Brain, Behavior, & Immunity - Health 23 (2022) 100480

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

The effect of tocilizumab on patient reported outcomes and inflammatory biomarkers in hematopoietic cell transplantation

Mallory R. Taylor [a,b,*], Cecilia J. Hillard [c], William R. Drobyski [d], Aniko Szabo [e], Bryon D. Johnson [d], Fenlu Zhu [f], Charles L. Raison [g,h], Steve W. Cole [i], Jennifer M. Knight [d,j,k]

[a] University of Washington School of Medicine, Department of Pediatrics, Division of Hematology/Oncology, Seattle, WA, USA
[b] Palliative Care and Resilience Lab, Center for Clinical and Translational Research, Seattle Children's Research Institute, Seattle, WA, USA
[c] Department of Pharmacology and Toxicology and Neuroscience Research Center, Medical College of Wisconsin, Milwaukee, WI, USA
[d] Section of BMT & Cellular Therapies, Division of Hematology/Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA
[e] Division of Biostatistics, Institute for Health & Society, Medical College of Wisconsin, Milwaukee, WI, USA
[f] Feinberg School of Medicine, Northwestern University, Department of Medicine, Division of Hematology/Oncology, Chicago, IL, USA
[g] Department of Human Development and Family Studies, School of Human Ecology, University of Wisconsin-Madison, Madison, WI, USA
[h] Department of Psychiatry, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA
[i] Departments of Psychiatry & Biobehavioral Sciences and Medicine, UCLA School of Medicine, Los Angeles, CA, USA
[j] Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, WI, USA
[k] Department of Microbiology & Immunology, Medical College of Wisconsin, Milwaukee, WI, USA

ARTICLE INFO

Keywords:
Hematopoietic cell transplantation
Cancer
Cytokines
Patient reported outcomes

ABSTRACT

Inflammatory physiology has been linked to behavioral and emotional symptoms in a variety of contexts and experimental paradigms. Hematopoietic cell transplantation (HCT) represents an intersection of significant immune dysregulation and psychosocial stress, and this biobehavioral relationship can influence important clinical outcomes. For those undergoing HCT with inflammation-related neuropsychiatric symptoms, using targeted agents such as the IL-6 receptor antagonist tocilizumab may be an effective therapeutic approach. We conducted an observational cohort study to explore patient reported outcomes (PROs) and inflammatory biomarkers among allogeneic HCT recipients who received tocilizumab compared to those who did not. Individuals on a larger trial of tocilizumab for prevention of graft-versus-host disease received a single dose of tocilizumab 24 h prior to stem cell infusion. Measures of anxiety, depression, pain, fatigue, and sleep quality and parallel blood samples for inflammatory cytokines were collected from participants and an analogous comparison cohort at baseline and Day 28 after stem cell infusion. Demographic and medical characteristics were reported; an analysis of covariance regression model was fitted to evaluate differences in PROs and distance correlation t-tests assessed for associations between biomarkers and PRO measures. For $n = 18$ tocilizumab-treated and $n = 22$ comparison patients, there were no significant differences between patient demographics, but the tocilizumab cohort had a different distribution of primary diagnoses ($p = 0.009$) with more patients with leukemias and a higher proportion of patients in their first remission (64% vs 28%, $p = 0.024$). Depression was higher at Day 28 compared to baseline in both groups (comparison group: +5.1 [95% CI 0.14–10, $p = 0.045$], tocilizumab: +8.6 [95% CI 2.3–15, $p = 0.011$]), though the difference between groups did not reach statistical significance. The tocilizumab group had significantly increased circulating IL-6 and decreased CRP at Day 28 (all $p < 0.05$). There was an association between collective baseline biomarkers and PROs (distance correlation dCor = 0.110, $p = 0.005$), but this same association was not present at Day 28 (dCor = −0.001, $p = 0.5$). In univariate analyses, a 10-fold increase in plasma IL-6 was associated with a 3.6-point higher depression score (95% CI 1.0–6.2, $p = 0.008$). In this exploratory analysis of PROs and inflammatory biomarkers in patients undergoing HCT, tocilizumab was not associated with favorable patient-reported symptom profiles. This finding is aligned with our prior work in the HCT population but diverges from hypothesized therapeutic effects of tocilizumab on depressive symptoms, thus highlighting the need for larger prospective translational studies in biobehavioral HCT research.

* Corresponding author. Seattle Children's Research Institute, 1920 Terry Ave, MS Cure 4, Seattle, WA, 98101, USA.
E-mail address: Molly.taylor@seattlechildrens.org (M.R. Taylor).

https://doi.org/10.1016/j.bbih.2022.100480
Received 23 December 2021; Received in revised form 17 March 2022; Accepted 5 June 2022
Available online 11 June 2022

1. Introduction

Inflammatory physiology has been linked to behavioral and emotional symptoms in a variety of contexts and experimental paradigms. For example, elevated levels of central nervous system (CNS) and peripheral pro-inflammatory cytokines have been strongly correlated with depressive symptoms, in addition to symptoms of anxiety and other neuropsychiatric disorders (Felger and Lotrich 2013; Miller and Raison 2016). This relationship is of particular relevance for medically ill individuals, where both inflammation and psychosocial distress may be more pronounced (Miller et al., 2009). For those with inflammation-related neuropsychiatric symptoms, specifically targeting inflammatory mechanisms and pathways may be an effective therapeutic approach (Kohler et al., 2014; Kappelmann et al., 2018). In a randomized trial of patients with treatment-refractory depression, Raison and colleagues tested the effects of the anti-tumor necrosis factor agent infliximab on depressive symptoms (Raison et al., 2013). They found that among those participants with baseline elevated inflammatory markers, infliximab was associated with significantly improved depressive symptoms at 12 weeks when compared to placebo. Similarly, blocking the pro-inflammatory cytokine interleukin-6 (IL-6) is of interest, as it has been reliably associated with depressive symptoms (Dowlati et al., 2010; Khandaker et al., 2014). Studies of the IL-6 receptor antagonist tocilizumab have been promising but limited by small sample sizes and methodological restrictions (Traki et al., 2014; Gossec et al., 2015).

The psychoneuroimmune network connecting inflammation and psychosocial experiences may be particularly important in the hematopoietic cell transplant (HCT) population. HCT is an intensive treatment for some malignancies, during which a patient's bone marrow is ablated with intensive chemotherapy with or without radiation, and then replaced with a donor's (allogeneic) or their own (autologous) stem cells. Patients undergoing HCT are often at the intersection of extreme immune dysregulation and emotional/environmental stress, and this biobehavioral relationship can have a significant impact on clinical outcomes (Costanzo et al., 2013; Knight et al., 2013). For example, patients with higher pre-HCT depression scores subsequently have a higher incidence of acute graft versus host disease (GVHD) and lower overall survival following transplant (El-Jawahri et al., 2017). An inflammatory gene expression profile called the conserved transcriptional response to adversity (CTRA) has been associated with lower socioeconomic status in HCT patients, and was also predictive of later cancer relapse and disease-free survival following transplant (Knight et al., 2016). Additionally, the prevalence of adverse psychosocial outcomes – poor mental health, financial stress, impaired quality of life (QOL) – is quite high in the HCT population (Kelly et al., 2021). Given the overlap of these physiologic and experiential processes, there is a unique opportunity to study and ultimately target these biobehavioral mechanisms in patients undergoing HCT.

In contrast to what would be hypothesized based on prior work, our group has reported that IL-6 signaling blockade with tocilizumab was associated with more, not less, depressive and other related symptoms in patients undergoing allogeneic HCT (Knight et al., 2021). Participants (n = 25) who received a single dose of tocilizumab prior to HCT had significantly higher depression scores at 28 days compared to controls (n = 62 participants at a neighboring institution), even after adjustment for relevant disease- and participant-related covariates. These results suggested an apparent conflict with what might be expected from IL-6 antagonism, and therefore additional in-depth investigation is warranted.

Few studies have collected simultaneous patient-reported outcomes (PROs) and biomarkers in the context of rigorously controlled anti-cytokine therapy delivery to better understand this relationship. Thus, analysis of a complete PRO-biomarker dataset could provide additional insights into the complex biobehavioral mechanisms involved in the development of depression and related symptomatology in the medically ill. Here, we report on both PROs and inflammatory biomarkers from our previously reported tocilizumab cohort and a comparison group at the same institution (n = 18) who did not receive tocilizumab. This study meaningfully builds upon the prior work by 1) analyzing correlative inflammatory biomarker data, and 2) using a comparison cohort from the same institution to more closely match conditions between the intervention and comparison groups.

2. Materials and methods

We conducted an observational cohort study to explore the effect of tocilizumab administration on PROs and inflammatory biomarkers among allogeneic HCT recipients. Parallel PROs and blood samples were collected from participants in an analogous comparison cohort at the same institution. All participants provided written informed consent; all procedures were approved by the Medical College of Wisconsin (MCW) Institutional Review Board.

2.1. Patient population

Individuals were recruited for this study from a larger single arm phase II open label trial of tocilizumab for prevention of acute GVHD (aGVHD) (NCT02206035) (Drobyski et al., 2018). Patients on this study received a single dose of intravenous tocilizumab (8 mg/kg) approximately 24 h prior to the hematopoietic stem cell infusion. Participants who consented were invited to provide PRO data and blood samples at multiple time points for the current study. Patients were enrolled from January 2015 through July 2016 at a single institution (MCW). Eligible participants included those 18–75 years of age undergoing allogeneic HCT for acute leukemia, chronic myelogenous leukemia (CML), myelodysplasia, other myeloproliferative disorders, or chemotherapy sensitive lymphoproliferative diseases. Patients were excluded if they had received a prior allogeneic HCT, had a history of intolerance to tocilizumab, or received a monoclonal antibody during conditioning. Twenty-five of the 35 patients enrolled in the larger intervention trial consented to this study. A volunteer comparison group of HCT patients not receiving tocilizumab was recruited from MCW from November 2016 through February 2018. Patients who met the study eligibility criteria were approached for consent once the decision to proceed to HCT was made by their medical team and a suitable donor was identified. Eligibility criteria and schedule of observations mirrored those of the intervention group.

2.2. Study measures

2.2.1. Patient-reported outcomes

All participants completed self-report surveys at baseline (pre-HCT, and prior to tocilizumab for the intervention group) and Day 28 post-transplant. Validated questionnaires assessed subjective symptoms of depression, anxiety, fatigue, sleep, and pain. Depression and anxiety were queried through the Inventory of Depression and Anxiety Symptoms (IDAS) (Watson, O'Hara et al., 2007). Depression was measured through the IDAS general depression subscale, and anxiety was assessed using two subscale items of the IDAS: panic and traumatic intrusions (Watson, O'Hara et al., 2007). The Fatigue Symptom Inventory (FSI) (Hann et al., 1998), Pittsburgh Sleep Quality Index (PSQI) (Carpenter and Andrykowski 1998), and Brief Pain Inventory (BPI) (Cleeland and Ryan 1994) were used to assess fatigue, sleep, and pain, respectively. Patients endorsing thoughts of suicidality or self-harm per the IDAS were contacted by the study principal investigator (JMK) and offered appropriate follow-up care.

2.2.2. Inflammatory biomarkers

Blood samples were collected from patients at baseline and on Day 28 post-transplantation. In addition to c-reactive protein (CRP), cytokine levels including IL-1ra, IL-2, IL-4, IL-6, IL-10, IFN-γ, TNF-α, and IL-

17A were measured using the BD Cytometric Bead Array Human Th1/Th2/Th17 Cytokine Kit (BD Biosciences). Serum samples were acquired on a BD FACSCanto II flow cytometer (BD Biosciences) and analyzed using the FCAP Array v3.0.1 software (BD Biosciences). Soluble IL-6 receptor (sIL-6R) levels were measured using the Human IL-6R alpha Quantikine ELISA Kit (R and D Systems, Minneapolis, MN). This assay detects three forms of the sIL-6R: free sIL-6R, sIL-6R in complex with IL-6, and sIL-6R in an immune complex with tocilizumab.

2.3. Sample size

As this study was a companion to the larger trial, resultant power for these outcomes was entirely dependent on the parent trial sample size. With the final sample size of 22 tocilizumab-treated and 18 comparison patients, the study has 80% power to detect effects of 0.91 standard deviations (SD) or higher. For the general depression subscale of the IDAS, with an expected SD of 11 points, this corresponds to a 10-point difference in an unadjusted comparison between 28-day values, or an 8.7-point difference in a comparison adjusted for a baseline value, assuming a correlation of 0.5.

2.4. Data analysis

Descriptive analyses were used to report demographic and medical characteristics of the cohort, including age, sex, race and ethnicity, income and education level, underlying disease, conditioning regimen, graft type, and acute GVHD grade. Wilcoxon's rank-sum tests, Fisher's exact tests, or Chi-square tests were used to evaluate differences in these baseline variables between the comparison and tocilizumab groups. To evaluate differences in PROs and inflammatory cytokines, an analysis of covariance (ANCOVA) regression model was fitted for all eligible patients, while covarying for baseline score and adjusting for myeloablative conditioning, disease status, and diagnosis as in previous studies (Knight et al., 2021). Cytokine values were summarized by geometric means and standard deviations, and then analyzed on a log10 scale. Zero values were replaced by half of the smallest measured value. IL-2, IL-4, IFN-g, and TNF-a were removed from the analyses due to high prevalence of values below the limit of detection. To assess for associations between cytokines and PRO measures, bias-corrected distance correlation t-tests were used (Szekely and Rizzo 2013). Distance correlation is a novel association measure taking values between −1 and 1 developed for high-dimensional data that quantifies overall association between two sets of measurements (here, all cytokines and all PRO measures). It can be viewed as an effect size measure and provides additional information beyond the p-value for the global test of association for the two multidimensional sets. Unlike usual correlation measures, distance correlation equals zero if and only if the measures are independent. These tests were performed at the level of individual cytokines (i.e., association of each cytokine with all PRO measures), as well as for the entire set of cytokines. Additionally, because of the known association between markers of inflammation and depressive symptoms, we conducted exploratory analyses of the effect of inflammatory biomarkers of interest on depression using linear regression and ANCOVA models. A random subject intercept was used to account for the repeated measurements within each participant. Analyses were conducted in R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 40 patients with evaluable PROs and biospecimens were included in this analysis (n = 22 in the tocilizumab group; n = 18 in the comparison group). Three patients from the prior tocilizumab cohort (Knight et al., 2021) did not have evaluable samples for inflammatory biomarkers, and so were excluded from this analysis.

3.1. Patient characteristics

There was no significant difference between groups with respect to age, gender, race and ethnicity, education, or income level (Table 1). There were differences in disease-related variables between groups. The tocilizumab cohort had a different distribution of primary diagnoses ($p = 0.009$) with more patients with leukemias and fewer patients with Hodgkin Lymphoma or myelodysplastic syndrome (MDS), and a higher proportion of patients in their first remission (64% vs 28%, $p = 0.024$). There were no differences in conditioning regimen type (MAC vs RIC/NST), graft source (BM vs PBSC), or incidence of acute GVHD between groups.

3.2. Patient reported outcome measures

There were no baseline differences in PRO scores between the comparison and tocilizumab groups (Fig. 1, Table 2). There were also no statistically significant differences in PRO scores between groups at Day 28 (after tocilizumab administration for the intervention group). When adjusting for baseline values and myeloablative conditioning, there were no statistically significant differences between groups (Supplemental Table 1). Within groups, however, there were statistically significant changes in symptoms over time. For both the tocilizumab and comparison cohorts, patients reported higher symptoms of depression (comparison group: +5.1 [95% CI 0.14–10, $p = 0.045$], tocilizumab: +8.6 [95% CI 2.3–15, $p = 0.011$]) and fatigue (comparison group: +1.3 [95% CI 0.03–2.5, $p = 0.045$], tocilizumab: +1.4 [95% CI 1.1–4.0, $p = 0.038$]). Patients in the tocilizumab group also reported an increase in pain interference symptoms at Day 28 [+1.2, (95% CI 0.25–2.2), $p = 0.017$]. (Table 2).

3.3. Inflammatory biomarkers

Inflammatory cytokine values at baseline and Day 28 for the tocilizumab and comparison groups are depicted in Fig. 2. Baseline cytokine values were similar for both groups. As would be expected with peripheral blockade of the IL-6 receptor, there were higher circulating levels of both IL-6 and IL-6R in the tocilizumab group at Day 28 ($p < 0.001$, Supplemental Table 2), confirming its biologic activity. Additionally, CRP levels were 78% lower in patients who received tocilizumab at Day 28 compared to comparisons when adjusting for baseline value and conditioning regimen [ratio 0.18 (95% CI 0.05–0.65), $p = 0.011$) (Supplemental Table 2).

3.4. Relationships between PROs and inflammatory biomarkers

Using the distance correlation test, the global associations between inflammatory biomarkers and PROs were assessed for the entire cohort (Fig. 3). When grouping all biomarkers together, there was an overall statistically significant association between these biomarkers and PROs at baseline (distance correlation [dCor] = 0.110, $p = 0.005$, Supplemental Table 3). This same association was not present at Day 28 (dCor = −0.001, $p = 0.5$). Individual inflammatory biomarkers were also assessed for their association with concurrently measured PRO scores (Supplemental Table 3). At baseline, IL-10 was significantly associated with global PRO scores (dCor = 0.201, $p = 0.00$). The relationship between baseline CRP and concurrent PRO scores approached significance (dCor = 0.057, $p = 0.088$); there were no other significant cytokine-PRO associations found.

3.4.1. Depression and inflammatory biomarkers

We conducted exploratory secondary analyses focused on depression and inflammatory biomarkers. The association between CRP, IL-6, IL-6R, and concurrently measured (Day 0 or Day 28) depression scores across groups was evaluated with regression analyses accounting for repeated measures from the same subject (Supplemental Table 4). In

Table 1
Demographics of patient population.

Characteristic	Overall, N = 40[1]	Comparison, N = 18[1]	Toci, N = 22[1]	p-value[2]
Age	60 (52, 65)	60 (52, 63)	62 (50, 66)	0.5
Gender				0.6
Female	15 (38%)	6 (33%)	9 (41%)	
Male	25 (62%)	12 (67%)	13 (59%)	
Race				>0.9
Asian	1 (2.5%)	0 (0%)	1 (4.5%)	
White	39 (98%)	18 (100%)	21 (95%)	
Ethnicity				
Non-Hispanic	40 (100%)	18 (100%)	22 (100%)	
Income Level				0.3
<$10,000	1 (2.8%)	1 (5.9%)	0 (0%)	
$10,001 - $25,000	4 (11%)	0 (0%)	4 (21%)	
$25,001 - $40,000	5 (14%)	3 (18%)	2 (11%)	
$40,001-$55,000	5 (14%)	2 (12%)	3 (16%)	
$55,001-$70,000	3 (8.3%)	1 (5.9%)	2 (11%)	
$70,001-$85,000	4 (11%)	1 (5.9%)	3 (16%)	
$85,001 - $100,000	5 (14%)	4 (24%)	1 (5.3%)	
>$100,000	9 (25%)	5 (29%)	4 (21%)	
Unknown	4	1	3	
Education Level				0.6
< 12 years	1 (2.6%)	0 (0%)	1 (5.0%)	
High School	9 (24%)	4 (22%)	5 (25%)	
Trade School	3 (7.9%)	2 (11%)	1 (5.0%)	
Some College	7 (18%)	3 (17%)	4 (20%)	
College Graduate	7 (18%)	3 (17%)	4 (20%)	
Post Graduate Degree	11 (29%)	6 (33%)	5 (25%)	
Unknown	2	0	2	
Primary diagnosis				0.009
Acute Lymphoblastic Leukemia	4 (10%)	1 (5.6%)	3 (14%)	
Acute Myeloid Leukemia	17 (42%)	4 (22%)	13 (59%)	
Chronic Myeloid Leukemia	1 (2.5%)	0 (0%)	1 (4.5%)	
Chronic Myelomonocytic Leukemia	3 (7.5%)	1 (5.6%)	2 (9.1%)	
Hodgkin Lymphoma	5 (12%)	5 (28%)	0 (0%)	
Myelodysplastic Syndrome	8 (20%)	6 (33%)	2 (9.1%)	
Non-Hodgkin Lymphoma	2 (5.0%)	1 (5.6%)	1 (4.5%)	
Disease status at transplant				0.024
First Complete Remission (CR1)	19 (48%)	5 (28%)	14 (64%)	
Other	21 (52%)	13 (72%)	8 (36%)	
Karnofsky Performance Score				0.048
70	3 (7.5%)	2 (11%)	1 (4.5%)	
80	18 (45%)	4 (22%)	14 (64%)	
90	13 (32%)	7 (39%)	6 (27%)	
100	6 (15%)	5 (28%)	1 (4.5%)	
Graft source				0.2
Bone Marrow (BM)	6 (15%)	1 (5.6%)	5 (23%)	
Peripheral Blood Stem Cell	34 (85%)	17 (94%)	17 (77%)	
Prior autologous transplant				0.005
N	34 (85%)	12 (67%)	22 (100%)	
Y	6 (15%)	6 (33%)	0 (0%)	
Conditioning Regimen Type				0.4
Myeloablative (MAC)	21 (52%)	8 (44%)	13 (59%)	
Reduced Intensity (RIC/NST)	19 (48%)	10 (56%)	9 (41%)	
Highest Grade of aGVHD				0.6
I	8 (20%)	2 (11%)	6 (27%)	
II	3 (7.5%)	2 (11%)	1 (4.5%)	
III	6 (15%)	3 (17%)	3 (14%)	
IV	1 (2.5%)	1 (5.6%)	0 (0%)	
None	22 (55%)	10 (56%)	12 (55%)	
aGVHD grade 2+ before day 28	2 (5.0%)	0 (0%)	2 (9.1%)	0.5

1 Median (IQR); n (%).
2 Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test with continuity correction.

univariate analyses, a 10-fold increase in IL-6 was associated with a 3.6-point higher depression score (95% CI 1.0–6.2, p value 0.008). There were no significant associations between depression score and concurrently measured CRP or IL-6R.

To evaluate whether baseline inflammatory biomarkers of interest predicted later depressive symptoms, adjusted ANCOVA models were used (Table 3). Conditioning regimen intensity (myeloablative vs reduced intensity) emerged as a significant covariate in the relationship between individual cytokine values and Day 28 depression score. We did not find other statistically significant predictive relationships.

4. Discussion

In this exploratory analysis of PROs and inflammatory biomarkers in patients undergoing HCT, there was not a significant association between administration of the IL-6 antagonist tocilizumab and any of the patient-reported symptoms as assessed in these cohorts. When evaluating inflammatory biomarkers, there was a global relationship between baseline biomarkers and PROs, meaning patients with similar PRO scores also had similar biomarker profiles. This association was not present at Day 28 following transplant. Not surprisingly, many symptoms related to QOL including depression, sleep, and fatigue worsened between baseline and Day 28 after HCT, but this did not differ between intervention and comparison groups.

Similar to our previous findings (Knight et al., 2021), these results failed to support the hypothesized antidepressant effects of tocilizumab in the HCT population. However, the underlying pathophysiology does not necessarily diverge from the widely accepted paradigm of depression and inflammation (Miller and Raison 2016). Tocilizumab inhibits peripheral inflammatory IL-6 signaling through binding of IL-6 receptors, which then leads to a concomitant rise in circulating levels of free IL-6 (Chen et al., 2016; Drobyski et al., 2018; Milligan et al., 2021). This unbound IL-6, but not large tocilizumab molecules, can cross the blood brain barrier and exert effects in the CNS unopposed. As a result, neuroinflammation and related depressive symptoms could be greater in the presence of the drug than in its absence. In further support of this hypothesis, there is some evidence that neurotoxicity may actually worsen following tocilizumab administration in patients who receive chimeric antigen receptor (CAR) T cells (Gust et al., 2017; Gust et al., 2020). Our data did show an association between concurrently measured peripheral IL-6 and depressive symptoms as expected. Therefore, careful consideration of pharmacologic mechanisms of action and inflammatory state of the patient during future study of anti-cytokine therapy for depression is warranted. Currently, neuropsychiatric symptoms are not listed as an adverse reaction for tocilizumab, but clinicians should closely monitor for exacerbation of such symptoms.

In our prior study, the same tocilizumab group was compared to a control cohort (n = 62) who increased an average of 2.1 points on the IDAS depression score from baseline to Day 28, and this was statistically significant (Knight et al., 2021). Despite a similar pattern between groups in this study (+5.1 in comparison group, +8.6 in tocilizumab group), the lack of significance in these data may be secondary to fewer patients in the current comparison group than in the prior study (18 vs

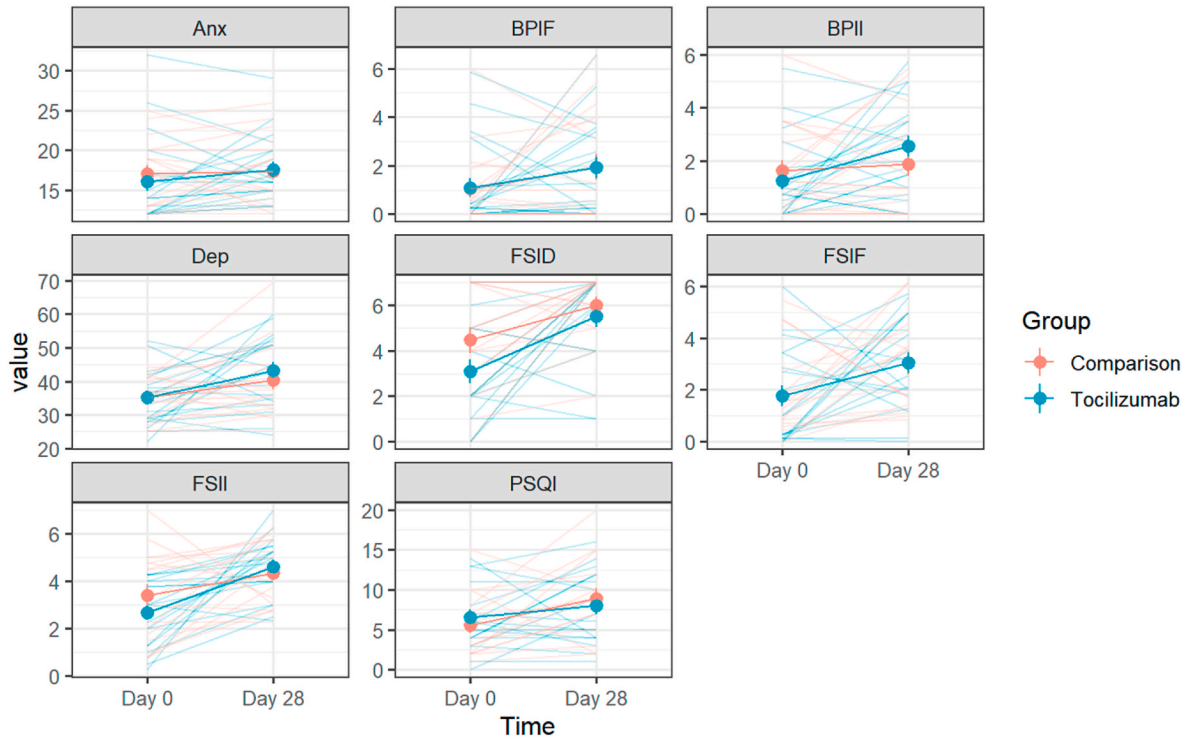

Fig. 1. Patient reported outcome measures. Self-reported symptoms of anxiety, depression, pain, fatigue, and sleep quality at baseline (Day 0) and Day 28 following stem cell infusion for the comparison and tocilizumab (Toci) groups. Anxiety (Anx) and depression (Dep) scores measured using the Inventory of Depression and Anxiety Symptoms (IDAS). BPIF = Brief Pain Inventory frequency subscale; BPII = Brief Pain Inventory interference subscale; FSID = Fatigue Symptom Inventory duration subscale; FSIF = Fatigue Symptom Inventory frequency subscale; FSII = Fatigue Symptom Inventory interference subscale; PSQI = Pittsburgh Sleep Quality Index.

Table 2
Patient reported outcome scores. Mean patient-reported symptoms with standard deviations are reported. Baseline (Day 0) and Day 28 values for all PRO measures were compared between the tocilizumab and comparison groups, as well as changes in score over time within groups.

Characteristic	Day 0			Day 28			Comp Day 0 vs Day 28			Toci Day 0 vs Day 28		
	Comparison, N = 18[1]	Toci, N = 22[1]	p-value[2]	Comparison, N = 18[1]	Toci, N = 22[1]	p-value[3]	Difference[4]	95% CI[4,5]	p-value[4]	Difference[4]	95% CI[4,5]	p-value[4]
Depression (IDAS)	35 (6)	35 (9)	>0.9	40 (11)	43 (11)	0.4	−5.1	−10, −0.14	0.045	−8.6	−15, −2.3	0.011
Anxiety (IDAS)	17.1 (4.3)	16.0 (5.3)	0.5	17.4 (4.3)	17.6 (4.2)	0.9	−0.29	−2.1, 1.5	0.7	−1.6	−3.8, 0.56	0.14
Sleep (PSQI)	5.6 (3.9)	6.6 (4.2)	0.5	8.9 (5.1)	8.0 (4.6)	0.6	−3.5	−6.6, −0.37	0.031	−1.4	−3.8, 1.0	0.2
Pain Interference (BPII)	1.63 (1.68)	1.25 (1.47)	0.5	1.87 (1.85)	2.55 (1.76)	0.3	−0.24	−1.1, 0.65	0.6	−1.2	−2.2, −0.25	0.017
Pain Frequency (BPIF)	1.06 (1.56)	1.10 (1.67)	>0.9	1.93 (2.21)	1.92 (1.95)	>0.9	−0.87	−2.0, 0.29	0.13	−0.75	−1.9, 0.44	0.2
Fatigue Interference (FSII)	3.38 (1.92)	2.65 (1.37)	0.2	4.34 (1.35)	4.61 (1.27)	0.5	−1.0	−2.1, 0.15	0.086	−2.1	−3.0, −1.1	<0.001
Fatigue Frequency (FSIF)	1.76 (1.68)	1.78 (1.79)	>0.9	3.03 (1.78)	3.04 (1.78)	>0.9	−1.3	−2.5, −0.03	0.045	−1.4	−2.6, −0.09	0.038
Fatigue Duration (FSID)	4.47 (2.35)	3.10 (2.36)	0.082	6.00 (1.50)	5.53 (2.17)	0.4	−1.5	−2.8, −0.27	0.021	−2.6	−4.0, −1.1	0.002

1 Mean (SD); n (%).
2 Welch Two Sample *t*-test; Pearson's Chi-squared test.
3 Welch Two Sample *t*-test; Fisher's exact test.
4 Paired *t*-test; McNemar's Chi-squared test.
5 CI = Confidence Interval.

62), decreasing the power to detect a difference in outcomes between groups. Additionally, in the present study, all participants were recruited from the same institution, whereas the previous comparison group was comprised of patients from another institution. This raises the possibility of a center effect as at least part of the explanation for the prior results.

There are some unique considerations when interpreting biobehavioral data such as this in the HCT population. For example, at the Day 28 timepoint, nearly all patients would have engrafted with *donor* stem cells, reflecting an entirely new immune repertoire compared to baseline

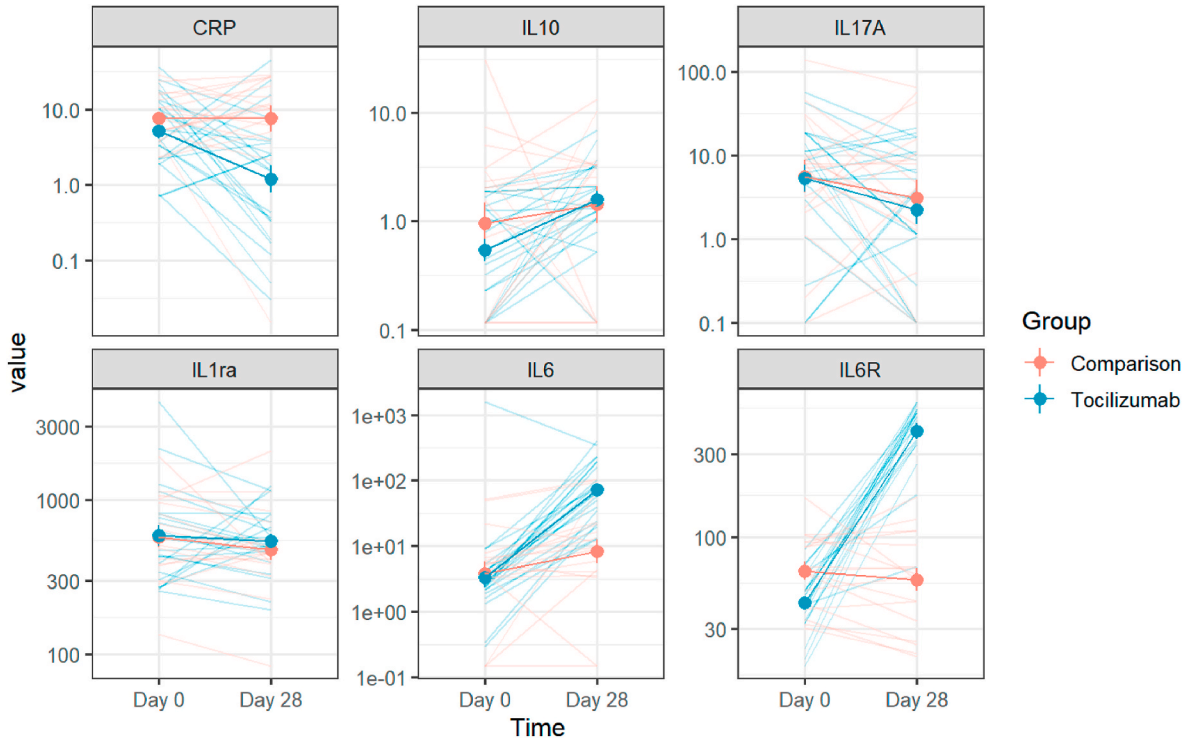

Fig. 2. Inflammatory biomarkers. Mean inflammatory biomarker values at baseline and Day 28 for patients in the tocilizumab (green) and comparison (red) groups. Cytokine values are summarized by geometric mean/SD and analyzed on a log10 scale. Interleukins 2 and 4 (IL-2 and IL-4), interferon-gamma (IFN-g), and tumor necrosis factor-alpha (TNF-a) were removed from the analyses due to the high prevalence of values below the limit of detection. CRP = c-reactive protein; IL-10 = interleukin 10; IL-17A = interleukin 17A; IL-1ra = interleukin 1 receptor antagonist; IL-6 = interleukin 6; IL-6R = interleukin 6 receptor. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

measurements. It is not yet known how donor immune profile may affect recipients, although this is an area of active investigation (Turcotte LM 2021). Additionally, studying biobehavioral relationships in the context of HCT is inherently challenging (Kelly et al., 2021), as the dynamic and profound immunologic derangements of the peri-transplant period may obscure more subtle associations between PROs and inflammatory markers. Neuroimmune signaling mechanisms are complex and influenced by a multitude of factors, including an organism's inflammatory milieu and psychosocial/environmental context (Haykin and Rolls 2021). We know that IL-6 and CRP are interrelated (Bermudez et al., 2002), and recent discoveries in immunology have shown that these are pleiotropic molecules that orchestrate not only inflammation, but also tissue regeneration, metabolism, and homeostasis (Del Giudice and Gangestad 2018; Kang et al., 2019). Thus, blockade of peripheral IL-6 signaling in an already immunologically complex condition like HCT may have more diverse and nuanced effects than in the general population.

This study has several important limitations to consider. First, the sample size was small (n = 40), thus restricting statistical power available to detect any potential relationship between IL-6 antagonism and depressive symptoms. The study sample also came from a single site, and that may limit generalizability to the larger HCT population and comparisons between groups. A distance-based correlation analysis approach is protective against the issue of multiple comparisons in high-resolution data, but this could have been present in other secondary exploratory analyses. Patients in both the tocilizumab and comparison cohorts voluntarily consented to this study, raising the possibility of an inherent difference from those patients who declined participation, and possibly introducing selection bias into the study design. The comparison cohort was also recruited after the larger tocilizumab study closed to accrual, so there may have been a temporal influence in our results. Of note, patients in both groups reported relatively low depression symptom scores on the IDAS, with means ranging from 35 to 43 (a score of 53 has been proposed as the cutoff for mild depression) (Stasik-O'Brien et al., 2019). This could have influenced the magnitude of any antidepressant effect of tocilizumab and would limit generalizability to patients with more significant neuropsychiatric symptom burden. This study represented a non-randomized post-hoc comparison of patient groups, and thus cannot provide definitive conclusions regarding the presence or absence of a causal effect (i.e., confounding cannot be ruled out).

However, this study is one of the few to report parallel inflammatory biomarker and PRO outcomes in the acute transplant setting, adding to the limited repository of biobehavioral HCT research. Further, compiling data on targetable cytokines like IL-6 has substantial therapeutic implication and has been limited to few other settings, also with medically ill individuals (Traki et al., 2014; Khandaker et al., 2018; Tiosano et al., 2020). These data are of particular relevance in a vulnerable HCT population. As drugs like tocilizumab become more widely used to treat severe inflammation in multiple contexts, as seen in cytokine release syndrome with CAR T cell therapy or COVID-19 infection (Kotch et al., 2019; Zhang et al., 2020), this study provides critical foundational data for interrogating the potential biobehavioral sequelae in medically complex patients. Future research should incorporate larger sample sizes and more frequent outcome assessments to represent the dynamic psychoneuroimmune processes in HCT more precisely.

In summary, this study did not detect a significant association between tocilizumab administration and PROs during the first month after HCT. There was an association between pre-HCT inflammatory markers and PROs, though this effect was no longer present at Day 28. Patients in the tocilizumab cohort had an average increase of +8.6 points on the IDAS depression subscale compared to +5.1 in the comparison cohort; this difference did not reach statistical significance but is a pattern consistent with our previous findings. This raises the question of deleterious effects of increased CNS penetration of free IL-6 following

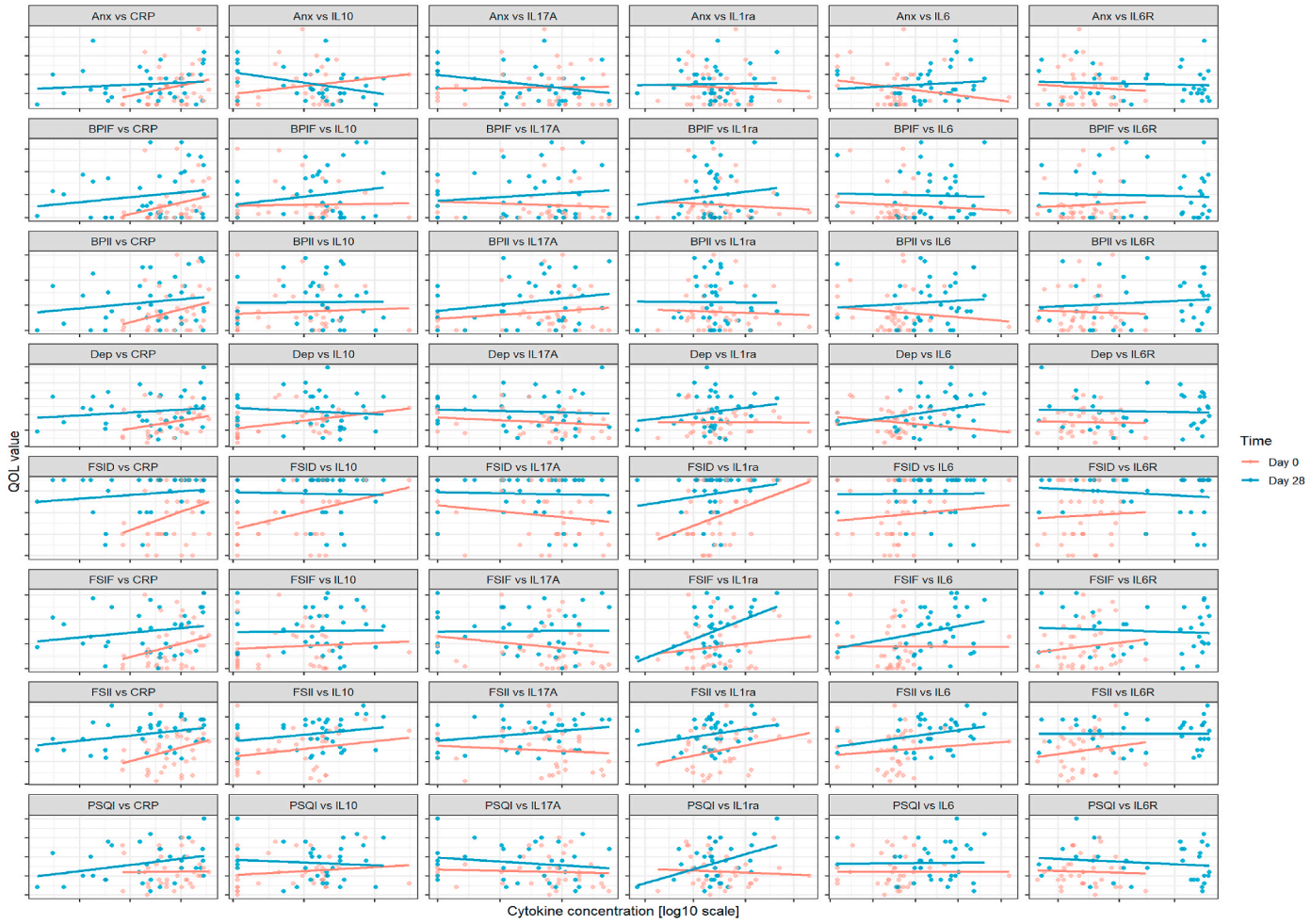

Fig. 3. Relationship between inflammatory biomarkers and patient reported outcomes. Overall association between log10-transformed inflammatory biomarkers and patient-reported outcome measures at Day 0 (red) and Day 28 (green) were assessed using distance correlation. Anxiety (Anx) and depression (Dep) scores measured using the Inventory of Depression and Anxiety Symptoms (IDAS). BPIF = Brief Pain Inventory frequency subscale; BPII = Brief Pain Inventory interference subscale; FSID = Fatigue Symptom Inventory duration subscale; FSIF = Fatigue Symptom Inventory frequency subscale; FSII = Fatigue Symptom Inventory interference subscale; PSQI = Pittsburgh Sleep Quality Index. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Relationship between baseline inflammatory biomarkers and Day 28 depression. ANCOVA models of Day 28 depression score based on individual baseline cytokines, adjusted for clinical covariates.

Characteristic	CRP			IL10			IL6			IL6R		
	Beta	95% CI[1]	p-value	Beta	95% CI[1]	p-value	Beta	95% CI[1]	p-value	Beta	95% CI[1]	p-value
Baseline Depression	0.44	−0.12, 1.0	0.12	0.34	−0.26, 0.94	0.3	0.39	−0.14, 0.92	0.14	0.40	−0.12, 0.93	0.13
Cytokine, 10-fold increase	−2.0	−11, 7.4	0.7	1.6	−5.8, 9.0	0.7	−1.3	−9.3, 6.8	0.8	−3.4	−24, 17	0.7
Conditioning (RIC/NST vs MAC)	−9.8	−18, −1.9	0.017	−9.4	−17, −1.3	0.025	−9.3	−18, −0.87	0.032	−9.3	−18, −1.1	0.028
Remission status (CR1 vs not)	−1.0	−8.9, 6.8	0.8	−1.5	−9.6, 6.7	0.7	−1.0	−8.9, 6.9	0.8	−0.88	−8.8, 7.0	0.8

peripheral IL-6R blockade, which aligns with hypothesized mechanisms of heightened neurotoxicity following tocilizumab administration in CAR T cell therapy (Gust et al., 2017; Gust et al., 2020). Therefore, in the dynamic peri-HCT period, the ideal schedule of tocilizumab administration to assess any subsequent neuropsychiatric effects may be dependent on the inflammatory state of the patient. Larger, randomized controlled trials are needed to address these questions in the HCT population.

Understanding the intricacies of biobehavioral relationships in HCT is challenging, but of paramount importance. As neuroimmune mechanisms are more clearly elucidated, new opportunities for risk stratification, therapeutic adaptation, and targeted supportive care will follow, providing promising opportunities to improve quality of life and clinical outcomes in this vulnerable population.

Funding/disclosures

This work was supported in part by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Numbers UL1TR001436, KL2TR001438, R01 HL154579 (WRD and CJH); the Research and Education Component of the Advancing a Healthier Wisconsin Research Endowment at the Medical College of Wisconsin; and the Laura Gralton Philanthropic Fund. Its contents are solely the responsibility of the authors and do not necessarily represent

the official views of the NIH.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mallory Taylor reports a relationship with American Society of Clinical Oncology that includes: funding grants. Mallory Taylor reports a relationship with St. Baldrick's Foundation that includes: funding grants. Bryon Johnson reports financial support was provided by Miltenyi Biotec. Bryon Johnson has patent #US 10,570,204 B2 issued to Bryon Johnson. Steve Cole declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Aniko Szabo declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Cecilia Hillard reports a relationship with Phytecs, Inc that includes: Member of the Scientific Advisory Board. Cecilia Hillard reports a relationship with Formulate Biosciences, Inc that includes stock options. William Drobyski declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Charles Raison reports a relationship with Usona Institute, Otsuka, Alfasigma, and Novartis that includes: funding and grants. Fenlu Zhu declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Jennifer Knight reports a relationship with Phytecs, Inc that includes: National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Numbers UL1TR001436 and KL2TR001438; the Research and Education Component of the Advancing a Healthier Wisconsin Research Endowment at the Medical College of Wisconsin; and the Laura Gralton Philanthropic Fund that includes funding grants. Jennifer Knight reports a relationship with National Institutes of Health and Medical College of Wisconsin that includes grants funding.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2022.100480.

References

Bermudez, E.A., Rifai, N., Buring, J., Manson, J.E., Ridker, P.M., 2002. Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. Arterioscler. Thromb. Vasc. Biol. 22 (10), 1668–1673.

Carpenter, J.S., Andrykowski, M.A., 1998. Psychometric evaluation of the Pittsburgh sleep quality Index. J. Psychosom. Res. 45 (1), 5–13.

Chen, F., Teachey, D.T., Pequignot, E., Frey, N., Porter, D., Maude, S.L., Grupp, S.A., June, C.H., Melenhorst, J.J., Lacey, S.F., 2016. Measuring IL-6 and sIL-6R in serum from patients treated with tocilizumab and/or siltuximab following CAR T cell therapy. J. Immunol. Methods 434, 1–8.

Cleeland, C.S., Ryan, K.M., 1994. Pain assessment: global use of the Brief pain inventory. Ann. Acad. Med. Singapore 23 (2), 129–138.

Costanzo, E.S., Juckett, M.B., Coe, C.L., 2013. Biobehavioral influences on recovery following hematopoietic stem cell transplantation. Brain Behav. Immun. 30 (Suppl. l), S68–S74.

Del Giudice, M., Gangestad, S.W., 2018. Rethinking IL-6 and CRP: why they are more than inflammatory biomarkers, and why it matters. Brain Behav. Immun. 70, 61–75.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctot, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatr. 67 (5), 446–457.

Drobyski, W.R., Szabo, A., Zhu, F., Keever-Taylor, C., Hebert, K.M., Dunn, R., Yim, S., Johnson, B., D'Souza, A., Eapen, M., Fenske, T.S., Hari, P., Hamadani, M., Horowitz, M.M., Rizzo, J.D., Saber, W., Shah, N., Shaw, B., Pasquini, M., 2018. Tocilizumab, tacrolimus and methotrexate for the prevention of acute graft-versus-host disease: low incidence of lower gastrointestinal tract disease. Haematologica 103 (4), 717–727.

El-Jawahri, A., Chen, Y.B., Brazauskas, R., He, N., Lee, S.J., Knight, J.M., Majhail, N., Buchbinder, D., Schears, R.M., Wirk, B.M., Wood, W.A., Ahmed, I., Aljurf, M., Szer, J., Beattie, S.M., Battiwalla, M., Dandoy, C., Diaz, M.A., D'Souza, A., Freytes, C. O., Gajewski, J., Gergis, U., Hashmi, S.K., Jakubowski, A., Kamble, R.T., Kindwall-Keller, T., Lazarus, H.M., Malone, A.K., Marks, D.I., Meehan, K., Savani, B.N., Olsson, R.F., Rizzieri, D., Steinberg, A., Speckhart, D., Szwajcer, D., Schoemans, H., Seo, S., Ustun, C., Atsuta, Y., Dalal, J., Sales-Bonfim, C., Khera, N., Hahn, T., Saber, W., 2017. Impact of pre-transplant depression on outcomes of allogeneic and autologous hematopoietic stem cell transplantation. Cancer 123 (10), 1828–1838.

Felger, J.C., Lotrich, F.E., 2013. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience 246, 199–229.

Gossec, L., Steinberg, G., Rouanet, S., Combe, B., 2015. Fatigue in rheumatoid arthritis: quantitative findings on the efficacy of tocilizumab and on factors associated with fatigue. The French multicentre prospective PEPS Study. Clin. Exp. Rheumatol. 33 (5), 664–670.

Gust, J., Hay, K.A., Hanafi, L.A., Li, D., Myerson, D., Gonzalez-Cuyar, L.F., Yeung, C., Liles, W.C., Wurfel, M., Lopez, J.A., Chen, J., Chung, D., Harju-Baker, S., Ozpolat, T., Fink, K.R., Riddell, S.R., Maloney, D.G., Turtle, C.J., 2017. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. Cancer Discov. 7 (12), 1404–1419.

Gust, J., Ponce, R., Liles, W.C., Garden, G.A., Turtle, C.J., 2020. Cytokines in CAR T cell-associated neurotoxicity. Front. Immunol. 11, 577027.

Hann, D.M., Jacobsen, P.B., Azzarello, L.M., Martin, S.C., Curran, S.L., Fields, K.K., Greenberg, H., Lyman, G., 1998. Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. Qual. Life Res. 7 (4), 301–310.

Haykin, H., Rolls, A., 2021. The neuroimmune response during stress: a physiological perspective. Immunity 54 (9), 1933–1947.

Kang, S., Tanaka, T., Narazaki, M., Kishimoto, T., 2019. Targeting interleukin-6 signaling in clinic. Immunity 50 (4), 1007–1023.

Kappelmann, N., Lewis, G., Dantzer, R., Jones, P.B., Khandaker, G.M., 2018. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. Mol. Psychiatr. 23 (2), 335–343.

Kelly, D.L., Syrjala, K., Taylor, M., Rentscher, K.E., Hashmi, S., Wood, W.A., Jim, H., Barata, A., Flynn, K.E., Burns, L.J., Shaw, B.E., Petersdorf, E., Yero, A.C., Emmrich, A.D., Morris, K.E., Costanzo, E.S., Knight, J.M., 2021. Biobehavioral research and hematopoietic stem cell transplantation: expert review from the biobehavioral research special interest group of the American Society for transplantation and cellular therapy. Transpl. Cell Therapy.

Khandaker, G.M., Oltean, B.P., Kaser, M., Dibben, C.R.M., Ramana, R., Jadon, D.R., Dantzer, R., Coles, A.J., Lewis, G., Jones, P.B., 2018. Protocol for the insight study: a randomised controlled trial of single-dose tocilizumab in patients with depression and low-grade inflammation. BMJ Open 8 (9), e025333.

Khandaker, G.M., Pearson, R.M., Zammit, S., Lewis, G., Jones, P.B., 2014. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. JAMA Psychiatr. 71 (10), 1121–1128.

Knight, J.M., Costanzo, E.S., Singh, S., Yin, Z., Szabo, A., Pawar, D.S., Hillard, C.J., Rizzo, J.D., D'Souza, A., Pasquini, M., Coe, C.L., Irwin, M.R., Raison, C.L., Drobyski, W.R., 2021. The IL-6 antagonist tocilizumab is associated with worse depression and related symptoms in the medically ill. Transl. Psychiatry 11 (1), 58.

Knight, J.M., Lyness, J.M., Sahler, O.J., Liesveld, J.L., Moynihan, J.A., 2013. Psychosocial factors and hematopoietic stem cell transplantation: potential biobehavioral pathways. Psychoneuroendocrinology 38 (11), 2383–2393.

Knight, J.M., Rizzo, J.D., Logan, B.R., Wang, T., Arevalo, J.M., Ma, J., Cole, S.W., 2016. Low socioeconomic status, adverse gene expression profiles, and clinical outcomes in hematopoietic stem cell transplant recipients. Clin. Cancer Res. 22 (1), 69–78.

Kohler, O., Benros, M.E., Nordentoft, M., Farkouh, M.E., Iyengar, R.L., Mors, O., Krogh, J., 2014. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatr. 71 (12), 1381–1391.

Kotch, C., Barrett, D., Teachey, D.T., 2019. Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome. Expet Rev. Clin. Immunol. 15 (8), 813–822.

Miller, A.H., Maletic, V., Raison, C.L., 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol. Psychiatr. 65 (9), 732–741.

Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16 (1), 22–34.

Milligan, C., Atassi, N., Babu, S., Barohn, R.J., Caress, J.B., Cudkowicz, M.E., Evora, A., Hawkins, G.A., Wosiski-Kuhn, M., Macklin, E.A., Shefner, J.M., Simmons, Z., Bowser, R.P., Ladha, S.S., 2021. Tocilizumab is safe and tolerable and reduces C-reactive protein concentrations in the plasma and cerebrospinal fluid of ALS patients. Muscle Nerve 64 (3), 309–320.

Raison, C.L., Rutherford, R.E., Woolwine, B.J., Shuo, C., Schettler, P., Drake, D.F., Haroon, E., Miller, A.H., 2013. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatr. 70 (1), 31–41.

Stasik-O'Brien, S.M., Brock, R.L., Chmielewski, M., Naragon-Gainey, K., Koffel, E., McDade-Montez, E., O'Hara, M.W., Watson, D., 2019. Clinical utility of the inventory of depression and anxiety symptoms (IDAS). Assessment 26 (5), 944–960.

Szekely, G.J., Rizzo, M.L., 2013. The distance correlation t-test of independence in high dimension. J. Multivariate Anal. 117, 193–213.

Tiosano, S., Yavne, Y., Watad, A., Langevitz, P., Lidar, M., Feld, J., Tishler, M., Aamar, S., Elkayam, O., Balbir-Gurman, A., Molad, Y., Ehrlich, S., Abu-Shakra, M., Amital, D., Amital, H., 2020. The impact of tocilizumab on anxiety and depression in patients with rheumatoid arthritis. Eur. J. Clin. Invest. 50 (9), e13268.

Traki, L., Rostom, S., Tahiri, L., Bahiri, R., Harzy, T., Abouqal, R., Hajjaj-Hassouni, N., 2014. Responsiveness of the EuroQol EQ-5D and hospital anxiety and depression

Scale (HADS) in rheumatoid arthritis patients receiving tocilizumab. Clin. Rheumatol. 33 (8), 1055–1060.
Turcotte, L.M., Wang, T., Beyer, K.M., Cole, S.W., Spellman, S.R., Allbee-Johnson, M., Williams, E., Zhou, Y., Verneris, M.R., Knight, J.M., 2021. Donor Socioeconomic Status as a Predictor of Altered Immune Function and Treatment Response Following Hematopoietic Cell Transplantation for Hematologic Malignancy. American Society of Hematology Annual Meeting, Atlanta GA.
Watson, D., O'Hara, M.W., Simms, L.J., Kotov, R., Chmielewski, M., McDade-Montez, E. A., Gamez, W., Stuart, S., 2007. Development and validation of the inventory of depression and anxiety symptoms (IDAS). Psychol. Assess. 19 (3), 253–268.
Zhang, C., Wu, Z., Li, J.W., Zhao, H., Wang, G.Q., 2020. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int. J. Antimicrob. Agents 55 (5), 105954.