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TITLE: Development of Dietary Polyphenol Preparations for Treating Veterans with Gulf War Illness

PRINCIPAL INVESTIGATOR: Giulio Maria Pasinetti MD., PhD

CONTRACTING ORGANIZATION:
Icahn School of Medicine at Mount Sinai (ISMMS)
1 Gustave L Levy Place
New York, NY 10029-6504

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14. ABSTRACT There are no treatments for Gulf War Illness (GWI) and there is an urgent need to develop novel interventions either to resolve underlying GWI mechanisms, or to alleviate major GWI clinical complications, particularly chronic fatigue, cognitive difficulties, muscle pain, as well as mood disturbances and sleep problems. Recent evidence from our group and from others revealed that certain dietary flavonoids may promote cognitive function and/or alleviate chronic fatigue. We hypothesized that dietary supplementation with a Flavonoid Rich Preparation (FRP), consisting of Concord Grape Juice (CGJ), may help alleviate clinical complications of GWI, particularly chronic fatigue and/or cognitive dysfunction. We propose to test the feasibility of dietary supplementation with FRP in Veterans with GWI, and to gather evidence supporting the efficacy of FRP in alleviating GWI-associated cognitive deficits and chronic fatigue. Purpose: To conduct a randomized, double-blind Phase I/IIA study to explore long-term dose compliance, safety, tolerability of FRP and to assess the efficacy of FRP in improving cognition function and alleviating chronic fatigue in Veterans with GWI. Scope: Evidence gathered by our proposed studies will provide the necessary proof of principle data and support future development of broader efficacy studies of a specific, readily available nutritional supplementation regimen, FRP, for treating Veterans with GWI. Progress: In fiscal year 5, we completed data collection for all participants consented prior to the enrollment closure date of July 19 th , 2018. The final endpoint was completed on January 17 th , 2019 and data analysis began shortly afterward. We are currently creating a manuscript describing our results to submit for publication in the future. To summarize our final enrollment numbers, we sent letters to 777 potential participants. Of those 777, we screened 72 potential participants with 46 of them screening eligible. Of the 46 who were eligible to continue, 36 came to the VANJHCS to be consented and enrolled in the study with 31 completing the 24-week protocol (5 dropouts).						
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1. INTRODUCTION

An estimated 174,300 to 230,000 US military service members deployed to Iraq and Afghanistan are affected by Gulf War Illness (GWI). GWI is characterized by the persistent presentation of multiple functional symptoms involving a combination of diverse complaints centering on chronic fatigue, cognitive difficulties, muscle pain, as well as mood disturbances and sleep problems that are not explained by established medical diagnoses. While the etiology of the GWI symptom complex is not known, GWI clinical complications typically persist over long-terms, cause significant pain and suffering, and interfere with the ability of affected Veterans to successfully integrate back into the civilian society. There are no treatments for GWI and there is an urgent need to develop novel interventions either to resolve underlying GWI mechanisms, or to alleviate major GWI clinical complications. Recent evidence from our group and from others revealed/highlighted the potential value of flavonoids, a subclass of organic chemical called polyphenols that are abundantly found in some plants and common dietary preparations, may help alleviate chronic fatigue and preserve against cognitive functions. Based on this, our overall goal is to test the potential efficacy of dietary supplementation with a Flavonoid-Rich Preparation (FRP) to alleviate clinical complications in Veterans with GWI. In particular, we proposed to conduct a randomized, double-blind Phase I/IIA study to explore long-term dose compliance, safety, tolerability of FRP and to assess the efficacy of FRP (Concord grape juice) in improving cognition function and alleviating chronic fatigue in Veterans with GWI. Evidence gathered by our proposed studies will provide the necessary proof of principle data and support future development of broader efficacy studies of a specific, readily available nutritional supplementation regimen, FRP, for treating Veterans with GWI.

2. KEYWORDS

Gulf War Illness
Polyphenol
Flavonoids
Flavonoid-Rich Preparation
Chronic fatigue
Cognitive difficulties
Muscle pain
Mood disturbances
Sleep problems

3. ACCOMPLISHMENTS

- *Major goals of the project*

Obtain IND/IRB approval (Year 0 to 0.5)

- obtain FDA IND approval
- Obtain local institutional IRB approval (from the Icahn School of Medicine at Mount Sinai and from the Department of Veterans Affairs, New Jersey Health Care System (DVANJHCS))
- Obtain approval from the U.S. Army Human Research Protection Office (HRPO)

Recruit 60 volunteers (Year 0.5 to 1.17)

- randomized volunteers into a treatment and a placebo arm, n=30 per arm
- complete baseline clinical assessments

- collect and bank baseline blood specimen

FRP treatment (Year 0.7 to 1.5)

- initial dose-escalation finding phase (6 weeks) followed by a stable treatment dose (18 weeks)
- complete clinical assessments during and post treatment
- collect and bank blood post treatment

Complete analysis of blood polyphenol contents (Year 0.5 to 1.7)

Complete data analysis and manuscript preparation (Year 1.8 to 5)

- ***Accomplishments under these goals***

We originally proposed to treat GWI subjects using an FRP comprised of combined Concord grape juice and a grape seed polyphenol extract. We obtained IND approval from the FDA (IND 123889) to conduct this trial using the FRP in veterans with GWI. Moreover, we submitted an IRB application to the Department of Veterans Affairs, New Jersey Health Care System (DVANJHCS) at East Orange, New Jersey for recruiting GWI cases for the study, treating and monitoring participant subjects, and collecting and banking de-identified plasma specimens from these subjects for subsequent biochemical analysis by investigators at the Icahn School of Medicine (ISMMS). We also submitted an IRB application to ISMMS for conducting biochemical analysis of banked de-identified blood specimen that will be provided by DVANJHCS.

Since submission of our initial IND and IRB documents, our research team decided that, to promote better compliance over the long term, we should amend our protocol by removing grape seed polyphenol extract from the protocol and treat GWI cases with an FRP comprised of only Concord grape juice. The range of Concord grape juice doses proposed is within the range of efficacy for improving cognitive function in the elderly, as was discussed in the application. This amendment does not change the goals and timelines in the SOW. But since we have removed grape seed polyphenol extract from the study, we have amended the SOW to reflect this modification. We have discussed this with our program officer, Mr. Brett Chaney, and he approved our proposed amendment. We submitted to FDA an amendment for using only Concord grape for our proposed studies in veterans with GWI and the amended protocol received FDA approval (IND 123889). We also submitted our amended protocol, using only Concord grape juice to the ISMMS IRB and the DVANJHCS IRB. The proposed amended protocol received ISMMS and DVANJHCS IRB approval. In our 1st DoD Annual Report, we have submitted our amended SOW, as well as documents from the FDA and from ISMMS and DVANJHCS IRBs confirming approval of our amended protocol.

As stipulated by both local institutional IRBs, we have since applied for and received annual re-approval of our protocol.

We have since obtained USAMRMC HRPO approval to procure investigatory reagents and begin the initial subject recruitment.

All study logs, policies, procedures, and data collection tools are now in place. Neuropsychological assessment instruments have been delivered as well as all other necessary study items. Research personnel have been appropriately trained to conduct research activities (screening, consenting, survey administration, neuropsychological testing, data entry, blood specimen processing).

All study team personnel at the clinical site (VANJHCS) are also in place:

Principal Investigator: Drew Helmer, M.D., M.S. (Departed VANJHCS in August 2019)

Study staff: Omowunmi Osinubi, MD (Investigator) (PI as of August 2019 due to Drew Helmer's departure)

David Litke PhD (Psychologist)

Jan Einhorn, RN (Study Nurse)

Lydia Patrick-DeLuca, RN (Study Nurse – Back Up)

Nancy Eager (Phlebotomist – Back Up)

William Van Doren (Research Assistant)

Michelle Deluca (Research Assistant - Back Up)

By the end of fiscal year 2, we identified 400 potentially eligible Gulf War Veterans for recruitment and sent out 137 recruitment letters to those that lived within a 100-mile radius of the clinical site (VANJHCS). We screened 10 Veterans, with 7 being eligible for participation. Of these, 5 were enrolled while the remaining 2 were lost to follow-up/no longer interested.

During fiscal year 3, we sent out an additional 382 recruitment letters. We screened 33 Veterans, with 20 being eligible for participation. Of these, 15 were enrolled while the remaining 5 were lost to follow-up/no longer interested.

During fiscal year 4, we sent out a final 258 recruitment letters. We screened 29 Veterans, with 19 being eligible for participation. Of these, 16 were enrolled while the remaining 3 were lost to follow-up/no longer interested. Due to financial constraints, we closed the study to new enrollees on July 19th, 2018 (date of VANJHCS Continuing Review). All subjects enrolled were allowed to complete the full 24-week protocol.

At time of enrollment closure, we had screened 72 Veterans total, with 46 of them being eligible for participation. Of these 46, 36 were consented/enrolled while the other 10 were lost to follow-up/no longer interested. Among the 36 who enrolled, 31 completed the full 24-week protocol (5 drop-outs).

Processed blood samples for the consented/enrolled participants were stored securely within an ultra-low temperature freezer at the clinical site (VANJHCS). They were shipped to Mt. Sinai for analysis upon completion of the final study endpoint in January 2019; back-ups are maintained at VANJHCS, if necessary.

During the past year (fiscal year 5), we completed the final data collection timepoints and began data analysis. ISMMS has completed blood specimen analysis. VANJHCS has started preparing a manuscript for submission/publication discussing the study results, specifically

the safety, tolerability, compliance to, and efficacy of FRP supplementation in Veterans with GWI.

- ***Opportunities for training and professional development the project provided***
Nothing to Report
- ***How were the results disseminated to communities of interest?***
Nothing to Report
- ***What do you plan to do during the next reporting period to accomplish the goals?***
We will complete data analysis and manuscripts for submission/publication.

4. IMPACT

- **What was the impact on the development of the principal discipline(s) of the project?**
Nothing to Report
- **What was the impact on other disciplines?**
Nothing to Report
- **What was the impact on technology transfer?**
Nothing to Report
- **What was the impact on society beyond science and technology?**
Nothing to Report

5. CHANGES/PROBLEMS

- **Changes in approach and reasons for change**
Due to financial constraints, we closed recruitment with a final n=36 rather than the originally approved n=60.
- **Actual or anticipated problems or delays and actions or plans to resolve them**
Nothing to Report
- **Changes that had a significant impact on expenditures**
Nothing to Report
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
Nothing to Report
- **Significant changes in use or care of human subjects**
Nothing to Report

- **Significant changes in use or care of vertebrate animals.**
Not applicable
- **Significant changes in use of biohazards and/or select agents**
Nothing to Report

6. PRODUCTS

- **Publications, conference papers, and presentations**
Manuscripts are in preparation for submission/publication. Poster submissions will be generated for presentation at national conferences yet to be determined (SGIM, etc.)
- **Journal publications.**
Manuscripts are in preparation for submission/publication.
- **Books or other non-periodical, one-time publications.**
Nothing to Report
- **Other publications, conference papers, and presentations.**
Presentation to the Gulf War Research Advisory Committee
Presenter: Dr. Drew A. Helmer
Date: September 29, 2015
Presentation Title: Development of Dietary Polyphenol Preparations for Treating Veterans with Gulf War Illness
- **Website(s) or other Internet site(s)**
ClinicalTrials.gov Identifier: NCT02915237
Warrelatedillness.va.gov
- **Technologies or techniques**
Nothing to Report
- **Inventions, patent applications, and/or licenses**
Nothing to Report
- **Other Products**
Using lessons learned from this current study, the Investigators submitted a grant proposal to the VA Clinical Science Research and Development (CSR&D) Gulf War Project aimed at investigating the feasibility and potential efficacy of dietary supplementation with a select Bioactive Dietary Polyphenol Preparation (BDPP) to alleviate cognitive dysfunction in Veterans with GWI. This proposal was denied funding, but the Investigators intend to submit a revised grant proposal focused on the same outcomes to the VA CSR&D Gulf War Project in March 2020.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Dr. Giulio Pasinetti (PI, ISMMS): no change

Dr. Drew Helmer (clinical PI, VANJHCS): Left VANJHCS; Dr. Osinubi now acting clinical PI

Dr. Omowunmi Osinubi (clinical PI, VANJHCS): Approved as clinical PI at VANJHCS in August 2019

Dr. Lap Ho (co-investigator, ISMMS): Departed Pasinetti lab at ISMMS

Dr. David Litke (Neuropsychologist): no change

Will Van Doren (Research Assistant): no change

Jan Einhorn (Study Nurse): no change

Nancy Eager (Phlebotomist): no change

Lydia Patrick-DeLuca (Study Nurse Back-Up): no change

Michelle Deluca (Research Assistant Back-Up): no change

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Drew Helmer, the former clinical PI at VANJHCS, accepted a new position in August 2019. Upon his departure, Omowunmi Osinubi, M.D., assumed responsibility as the new clinical PI. This change was formally approved by the VANJHCS IRB in August 2020.

- **What other organizations were involved as partners?**

VA- New Jersey Health Care System

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** N/A

- **QUAD CHARTS:** N/A

9. APPENDICES: None