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14. ABSTRACT The objective of this clinical trial is to find an evidence-based treatment for Gulf War Illness (GWI). Elevated biomarkers of inflammation were observed in our pilot observational study of GWI. Thus, chronic inflammation appears to be part of the underlying pathophysiology of GWI. Reducing GWI-associated inflammation may alleviate some symptom of the disorder and improve the health-related quality of life of veterans with GWI. This is a randomized, two-group, double-blind, placebo-controlled clinical trial of delayed-release prednisone versus matching placebo. A total of 100 veterans with GWI will be enrolled in the trial. Prednisone was chosen as the study drug because of its well-established pleiotropic anti-inflammatory properties. The specific aims of the study are to measure the effects of the treatment on the following: 1) physical and mental functioning 2) pain, fatigue, and cognitive dysfunction 3) biomarkers of inflammation. All regulatory approvals for this clinical trial have been received. Recruitment and enrollment have begun. A successful trial with improved clinical outcomes and reduced proinflammatory biomarkers would be direct evidence of the role that chronic inflammation plays in the underlying pathophysiology of GWI. Thus, a new paradigm for the diagnosis and treatment of GWI would be established. The potential impact of this new paradigm on the health and well-being of veterans with GWI is very significant.					
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Introduction

From August 2, 1990 to July 31, 1991 approximately 697,000 United States military personnel were deployed to the Kuwaiti Theater of Operations during Operation Desert Shield and Operation Desert Storm (Gulf War). Many veterans of this conflict now suffer from an unexplained chronic multi-symptom disorder known as Gulf War Illness (GWI). The symptoms most frequently associated with GWI are widespread pain, unexplained fatigue, and cognitive difficulties. Comprehensive reviews of GWI have been published by the Research Advisory Committee on Gulf War Veterans' Illnesses (1) and the Institute of Medicine (2).

The Department of Veterans Affairs (VA) Office of Public Health has conducted survey studies of the mental and physical health of a population-based cohort of 30,000 Gulf War and Gulf War era Veterans. The most significant health-related difference revealed by these studies was the higher prevalence of unexplained chronic multi-symptom illnesses in the deployed veterans group. Ten years post-deployment the difference was 28.9% vs 15.8% (adjusted odds ratio=2.16) (3). Fourteen years post-deployment the difference was 36.5% vs 11.7% (adjusted risk ratio=3.05) (4). Twenty years post-deployment the difference was 43.9% vs 20.3% (adjusted odds ratio=3.06) (5). Thus, a chronic unexplained multi-symptom illness is the signature health-related outcome of the 1990-1991 Gulf War and the incidence of GWI in the Gulf War veteran population continues to increase.

The absence of information regarding the underlying pathophysiology of GWI has hindered efforts to develop effective treatments. Therefore, we performed a pilot study comparing blood samples from Gulf War veterans with and without multiple symptoms of pain, fatigue, and cognitive dysfunction (6). The goal of the pilot study was to discover a biomarker fingerprint that would identify a potential therapeutic target for the treatment of GWI. Examination to the peripheral blood revealed the biomarker signature of innate immune system activation in veterans with GWI. Thus, chronic inflammation was identified as a potential therapeutic target.

Key Words

Gulf War Illness, Chronic Inflammation, Delayed-Release Prednisone, Evidence-Based Treatment, Clinical Trial, Pain, Fatigue, Cognitive Dysfunction

Accomplishments

1st Quarter

- Screening and enrollment of Gulf War veterans into the Gulf War Illness Inflammation Reduction Trial (GW 130025) continues.

2nd Quarter

- Screening and enrollment of Gulf War veterans into the Gulf War Illness Inflammation Reduction Trial (GW 130025) continues.

3^d Quarter

- Screening and enrollment of Gulf War veterans into the Gulf War Illness Inflammation Reduction Trial (GW 130025) continues.
- The results of the pilot study that are the basis for this clinical trial were published in the online journal PLOS ONE (6).

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0157855>

- Outreach efforts to the Gulf War veteran community were initiated to enhance enrollment and overcome seasonal fluctuations.

4th Quarter

- Screening and enrollment of Gulf War veterans into the Gulf War Illness Inflammation Reduction Trial (GW 130025) continues.

Progress as of 30-09-2016:

Veterans Screened.....73
Potential Subjects Consented.....40
Subjects Enrolled.....30
Subjects Withdrawn.....2
Enrollment Rate from 07-06-2015 to 01-09-2016.....1.9 Subjects per Month

Impact

The underlying pathophysiology of GWI is not understood. Therefore, we performed a pilot study comparing blood samples from Gulf War veterans who were GWI- with blood from veterans who were GWI+ (6). The GWI status was determined by the assessment of multiple symptoms of pain, fatigue, and cognitive dysfunction using the CDC 10 survey instrument. The objective of the study was to determine if there are quantifiable differences in blood that could be used to identify potential therapeutic targets for the treatment of GWI. The blood analyses included a complete blood count with differential, plasma proteomics, platelet function studies, and the measurement of multiple coagulation parameters.

The pilot study results provide strong evidence of chronic inflammation in veterans with GWI. This entirely new and provocative line of evidence presents an exciting opportunity to test an intervention that has the potential to both reduce symptoms and further define the pathophysiology of GWI.

The goal of this proof-of-principal trial is to determine if reducing inflammation is an effective treatment for GWI. A successful trial with improved clinical outcomes and reduced biomarkers of inflammation would establish a new paradigm for the diagnosis and treatment of GWI. Evaluating the effects of other anti-inflammatory interventions on clinical outcomes and biomarkers of inflammation in randomized placebo-controlled clinical trials could produce additional improvements in GWI treatment beyond those achieved in this trial. Thus, the immediate and long-term positive consequences for the health and well-being of veterans with GWI would be very significant.

Changes/Problems

In the 1st Quarter and 2nd Quarter we observed a decline in the rate of enrollment. We attribute this fluctuation in enrollment to the “Minnesota winter effect.” Gulf War veterans may be reluctant to travel significant distances to participate in this study during the winter months. This hypothesis is supported by the fact that the enrollment rate returned to the pre-winter level in the 3rd Quarter and 4th Quarter.

Since there appear to be seasonal fluctuations in enrollment we have initiated a plan to enhance recruitment and overcome the winter dip. In particular, outreach efforts to the Gulf War veteran community aimed at increasing awareness of the Gulf War Illness Inflammation Reduction Trial are underway. Print media, radio programs targeting veterans, and the internet are being employed. Some of the efforts to connect with Gulf War veterans are presented in the following links:

http://www.91outcomes.com/2016_09_01_archive.html

<http://minnesotamilitaryradiohour.com/20160925-gulf-war-illness-minnesota-power>

<http://www.research.va.gov/currents/0716-1.cfm>

<http://www.minneapolis.va.gov/MINNEAPOLIS/research/index.asp>

http://www.eurekalert.org/pub_releases/2016-07/varc-syp071116.php

<http://www.startribune.com/still-sick-25-years-after-the-gulf-war-a-vet-seeks-answers-and-the-minneapolis-va-may-have-them/390138371/>

The initial results of this campaign with respect to enhancing enrollment look promising.

Products

None

Participants & Other Collaborating Organizations

Name:	Ronald R. Bach, PhD
Project Role:	P.I.
Nearest person month worked:	3
Contribution to Project:	Dr. Bach has overseen the efforts of other study personnel with respect to the regulatory approval process as well as screening, enrollment, and conduct of the study.

Name:	Rebecca Rudquist, BSN
Project Role:	Study Coordinator
Nearest person month worked:	12
Contribution to Project:	Ms. Rudquist has participated in all aspects of the regulatory approval process as well as the screening and enrollment of subjects and the conduct of the study.

Name:	Susan Johnson, LPN
Project Role:	Study Staff
Nearest person month worked:	2
Contribution to Project:	Ms. Johnson has participated in all aspects of the regulatory approval process as well as the screening and enrollment of subjects and the conduct of the study.

Special Reporting Requirements

None

Appendices

None

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