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TITLE: Clinical Evaluation of Montelukast on Cognitive and Mood Dysfunction and Neuroinflammation in Veterans with Gulf War Illness (GWI)

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14. ABSTRACT

Among the 700,000 service personnel who served in the 1990-1991 Gulf War, 30-40% suffer from GWI. While the precise causes of GWI remain unclear, epidemiological, and animal model studies have suggested that a combination of exposures encountered by service personnel during the 1990-1991 Gulf War resulted in a variety of brain impairments, including learning, memory, and mood dysfunction. The chemical exposures implicated include the pyridostigmine bromide (PB) pills consumed daily during the war to protect against nerve gas and pesticides that included the insecticide permethrin (PER) and insect repellent N, N-diethyl-m-toluamide (DEET). The chemical exposures combined with the war-related stress are thought to have produced the neurological symptoms frequently suffered by Veterans with GWI. This project will examine the pre-clinical promise of Montelukast (MLK) for improving neuroinflammation in veterans with GWI by assessing change in a novel peripheral blood marker of neuroinflammation. MLK, an FDA-approved drug for asthma, has shown efficacy in an animal model of GWI to improve cognitive and mood function through modulation of leukotriene signaling and suppression of neuroinflammation. This study will consist of sixty Gulf War Veterans of the U.S. military deployed on military orders to the Persian Gulf Region between August 2, 1990, and December 31, 1991. Participants will also need to meet criteria for GWI (both Kansas and CDC case definitions) with self-reported cognitive dysfunction based on testing.

15. SUBJECT TERMS

Veteran, Montelukast, neuroinflammation, Gulf War Illness, leukotrienes, extracellular vesicles

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1.INTRODUCTION:

This project examines the pre-clinical promise of Montelukast (MLK) for improving neuroinflammation in veterans with Gulf War Illness (GWI) by assessing change in a novel peripheral blood marker of neuroinflammation, leukotriene concentrations in peripherally circulating brain-derived extracellular vesicles. MLK, an FDA-approved drug for asthma, is a potent inhibitor of Cys-Leukotriene (CysLT) receptors, reducing inflammation. It has demonstrated efficacy in an animal model of GWI to improve cognitive and mood function through modulation of leukotriene signaling and suppression of neuroinflammation. There are ongoing clinical trials of MLK to treat mild cognitive impairment and Alzheimer's disease.

2.KEYWORDS:

Veteran, Montelukast, leukotrienes, extracellular vesicles, neuroinflammation, Gulf War Illness

3.ACCOMPLISHMENTS:

The research team met regularly to advance regulatory approvals, discuss project workflow, update the protocol per IRB, gather and organize materials, and other study planning. A research coordinator (Carl Berghult) was hired to assist with study planning and recruitment, enrollment, and data collection. The research team coordinated with collaborators at Texas A&M School of Medicine for the proper planning of future study material transfers. A comprehensive safety plan was developed to address adverse neuropsychiatric effects.

The research team obtained IRB approval at Michael E. DeBakey VA Medical Center and Baylor College of Medicine. As required by the IRB, the research team obtained a U.S. Food and Drug Administration (FDA) Investigational New Drug (IND) exemption for use of 40mg of Montelukast daily for the 10 weeks of the study intervention.

4.IMPACT:

None this fiscal year.

5.CHANGES/PROBLEMS:

The local IRB required several changes that took time to address, including FDA IND exemption. Even after an FDA IND exemption approval for the use of 40mg Montelukast daily, the local IRB tabled the protocol multiple times with concerns about participant safety at this dose. The research team provided an exhaustive literature review of the safety profile of montelukast looking back more than 25 years and summarizing the FDAs documented rationale and its own research into concerns about neuropsychiatric side effects. More recent explorations of the use of higher doses of montelukast in ongoing studies of benefit in Alzheimer's and other dementias also bolstered the justification for the higher dose in this first-in-condition (GWI) study of montelukast. To assuage IRB concerns about the risk benefit ratio, the research team enhanced the comprehensive safety plan and increased the frequency of monitoring for neuropsychiatric side effects. We will now perform telephone monitoring weekly instead of biweekly during the study intervention.

6.PRODUCTS:

None this fiscal year.

7.PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

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 Funding Support: Funding contributed by VA

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Funding Support: Funding contributed by TAMU

8.SPECIAL REPORTING REQUIREMENTS ◦ COLLABORATIVE AWARDS:

None

9.APPENDICES:

None.