression, was not used regularly during the study period.

Given that B2M represents a marker of the immunogenetic system, as one of the domains of human leukocyte antigen, and that elevated B2M was reported as one of the prognostic factors for poor progression-free survival in relapsed or refractory MM [25], the significant association between relatively higher β 2M and high-symptom group membership in the current study supports the notion that inflammatory activity is related to high symptom burden even in low-level, ongoing disease.

The current study has several limitations. First, the inflammatory relevance of the study is exploratory in nature due to the limited sample size. As a result of scheduling conflicts, only 33 of 51 patients contributed baseline serum samples for the translational component of the study. Because no significant differences in TNF- α concentration levels by maintenance-therapy status were found, we treated all 33 patients as the same group. Nevertheless, even with limited samples, the multivariate regression analysis was able to detect a significant association between TNF- α and high-symptom group membership on the basis of the first step of screening for relevant markers, indicating a large-enough effect size. A future study

with a larger sample and a more comprehensive time frame may confirm the existence of inflammation-driven symptom burden in this patient population. Second, because toxicity data is lacking in this study, we missed the opportunity to review the high symptom burden in relation to clinical conditions. Third, given the small proportion of elderly in the sample (27% > 65 years old, mainly because of the qualification for AuSCT), we did not observe the levels of fatigue, poor appetite, and bone pain in these elderly patients that have been reported in the literature. Finally, we observed more drop-off during the last 2 months of the study in the observational follow-up group than in the maintenance therapy group. However, the trajectory analysis took drop-off into consideration, so the group membership results should not have been affected by this factor.

Mechanism-based symptom management, such as anti-inflammatory intervention, in both animal and clinical studies in MM is warranted to further confirm the role of inflammation in the development of high symptom burden. Etanercept, used clinically to decrease the effects of TNF- α , has shown evidence of lowering pain, inflammation, and joint destruction in rheumatoid arthritis [26]. Although TNF- α has been studied for its role as a growth factor for MM [8], its effects on symptom production have not been examined in a human intervention study. Recent findings have implied that TNF- α is not required for anthracyclines to elicit therapeutic anticancer immune responses [27], suggesting that cytokine inhibition might be useful for symptom control. Given the effect of bortezomib on the immune system [28], consideration should be given to conducting a clinical trial during the post-AuSCT period rather than during bortezomib-based induction therapy.

In summary, this study defined the major symptom burden in MM patients 3–6 months post-AuSCT. Although not a majority, 35% of patients reported a cluster of moderate to severe symptoms that were quite stable over this period. Higher levels of TNF- α after recovery from AuSCT (3 months posttransplant) were significantly associated with greater symptom severity over the next 6 months, whether or not patients were undergoing maintenance therapy. These results are a step toward establishing a better understanding of the nature of disease-driven and treatment-induced symptom burden in MM.

Acknowledgments

This study was supported by grants from the NCI, including NCI P01 CA124787 to Charles Cleeland and MD Anderson Cancer Center Support Grant NCI P30 CA016672. Robert Orłowski acknowledges support from the MD Anderson Cancer Center SPORE in Multiple Myeloma (NCI P50 CA142509) and the Diane & John Grace Family Foundation.

The authors acknowledge editorial assistance from Jeanie F. Woodruff, BS, ELS and data collection and management from Jackie Joy, Venus M. Ilagan, BA, CCRP, Brooke White, and Gary M. Mobley, BS, MA.

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Figure 1.

High-symptom versus low-symptom group membership in patients with multiple myeloma 3–9 months after autologous stem cell transplant ($n = 51$)

Abbreviation: MDASI-MM, MD Anderson Symptom Inventory multiple myeloma module.

Figure 2.

TNF-α concentrations by symptom-severity group membership*

*Wilcoxon rank sum test comparing the means of the marker values between groups.

Table 1Patient characteristics, by symptom-severity group ($n = 51$).

Characteristic	Low-Symptom Group ($n = 33$)		High-Symptom Group ($n = 18$)	
	Mean	SD	Mean	SD
Age	59.42	9.38	58.89	7.00
BMI	29.81	6.36	60.70	5.44
Characteristic	Value	n	%	%
Sex	Male	23	69.70	61.11
	Female	10	30.30	38.89
Race	White	24	72.73	77.78
	Other	9	27.27	22.22
Education	College or higher	28	84.85	66.67
	High school or lower	5	15.15	33.33
Marital status	Married	26	78.79	61.11
	Unmarried	7	21.21	38.89
Employment	Employed	16	48.48	3
	Unemployed	17	51.52	15
Cancer stage	1	21	63.64	7
	2	4	12.12	8
	3	7	21.21	3
Comorbid conditions	0	21	63.64	11
	1	12	36.36	7
Tumor response 3 months post-AuSCT	Complete response or very good partial response	23	69.70	8
	Other	10	30.30	10
Tumor response 9 months post-AuSCT	Complete response or very good partial response	19	63.33	7
	Other	11	36.67	6
Maintenance therapy	Yes	13	39.39	9
	No	20	60.61	9
Blood chemistry	Mean	SD	Mean	SD
Hemoglobin	12.48	1.48	11.83	1.17

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Characteristic	Low-Symptom Group (n = 33)		High-Symptom Group (n = 18)	
	Mean	SD	Mean	SD
White blood cell count	4.76	1.45	5.33	1.37
Platelets	193.77	63.40	181.33	45.22
Creatinine	0.91	0.29	0.93	0.38
Calcium	9.05	0.43	9.37	0.63
Albumin	4.25	0.44	4.09	0.40
β 2M	2.05	0.58	2.96	1.26
M-proteins				
Paraprotein	0.88	0.68	0.82	0.51
Kappa	18.09	30.38	13.74	8.64
Lambda	31.66	117.37	17.11	24.64
Kappa/lambda ratio	2.14	2.94	2.01	2.36
IgG	891.27	378.66	1059.00	473.17
IgA	69.57	44.71	125.71	247.92
IgM	42.17	25.96	45.86	27.66
Days from AuSCT as baseline	94.85	5.11	92.39	2.62

AuSCT, autologous stem cell transplant; β 2M, β 2 microglobulin; BMI, body mass index; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; SD, standard deviation.

Table IISymptom and clinical characteristics, by symptom-severity group membership ($n = 51$).

	Measure	High-symptom group	Low-symptom group	<i>p</i> -Value
Trajectory analysis				
All patients	<i>n</i> (%)	18 (35%)	33 (65%)	0.465
Without maintenance therapy		9 (31%)	20 (69%)	
With maintenance therapy		9 (41%)	13 (59%)	
Trajectory analysis of symptom trends over time				
Linear model	Estimate	−0.10	−0.029	*
Quadratic model	Estimate	0.004	0.0004	*
Symptom severity [†] post-AuSCT				
3 months post-AuSCT	Mean (SD)	4.65 (1.41)	1.51 (0.99)	< 0.001
6 months post-AuSCT		4.33 (1.53)	1.41 (1.42)	< 0.001
9 months post-AuSCT		4.78 (1.62)	1.15 (0.70)	< 0.001

AuSCT, autologous stem cell transplant; SD, standard deviation.

* Change over time within these four groups was not significant. *P* values for the high-symptom group were $p = 0.091$ (linear) and $p = 0.063$ (quadratic) and for the low-symptom group were $p = 0.364$ (linear) and $p = 0.752$ (quadratic).

[†] Symptom severity is for the component score, which is the mean of the five most-severe MDASI-MM items over 6 months: fatigue, pain, numbness/tingling, bone aches, and muscle weakness.

Table III

Mean concentrations of inflammatory markers, by symptom-severity group membership ($n = 33$).

Component score, five most-severe symptoms												
	Low-symptom group (<i>n</i> = 22)					High-symptom group (<i>n</i> = 11)					<i>p</i> -Value*	
	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max		
IL-6	5.84	16.24	1.92	0.00	77.54	23.63	35.35	6.83	0.00	105.31	0.002	
sIL-1R2	12091.88	4778.53	12025.19	148.02	21551.81	5864.48	3724.42	6570.03	140.58	11422.00	0.001	
sIL-2RA	1205.22	645.69	1064.30	86.10	2565.58	762.80	453.43	674.57	53.85	1391.52	0.045	
TNF-α	7.64	3.77	6.51	2.52	17.11	18.50	16.90	13.44	4.06	64.24	0.007	
IL-1RA	429.51	182.03	460.61	164.84	761.97	589.25	266.10	543.49	301.09	1151.37	0.122	
sTNF-R1	2633.21	2803.93	1815.53	201.92	13192.08	1624.43	812.29	1819.93	227.72	2780.91	0.717	
sTNF-R2	12268.27	12355.11	9193.01	1316.81	56047.49	8706.33	5995.70	8793.55	1294.69	22628.74	0.689	
sIL-6R	36160.30	21220.50	30924.72	7719.85	95592.02	26386.75	17257.51	28511.54	5417.27	57436.80	0.188	
IL-8	30.19	75.77	9.70	1.81	355.71	152.20	309.61	14.11	3.38	966.07	0.215	
IL-10	19.69	24.55	12.07	0.00	88.62	36.74	48.30	9.87	2.16	142.22	0.633	
CRP	73.07	94.19	44.46	0.44	385.31	186.31	260.71	62.36	6.27	835.28	0.412	
MCP-1	678.11	370.79	562.73	0.26	1586.79	920.84	370.14	890.92	411.33	1794.28	0.070	
MIP-1α	14.51	13.13	9.74	0.17	41.68	21.43	16.82	13.66	4.77	52.20	0.180	

Max, maximum value found; Min, minimum value found; SD, standard deviation.

* Wilcoxon rank sum test comparing the means of the marker values between groups. Bold indicates significant difference between groups.

Table IV

Association between inflammatory marker level and membership in the high-symptom group ($n = 33$, logistic regression with stepwise selection).

Marker	Estimate	SE	<i>p</i> -Value*
Five most-severe symptoms [†]			
Log_TNF- α	2.22	0.91	0.014
Fatigue			
Log_TNF- α	2.61	1.06	0.014
Numbness			
Log_IL-6	0.59	0.29	0.046
Muscle weakness			
Log_TNF- α	2.28	0.91	0.012
Bone aches			
Log_TNF- α	2.41	0.95	0.011

95% CI, 95% confidence interval; OR, odds ratio; SE, standard error of the mean.

* All associations between the four candidate markers and high-symptom group membership were significant in the mean comparison in the Wilcoxon rank sum test (Table III), transformed on a natural log scale. Each model was adjusted for age, sex, stage, body mass index, and maintenance-therapy status.

[†] The five most-severe MDASI-MM items over 6 months were fatigue, pain, numbness/tingling, bone aches, and muscle weakness.