Adjunctive Minocycline for Treatment of Posttraumatic Stress Disorder

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ABSTRACT

Introduction: Posttraumatic stress disorder (PTSD) is a chronic, debilitating anxiety disorder. While there is evidence that antibiotics such as minocycline may help to improve symptoms in some psychiatric disorders, no human studies have evaluated their potential as a treatment for PTSD.

Methods: We present results from 4 men aged 33 to 59 years who completed a 12-week pilot, prospective, nonrandomized, open-label clinical trial of adjunctive minocycline for veterans diagnosed with PTSD.

Results: All 4 patients showed reduction in PTSD symptoms at the end of the 12-week study, and 3 patients showed reduction in depression symptoms. Observed changes in inflammatory biomarkers are discussed.

Discussion: Previous studies have reported increased inflammation in PTSD, though evidence of a potential therapeutic effect of minocycline for PTSD has not been reported previously in humans.

Conclusion: These findings suggest that antibiotics like minocycline may help to reduce symptoms of PTSD, though further investigation is needed to confirm these findings.

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a debilitating disorder characterized by re-experiencing aspects of an original trauma, avoidance and numbing of trauma reminders, and general hyperarousal. Lifetime prevalence of PTSD in community samples is around 6.8%. A study looking at prevalence of current PTSD in Vietnam veterans was higher at 15%.[1]

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Cumulative stress has been suggested to play an important role in the development of PTSD.[2] For example, there is evidence that the risk of PTSD is greater in military units with longer deployments and shorter intervals between deployments.[2] Studies have shown that the chronic stress associated with PTSD also may be related to chronic inflammation, observed through levels of proinflammatory markers.[3] Elevated levels of these markers, such as interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor alpha (TNF-α), have been observed in patients with PTSD. Groer et al studied levels of inflammation in active military personnel and found that increased CRP levels were associated with depression and PTSD symptoms.[3] Another study comparing proinflammatory marker levels in 2 groups of combat-exposed veterans—one group with PTSD and one without—found that the veterans with PTSD exhibited higher levels of the markers, even when accounting for depression as a comorbidity.[4] Elevated inflammatory cytokine activity may result from cortisol, a stress hormone, inadequately performing its regulatory functions.[5] Low cortisol levels promote excessive catecholamine production, and increased levels of these catecholamines lead to excessive sympathetic activity. This overactive sympathetic response can accentuate flashbacks and lead to other PTSD symptoms.[5,6] PTSD has been linked to an increased risk of serious diseases, such as cardiovascular and autoimmune diseases.[7] These diseases have an inflammatory aspect, further supporting the relationship between immune dysregulation and PTSD.[7] Furthermore, in a prospective study, Eraly et al examined levels of CRP in active-duty military

Table 1. Patient Demographics and Results for Primary Efficacy Measures

Patient	Age/Sex	CAPS		CRP (mg/dL)		IL-6 (pg/mL)		TNF-α (pg/mL)	
		Baseline	Week 12	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
A	33 y/male	23	15	< 0.5	< 0.5	0.83	1.04	1.4	1.14
B	39 y/male	40	29	1.5	1.0	1.59	1.29	1.4	1.19
C	59 y/male	29	18	1.0	0.8	1.79	2.56	0.97	1.26
D	46 y/male	34	30	< 0.5	< 0.5	0.87	1.68	0.78	0.93

Abbreviations: CAPS, Clinician-Administered PTSD Scale; CRP, C-reactive protein; IL-6, interleukin 6; TNF-α, tumor necrosis factor alpha; y, years.

personnel 3 to 6 months after returning from deployment. Those with elevated predeployment levels of CRP were more likely to develop PTSD, suggesting that individuals with more inflammation at baseline may be more likely to develop PTSD.[8]

The above studies suggest that the inflammatory response may serve as a potential target for treatment of individuals with PTSD. To our knowledge, the efficacy of anti-inflammatory medication has not been examined in patients with PTSD. However, a study using a rat model of PTSD showed that treatment with ibuprofen reduced both inflammatory cytokine levels and behavioral symptoms.[9] Minocycline is a broad-spectrum tetracycline antibiotic with anti-inflammatory and neuroprotective properties. It has been shown to reduce levels of proinflammatory markers and inhibit microglial cells. Microglial cells—the primary effector immune cells of the brain and a source of central proinflammatory cytokines—appear to play a key role in stress-induced behavioral changes in rodents.[10]

Several studies have reported evidence indicating that minocycline may help in treating symptoms of psychiatric disorders such as schizophrenia[11,12] and depression.[13,14] These treatments also could prove beneficial in treating health conditions associated with chronic inflammation that are often comorbid with PTSD, such as chronic pain, arthritis, diabetes, and cardiovascular disease.[5] Two studies using animal models of PTSD have shown how the anti-inflammatory effects of minocycline may help to alleviate PTSD symptoms.[10,15] Decreased levels of cytokines were found in the animal models treated with minocycline compared to the control.[10,15] In addition, a recent study of fear conditioning in humans found attenuated fear memory in individuals administered doxycycline—another tetracycline antibiotic—suggesting that such medications may help to improve symptoms of PTSD.[16] Despite these findings, to date there have been no published data on the efficacy of minocycline treatment in veterans with PTSD.

METHODS

We reviewed existing medical records of patients who participated in a previous study conducted at the Nebraska-Western Iowa Health Care system. The study was a 12-week open-label pilot study to evaluate the efficacy of minocycline in treating PTSD. The data reported here were obtained from 4 patients who completed the 12-week study. The study enrolled veterans on a stable dose of psychotropic medications for a minimum of 8 weeks at the time of study entry. Use of statins was not permitted during the study. All patients were instructed to take 100 mg/day of adjunctive minocycline for 7 days, followed by 200 mg/day for the remainder of the study. They also were asked to report any changes in medications or behavioral therapies during the study period.

Data were collected using the following clinical measures: the Mini-International Neuropsychiatric Interview (MINI), used to screen for comorbid psychiatric disorders; the PTSD Checklist for DSM-5 (PCL-5), used to confirm diagnosis of PTSD; and the Beck Depression Inventory-II (BDI-II), which assessed depression symptoms in these patients. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) was used to assess current (past month) PTSD symptoms. The Clinical Global Impressions-Severity (CGI-S) scale was used to assess overall severity of symptoms. Medical history and concomitant medications were noted. Laboratory samples collected include CRP, IL-6, and TNF-α. Review of medical records was performed as needed to obtain medical data and treatment history relevant to the study.

Primary efficacy measures included (1) change in CAPS-5 score from baseline to the end of study and (2) levels of the inflammatory markers CRP, IL-6, and TNF-α from screening to the end of the study. Secondary efficacy measures included change in BDI-II and CGI scores from baseline to the end of the study.

RESULTS

Demographics and primary efficacy measure results are summarized in the Table. Patient A is a 33-year-old man diagnosed with PTSD in September 2014. He served active duty in the US Army from 2006 to 2014. Comorbid conditions included obstructive sleep apnea, tinnitus, lower back pain, and obesity. Prior to minocycline treatment, he took duloxetine 60 mg/day. Diagnosis of PTSD was clinically confirmed by his PCL-5 score of 38 at his screening visit. Starting with measures of primary efficacy, his CAPS score at baseline was 23 and reached 15 at the end of the study. CRP measurements remained below 0.5 mg/dL at both visits, IL-6 increased from 0.83 pg/mL to 1.04 pg/mL, and TNF-α decreased from 1.4 pg/mL to 1.14 pg/mL. His BDI-II started at 18 and dropped to 13 at end of study, so it was never above the threshold of 20 to indicate moderate/severe depression. Patient A's CGI-S score remained at the same value of 4 throughout the study, indicating that the severity of his clinical symptoms did not change.

Patient B is a 39-year-old man. He experienced several trau-

matic events as he served as a combat medic in Iraq from 2003 to 2005. He was diagnosed with PTSD in July 2013. He had previously received diagnoses of alcohol use disorder and cocaine use disorder. Medications he used prior to the study include sertraline 100 mg/day and prazosin 1 mg/day. Additionally, he participated in PTSD group therapy. He had a PCL-5 score of 38 at his screening visit, clinically confirming his diagnosis. His CAPS score decreased from 40 to 29. Changes in his inflammatory cytokine levels from the beginning to the end of the study were as follows: CRP, 1.5 mg/dL to 1.0 mg/dL; IL-6, 1.59 pg/mL to 1.29 pg/mL; and TNF-α, 1.4 pg/mL to 1.19 pg/mL. His BDI-II score of 11 did not meet the threshold for moderate/severe depression, but at the end of the study it had increased to 23, indicating depression. Patient B's CGI-S score was 5 at his initial evaluation and decreased to 4 by the end of the study.

Patient C is a 59-year-old man diagnosed with PTSD in September 2016. He witnessed traumatic events during his service as both a civilian and military firefighter emergency medical technician, including experience with dead and mutilated bodies. Along with PTSD, he experienced sciatic nerve pain, degeneration of intervertebral disk, and hearing loss. Patient C's medication taken prior to and during the study included 100 mg/day of the selective serotonin reuptake inhibitor sertraline and 4 mg/day of the antihistamine cyproheptadine. For the study, Patient C received a PCL-5 score of 45 recorded at screening, which indicates a PTSD diagnosis (PCL-5 score ≥ 33). He also had a BDI-II score of 29 at the first visit, indicating moderate depression. Over the course of the study, data indicated a rise in concentrations for IL-6, 1.79 to 2.56 pg/mL, and TNF-α, 0.97 to 1.26 pg/mL. CRP levels dropped from 1.0 to 0.8 mg/dL. Patient C's BDI-II score at the end of the study measured 23, and his CGI-S score remained at 4 throughout the study. The CAPS score decreased from baseline measurement to end of study tests, 29 to 18.

Patient D is a 46-year-old man who was diagnosed with PTSD in January 2014. He served in active military from 1993 to 1997 in Haiti, Kuwait, and Bosnia as a reconnaissance scout. He attributes the cause of his trauma to experiences dealing with dead bodies, especially infants. Other than PTSD, Patient D was diagnosed with hyperthyroidism and hyperlipidemia. Medications taken prior to and during the study on stable dose included paroxetine 40 mg/day for anxiety and quetiapine fumarate 425 mg/day for PTSD. At screening, he scored a 53 on the PCL-5, indicating a PTSD diagnosis. He also had a BDI-II score of 40 at screening, indicating severe depression. Concentrations of IL-6, CRP, and TNF-α measured from baseline to end of study were as follows: IL-6, 0.87 to 1.68 pg/mL; TNF-α, 0.78 to 0.93 pg/mL. CRP levels stayed below 0.5 mg/dL for both measurements. Patient D's BDI-II score at the end of study measured 24, and his CGI-S score remained at 4 throughout the study. The CAPS score decreased from 34 to 30 at the end of study.

DISCUSSION

In this study, we hypothesized that minocycline treatment would be associated with reduced inflammation (measured by decreasing levels of inflammatory markers) and decreased PTSD severity, along with mood symptoms. All 4 patients had decreased CAPS scores by the end of the study, and 3 of the 4 patients had decreased scores on the BDI-II.

Consideration should be given to the biomarker results of the study, in which all 4 subjects' levels of CRP decreased or remained below 0.5 mg/dL, while 3 of the subjects' IL-6 levels and 2 patients TNF-α levels increased. The observed increases are contrary to minocycline's proposed mechanism of action.[5,6] As IL-6 and TNF-α are among the main regulators of CRP release,[17] it was expected that elevations of CRP should mirror elevations of IL-6 and TNF-α. However, the results of this study showed the inflammatory markers diverge. While this finding was unexpected, it is not without precedent. Garvin et al discussed such a phenomenon where divergent patterning occurs.[18] The results may stem from the fact that kinetics between CRP and the other biomarkers differ in both release pattern and concentration. Additionally, CRP has a much longer half-life than IL-6 or TNF-α. Possibly, elevations in IL-6 and TNF-α without CRP could be attributed to various acute phase responses in individuals with differing subclinical inflammation. Whereas a subclinical infection would possibly not see a rise in all biomarkers, in a true clinical infection, all biomarkers would likely show a notable increase. Further studies utilizing larger samples of participants and measurement of inflammatory markers could help to better understand the interactions between these inflammatory factors.

Limitations of this research include the fact that it was an open-label trial with no placebo arm. A 12-week treatment duration may have been too short to see long-lasting benefits, but future studies could address this by extending the trial length. Adjunctive minocycline was not associated with any serious adverse events or significant laboratory abnormalities in our cohort; however, it is important to pay attention to potential side effects from long-term antibiotic use.[19] No follow-up was done to evaluate patients' PTSD symptoms after the study, so we are unaware of long-term benefits regarding this intervention. Lastly, a larger sample size could create more generalizable information.

Further neuroprotective efforts also should be explored when considering minocycline treatment. Patients A, C, and D's BDI-II scores decreased by a notable margin during the study. Previous studies evaluating minocycline therapy for depression have reported significant improvement in symptoms.[13,14] Larger scale double-blind clinical trials should be considered in further research of this inexpensive and generally safe drug in PTSD.

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