

Inflammation and the brain: tocilizumab may redefine our understanding of depression and related symptoms in the medically ill

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Introduction: As consultation-liaison (CL) psychiatrists, we are expert at understanding and treating inflammation-associated mood disorders and symptom clusters in the medically ill. Despite our best efforts, these patients are often treatment-resistant to currently available psychopharmacologic and other psychosocial treatment modalities. With depression remaining a significant predictor of increased morbidity and mortality among medically ill patients, it is critical that we better understand and treat such mood disorders in this population.

Inflammation – specifically interleukin-6 (IL-6) – has long been associated with worse mood and other quality of life (QOL) symptoms,¹ with recent evidence suggesting that blocking pro-inflammatory cytokine receptors associated with depression (TNF-alpha) reduces depressive symptoms in individuals with high levels of inflammation.² Despite this accumulating evidence, tocilizumab, an IL-6 receptor antagonist, has never been evaluated for its possible role in improving mood or preventing mood deterioration in association with pro-inflammatory medical conditions. Allogeneic hematopoietic cell transplantation (alloHCT) recipients experience a high degree of psychiatric morbidity and inflammation-associated medical complications, including graft-versus-host disease (GVHD). Further evidence from our group suggests that worse mood and inflammation are associated with adverse alloHCT clinical outcomes.^{3,4} Blocking IL-6 represents a novel approach for targeting treatment-resistant depressive and other mood symptoms in medically ill populations with the goal of improving mental and physical health.

Aims: Given that IL-6 is implicated in depressive symptomatology and other immunomodulators have been successful at ameliorating depressive symptoms in inflamed patients, we aimed to assess whether the immunomodulator and IL-6 antagonist tocilizumab may be effective in reducing depressive symptoms among individuals undergoing alloHCT (primary aim). As anxiety, fatigue, sleep, and pain may also be associated with IL-6, we also aimed to evaluate the effect of tocilizumab on these symptoms (secondary aims). **Hypothesis:** Tocilizumab will reduce depression and other behavioral symptoms linked to inflammation, including anxiety, fatigue, sleep disturbance, and pain, in individuals undergoing alloHCT.

Methods: This clinical trial compared QOL data from 25 patients receiving one dose of tocilizumab prior to alloHCT (drug remains in systemic circulation for 1 month) to an historical control group of 63 alloHCT patients not receiving tocilizumab. Individuals receiving tocilizumab were part of a parent trial evaluating the efficacy of this drug to prevent acute GVHD among alloHCT recipients. Participants completed QOL self-report measures at the following 4 time points: pre-HCT/pre-tocilizumab administration; at day +28 (D+28, with respect to day of transplant being Day 0), D+100, and D+180 post-transplant. Self-report measures included the following: Inventory of Depression and Anxiety Symptoms (IDAS; depression and anxiety), Fatigue Symptom Inventory (FSI; fatigue), Pittsburgh Sleep Quality Index (PSQI; sleep), and Brief Pain Inventory (BPI; pain). A linear mixed-effects model was fitted covarying for baseline QOL and presence of aGVHD (grade 2-4) to evaluate the effects of tocilizumab on these behavioral outcome variables. Propensity score weighting was used to adjust for imbalances on patient-, disease-, and transplant-related variables between the intervention and control populations. Ethical approval as per institutional IRB was obtained.

Results: The only demographic variable significantly different between the tocilizumab vs. control group was age, with the tocilizumab cohort being older (60.2 vs. 53.9, $p < .004$). The tocilizumab-exposed group was found to have significantly higher depression scores (primary outcome) as compared to the non-exposed group at Day +28 ($p = .02$), although this effect was not significant at D+100 and D+180 (Figure 1). Patients receiving tocilizumab also reported significantly more anxiety symptoms at all time points (all $p < .05$), more severe pain at D+28 ($p = .01$), and worse sleep at D+28 ($p = .04$) and D+180 ($p = .02$), with a trend toward poorer sleep quality at D+100 ($p = .06$). Fatigue did not significantly differ between the two groups, though subset analyses indicated that while control patients exhibited significant positive correlations between baseline and post-HCT fatigue scores ($p < .001$ at D+28; $p < .01$ at D+100; $p < .001$ at D+180), baseline fatigue of tocilizumab recipients did not correlate with any post-HCT values. This is in contrast to depression, anxiety, pain, and sleep scores which demonstrated correlation between baseline and post-HCT time points in both tocilizumab and control groups.

Discussion: Despite prevailing psychiatric gestalt,⁵ and contrary to our initial predictions, alloHCT patients administered tocilizumab to block IL-6 experienced significantly worse – not better – depression, anxiety, pain, and sleep as compared to alloHCT patients who did not receive the drug. Antagonizing IL-6-mediated inflammation was not only ineffective at preventing adverse QOL symptoms, it exacerbated them. These findings have clinical implications for treatment-related QOL and QOL in the medically ill, further informing our understanding of biological processes underlying the basis for depression and related sickness symptoms in the medically ill. Our data also suggest that the specific sickness symptom of fatigue may be a more complex process with unique or nuanced inflammatory or other etiologies.

An improved understanding of the biology contributing to depression and related sickness symptoms is necessary to identify and develop the most appropriate interventions for psychiatric symptoms in the medically ill. While IL-6 has previously been implicated as a “bad guy” for its associations with adverse mental and physical health outcomes, in addition to our data, there is emerging preclinical evidence demonstrating otherwise.⁶ For example, IL-6 additionally has anti-inflammatory properties and has been shown not to cause sickness behavior in the absence of its more pro-inflammatory counterparts IL-1 or TNF-alpha. Further, these pro- vs. anti-inflammatory IL-6 effects may be the result of its agonism of differing receptor subtypes (soluble vs. membrane-bound). Finally, dysregulation of different but related pathways, such as tryptophan metabolism,⁷ may play a more pivotal role than IL-6 alone, as previously thought. As CL psychiatrists, we play a critical role in continuing to identify the biologic underpinnings of psychopathology in our medically ill patients. Concomitantly, we have a responsibility to educate our medical colleagues regarding these nuances, guide continued investigation into alternative purposing of existing pharmacologic agents, and explore new drug alternatives with the goal of achieving better mental and physical health outcomes for our patients.

Conclusion: Tocilizumab, an IL-6 receptor antagonist, is associated with worse depression, anxiety, pain, and sleep following alloHCT, disrupting the current psychiatric paradigm that depression and related symptoms in the medically ill are associated with acute inflammation, lending further breadth and depth to our subspecialty.

References:

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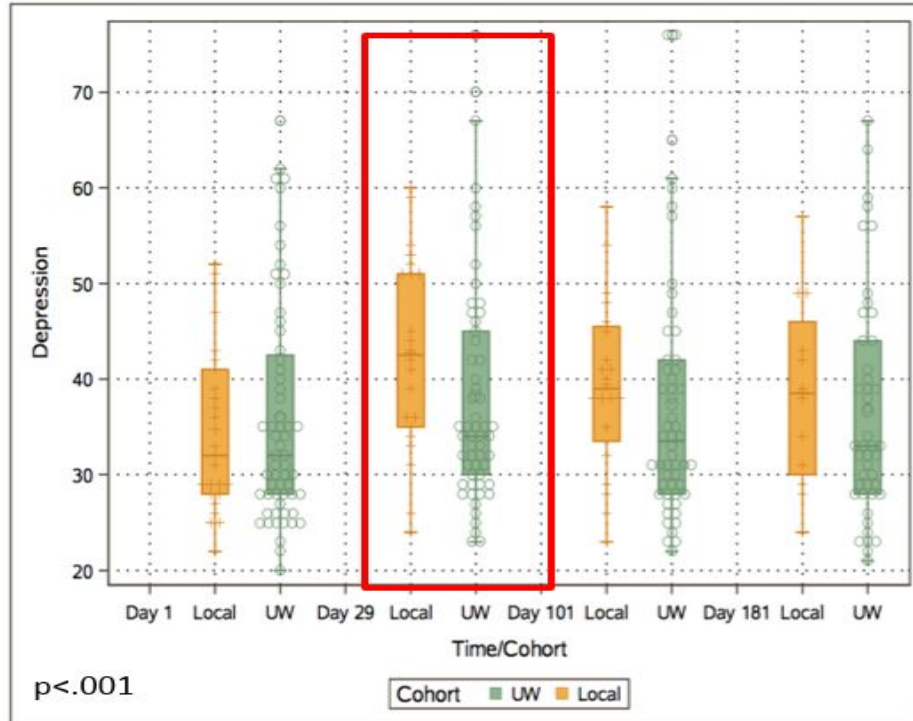


Figure 1. Depression scores were higher in alloHCT patients administered tocilizumab on Day +28 following transplant as compared to the historical comparison group.