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14. ABSTRACT

The objective of this study is to determine the underlying cause of Gulf War Illness (GWI) symptoms. Elevated blood biomarkers of inflammation were observed in our pilot observational study of GWI. Thus, we hypothesized that chronic inflammation is an underlying cause of GWI and reducing the inflammation may alleviate symptoms and improve the health-related quality of life. This is a randomized, two-group, double-blind, placebo-controlled clinical trial of modified-release prednisone (MR-prednisone) versus matching placebo. A total of 95 Gulf War Veterans were enrolled and 83 were randomized. MR-prednisone was chosen as the study drug because of its pleiotropic anti-inflammatory properties. The specific aims of the study are to measure the effects of the MR-prednisone versus placebo: 1) physical and mental functioning 2) pain, fatigue, and cognitive dysfunction 3) biomarkers of inflammation. All regulatory approvals for this clinical trial were received. The active phase of this study has been completed, and the data analysis phase is ongoing. 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 may be established. The potential impact of a successful study on the health and well-being of veterans with GWI is high.

15. SUBJECT TERMS

Gulf War Illness, Chronic Inflammation, Modified-Release Prednisone

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Introduction

Nearly 700,000 U.S. military personnel served in the 1990-91 Gulf War, Operations Desert Shield and Desert Storm. Today many Gulf War Veterans suffer from an unexplained deployment-related chronic multisymptom illness know as Gulf War illness (GWI). Symptoms of this disorder include cognitive impairments, chronic fatigue, musculoskeletal pain, sleep disturbances, gastrointestinal problems, respiratory difficulties, and skin rashes {1-5].

The mission of GWI research is to improve the health-related quality of life (HRQOL) of Gulf War Veterans via the discovery of interventions which alleviate GWI-associated symptoms, stop disease progression, and mitigate the long-term health effects of the disorder. We have employed a translational research strategy in pursuit of this goal. The first step in the process was a search for GWI-associated biomarkers. By comparing blood from Gulf War Veterans with and without GWI, fourteen significant blood biomarker differences were identified. Further analysis revealed the proinflammatory nature of this blood biomarker fingerprint. Thus, we identified inflammation as a component of GWI pathophysiology and a potential therapeutic target [6].

The characteristics of the GWI blood biomarker fingerprint were the basis for the selection of prednisone, an inhibitor of proinflammatory gene expression, as the evidence-based intervention. The effects of low-dose prednisone chronotherapy on HRQOL, GWI-associated symptoms, and blood biomarkers are measured in the Gulf War Illness Inflammation Reduction Trial (GWI-IRT, ClinicalTrials.gov Identifier: NCT02506192). GWI-IRT is a hybrid proof-of-mechanism/proof-of-principle study employing a randomized controlled trial (RCT) design to test the hypothesis that GWI is a chronic inflammatory disease.

Key Words

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

Accomplishments

1st Quarter

- Screening and enrollment of Gulf War Veterans into the Gulf War Illness Inflammation Reduction Trial (GWI-IRT, GW 130025) was completed.

2nd Quarter

- Final subject finished the study and the blind was broken
- Data analysis of primary outcomes (SF-36v, HRQOL)commenced

3d Quarter

- The NCE for FY21 was requested and approved.
- Plasma samples were sent to Myriad-RBM for biomarker analysis
- Data analysis secondary outcome commenced
- The first manuscript describing the primary outcome data has been written and awaits submission

4th Quarter

- The first manuscript will be submitted to Life Science special issue on GWI SOTS
- Data analysis of secondary outcome, both subjective symptoms surveys and objective blood biomarker levels, will continue
- Additional GWI-IRT manuscripts will be prepared and submitted.

Progress as of 09-30-2020

	# Subjects
Telephone Screen (Kansas Case-Definition)	198
Consented/Enrolled	95
Randomized (Passed Safety Screen)	83
Withdrawn	2

	Total Enrollment	Running Enrollment Rate (subjects/month)
09-30-2015	11	3.7
12-31-2015	16	2.7
03-31-2016	24	2.7
06-30-2016	29	2.4
09-30-2016	40	2.7
12-31-2016	41	2.3
03-31-2017	47	2.2
06-30-2017	54	2.3
09-30-2017	64	2.4
12-31-2017	70	2.3
03-31-2018	73	2.2
06-30-2018	77	2.1

09-30-2018	78	2.0
12-31-2018	83	2.0
03-31-2019	85	1.9
06-30-2019	86	1.8
09-30-2019	92	1.8
12-31-2019	95	1.8

Impact

The underlying pathophysiology of GWI is not understood. Therefore, we performed a pilot study comparing blood samples from Gulf War veterans who very 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 [3]. 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 hybrid proof-of-mechanism/proof-of-principle RCT 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

A no cost extension (NCE) was and approved with the effective date of 28 August 2020.The purpose of this modification is to extend the period of performance by 12 months, at no additional cost to the Government. Quarterly reports and submission of SF-425s shall continue during the no-cost extension period. All terms and conditions of the award remain unchanged.

We met our accrual goal and finished the active phase of the study in study period. The study is closed to further enrollment, the study has been unblinded, and data analysis is ongoing.

The preliminary analysis of the primary outcome data, i.e., the SF-36v Physical Component Summary score, were presented at the VA-DoD 2020 Gulf War Illness State of the Science Virtual Conference on August 18, 2020. A first manuscript of the GWI-IRT study data has been written and is awaiting submission to special Gulf War Illness issue of Life Sciences.

In the previous period we published a quality improvement study highlighting deficiencies in the delivery of health care to Gulf War Veterans [7]. The study evaluated VA health care for Veterans with GWI from the Veteran's perspective. This quality assessment was based on interviews with 30 GWI+ Veterans at the Minneapolis VA Health Care System who were enrolled in the GWIIRT. The Kansas case definition was used to determine GWI status [8]. One clear message, based on the personal experiences of these Gulf War Veterans, was VA physicians and other health care professionals are ill-equipped to recognize, diagnose, and manage GWI. This information gap is likely to be even greater in health care systems outside VA.

Our study recommended specific improvements in education as well as a major overhaul of the way VA delivers health care to Veterans with GWI. The initiative would include GWI-specific education for VA physicians and trainees, and improved communication between VA physicians who see Gulf War Veterans in their clinics. The recommendation for improved health care delivery centered on the establishment an interdisciplinary GWI clinic with a referral system. Since Veterans are the essential stakeholders in this process, an additional recommendation was to reach out to Veteran networks to update them on GWI research, education, and available health care.

The conclusions of the quality improvement study align with recommendations in a 2013 IOM report to VA entitled: "Gulf War and Health: Treatment for Chronic Multisymptom Illness" [9]. A concise summary of this voluminous IOM report was recently published [10]. The summary emphasized the need to enhance the dissemination of information. "The VA's ability to effectively manage veterans with CMI hinges on proper training of clinicians and teams of professionals who care for these patients, using the VA's existing training infrastructure. Each VA medical center should have a CMI "champion" to serve as an internal resource for clinicians seeking additional information about how best to serve patients with CMI. In addition, the VA should develop peer networks to facilitate sharing information and skills related to managing veterans who have CMI…." The recent statements by Gulf War Veterans in the Minnesota study underscore the need for improved training, education, and information sharing as recommended in the IOM report.

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 oversees 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 participates 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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