AWARD NUMBER: W81XWH-14-1-0477

TITLE: Gulf War Illness Inflammation Reduction Trial

PRINCIPAL INVESTIGATOR: Ronald R. Bach, Ph.D.

CONTRACTING ORGANIZATION: Minneapolis VA Medical Center Minneapolis, MN 55417

REPORT DATE: October 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release; Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT	DOCUMENTATION PAGE	Form Approved
Public reporting hurden for this collection of info	motion is estimated to average 1 hour per response, including the time for re-	UMB NO. 0704-0188
data needed, and completing and reviewing this this burden to Department of Defense, Washing 4302. Respondents should be aware that notwi currently valid OMB control number. PLEASE [collection of information. Send comments regarding this burden estimate or a ton Headquarters Services, Directorate for Information Operations and Report thstanding any other provision of law, no person shall be subject to any penalty O NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.	ny other aspect of this collection of information, including suggestions for reducing s (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202- y for failing to comply with a collection of information if it does not display a
1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2017	Annual	29Sep2016 - 28Sep2017
4. TITLE AND SUBTITLE		5a. CONTRACT NUMBER
Gulf War Illness Inflammation Reduction Trial		5b. GRANT NUMBER W81XWH-14-1-0477
		SC. PROGRAW ELEMENT NUMBER
6. AUTHOR(S)		5d. PROJECT NUMBER
Ronald R. Bach, PhD		5e. TASK NUMBER
E-Mail: Ronald Bach@va.gov	,	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION	NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT
Minneapolis VA Medical Center Research Service (151)		NUMBER
One Veterans Drive		
Minneapolis, MN 55417		
9. SPONSORING / MONITORING A	GENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
U.S. Army Medical Research	and Materiel Command	
Fort Detrick, Maryland 21702	2-5012	11. SPONSOR/MONITOR'S REPORT
		NUMBER(S)
12. DISTRIBUTION / AVAILABILITY	STATEMENT	
Approved for Public Release;	Distribution Unlimited	
13. SUPPLEMENTARY NOTES		
14. ABSTRACT		
The objective of this clinical inflammation were observed underlying pathophysiology of	trial is to find an evidence-based treatment fo in our pilot observational study of GWI. Thus f GWI Reducing GWI-associated inflammation	r Gulf War Illness (GWI). Elevated biomarkers of s, chronic inflammation appears to be part of the b 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		
iunctioning 2) pain, fatigue, and cognitive dysfunction 3) biomarkers of inflammation. All regulatory approvals for this clinical		
rial 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 G	VI is very significant.
15. SUBJECT TERMS Gulf War Illness, Chronic Infl	ammation Delayed-Release Prednisone	

Inflammation, Delayed-Release Prednisone ar iline ٧V

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE	Unclassified	0	19b. TELEPHONE NUMBER (include area code)
Unclassified	Unclassified	Unclassified		9	

Table of Contents

Page

ntroduction	.4
Keywords	.4
Accomplishments	.5
Progress as of 30-09-2017	.6
mpact	.6
Changes/Problems7	
Products	.8
Participants & Other Collaborating Organizations8	
Special Reporting Requirements	.9
Appendices	9
References	9

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. Outreach efforts to the Gulf War veteran community were initiated to enhance enrollment and overcome seasonal fluctuations. Details of the efforts are described in Changes/Problems.
- Senator Amy Klobuchar visited the Minneapolis VAMC on February 7, 2017. The purpose of her visit was to receive a briefing from me about our work on Gulf War Illness. The visit was triggered by the Senator's interest in deploymentrelated illness. This interest is clearly demonstrated by her Helping Veterans Exposed to Burn Pits Act. The "Burn Pit" Act has passed the U.S.Senate and is awaiting a vote in the U.S. House of Representatives. I continue to communicate with the Senator and her staff.

2nd 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) on June 23,2016. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0157855
 I am delighted to report that there is objective evidence indicating the paper is being widely read. The journal informed us on May 25, 2017 that there have been 15,149 views and 480 downloads of the paper. That puts us in the top 1% most downloaded for all PLOS ONE research articles published in 2016!
- I gave a PowerPoint presentation on GWI at the National Association of State Women Veterans Coordinators 2017 Annual Training Conference.

3^d Quarter

- Screening and enrollment of Gulf War veterans into the Gulf War Illness Inflammation Reduction Trial (GW 130025) continues.
- We observed the first evidence that enhanced recruitment methods are having a positive effect. The decline in the running rate of enrollment has reversed.

4th Quarter

• Screening and enrollment of Gulf War veterans into the Gulf War Illness Inflammation Reduction Trial (GW 130025) continues. Additional evidence that enhanced recruitment methods are having a positive effect is observed. For the second straight quarter the running rate of enrollment has increased.

Progress as of 30-09-2017

	# Subjects
Telephone Screen (Kansas Case Definition)	131
Consented/Enrolled	64
Randomized (Passed Safety Screen)	53
Withdrawn	2

	Total Enrollment	Running Enrollment Rate (subjects/month)
09/30/15	11	3.7
12/30/15	16	2.7
03/31/16	24	2.7
06/30/16	29	2.4
09/30/16	40	2.7
12/31/16	41	2.3
03/31/17	47	2.2
06/30/17	54	2.3
09/30/17	64	2.4

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. 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

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-answersand-the-minneapolis-va-may-have-them/390138371/

The initial results of this campaign with respect to enhancing enrollment look promising. Increases were observed in the 3rd and 4th quarters of 2017. We are expanding our effort to increase the rate of enrollment. In the previous quarter the study was posted on the Minneapolis VA intranet and internet sites. The study has also been posted on the "Gulf War Illness" Facebook page. In addition, we are beginning to see a fair number of word of mouth recruits. In this quarter, new VA Research Study Kiosks were installed in the lobby of the Minneapolis VAMC. The flyer for the GWIIRT is located there.

Two additional recruitment enhancement methods were introduced this year. We have reached out to the staff responsible for Veterans affairs in the offices of three Minnesota Congressmen and one Minnesota Senator. Information about the GWIIRT was included in the communication along with a request to have the material distributed to their contacts in the Veterans. In addition, on June 27 I gave a talk on GWI at the National Association of State Women Veterans Coordinators Annual Training Conference. At the conference, I talked with two employees of the state of from Minnesota with established networks of communication within the Minnesota Veteran community. One is the Gold Star Family & Women Veterans Coordinator in the Minnesota Office of Veterans Affairs. The other is in the Director of Military Outreach in State of Minnesota Department of Military Affairs. Both were very interested in what I had to say about GWI and expressed willingness to distribute GWIIRT information to their Gulf War Veterans. The effects of these efforts on recruitment should be evident in numbers presented in the next quarterly report.

On March 25, 2017 I spoke about GWI at the 7th Annual Vietnam Veterans Day festivities at the American Legion Hall in Chippewa Falls, Wisconsin. Gulf War Veterans or their family members were present. Thus, several study subjects were recruited.

Press releases have been issued by VA Office of Research and Development in Washington DC and the Minneapolis VA Health Care System announcing the

publication of our observational study of GWI (see ref 4). We hope the local and national publicity generated by these publications will have a positive effect on enrollment. The following are links to some recent media reports on this clinical trial:

http://www.research.va.gov/currents/0716-1.cfm www.npr.org/2013/03/22/175054277/scientists-search-for-gulf-war-illness-answers www.research.va.gov/currents/0716-1.cfm http://minnesotamilitaryradiohour.com/20160925-gulf-war-illness-minnesota-power

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

References

- 1. Research Advisory Committee on Gulf War Veterans' Illnesses. *Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations*. Washington, D.C.: U.S. Government Printing Office, November, 2008.
- 2. Institute of Medicine of the National Academies Committee on Gulf War and Health. *Gulf War and Health, Volume 8: Update of Health Effects of Serving in the Gulf War.* Washington, DC: The National Academies Press. 2009.
- 3. Kang HK. Mahan CM. Lee KY. Magee CA. Murphy FM. Illnesses among United States veterans of the Gulf War: a population-based survey of 30,000 veterans. J Occup Environ Med. 2000; 42:491-501.
- Kang HK. Li B. Mahan CM. Eisen SA. Engel CC. Health of US Veterans of 1991 Gulf War: A Follow-Up Survey in 10 Years. J Occup Environ Med. 2009; 51:401-410.
- Dursa EK, Barth SK, Schneiderman AI, Bossarte RM. Physical and Mental Health Status of Gulf War and Gulf Era Veterans: Results From a Large Population-Based Epidemiological Study. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine. 2016;58(1):41-6. Epub 2015/12/31.
- Johnson GJ, Slater BCS, Leis LA, Rector TS, Bach RR, Blood Biomarkers of Chronic Inflammation in Gulf War Illness, PLOS ONE 2016; 11(6): e0157855. doi:10.1371/journal.pone.0157855.