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TITLE: Probiotic (VSL#3) for Gulf War Illness

PRINCIPAL INVESTIGATOR: Ashok Tuteja, M.D., M.P.H.

CONTRACTING ORGANIZATION: Western Institute For Biomedical Research
Salt Lake City, UT 841148-0001

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Ashok Tuteja, M.D.

E-Mail: ashok.tuteja@hsc.utah.edu

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14. ABSTRACT

The overall objective of the study was to determine whether Bifidobacterium infantis 35624 (Align®) will improve symptoms of GW illness. We have not started the study as yet. This is due to inability to get IND (Investigational New Drug) number for the probiotic, Bifidobacterium infantis 35624 (Align®). The manufactures of Bifidobacterium infantis 35624 (Align®), Procter & Gamble could not provide the necessary manufacturing information to Food and Drug Administration (FDA). We requested the Department of Defense to allow us to use another commonly used probiotic, VSL#3. The Department of Defense contract has been modified to include this change. The Confidentiality Disclosure Agreement between VSL Pharmaceuticals and the Department of Veterans Affairs has been agreed.

15. SUBJECT TERMS
Irritable bowel syndrome, probiotic, Gulf War Illness, diarrhea

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Introduction:

Gastroenteritis during deployment is a risk factor for the development of irritable bowel syndrome (IBS) after deployment. Gulf War Veterans with IBS are more likely to report fatigue, joint pain, general stiffness and headache- common clinical features of GW Illness. Gastroenteritis plays a major role in changing the gut microflora. Gut microflora are also known to change with travel, stress and diet changes- factors which are relevant to GW Veterans. Altered gut flora may be the etiological factor for IBS and GW Illness. Probiotics are living organisms that improve health by re-establishing a normal gut flora.

The overall objective of the study was to determine whether Bifidobacterium infantis 35624 (Align®) will improve symptoms of GW illness. We will study patients who have GW illness or chronic multi-symptom illness and IBS.

We have not started the study as yet. This is due to inability to get IND (Investigational New Drug) number for the probiotic, Bifidobacterium infantis 35624 (Align®). The manufactures of Bifidobacterium infantis 35624 (Align®), Procter & Gamble could not provide the necessary manufacturing information to Food and Drug Administration (FDA). We requested the Department of Defense to give us permission to use another commonly used probiotic, VSL#3. The Department of Defense contract has been modified to include this change.

Body

Thus far we have created informed consent form and formatted the surveys to evaluate IBS, dyspepsia, post traumatic stress disorder (PTSD) and fatigue for administration before, during and after treatment with the probiotic. We submitted these documents to the University of Utah Institutional Review Board (IRB). The IRB determined that we needed to obtain either an Investigational New Drug (IND) application or a waiver for an IND from the Food and Drug Administration (FDA).

We submitted the request for IND to the FDA. The FDA informed us to withdraw the application because more manufacturing data was required from the Proctor & Gamble.

We re-submitted the application to the FDA along with the expanded protocol to meet the requirements of the FDA and necessary manufacturing information of the probiotic. However, the FDA required detailed manufacturing information from P&G.

We have also been in contact with the University of California, Berkeley IRB. We have submitted a protocol summary for their approval. They approved of our protocol and pending University of Utah IRB approval, we will immediately gain University of California, Berkeley IRB approval.

We continued to have problems in procuring the required manufacturing information from the distributors of the probiotic, Align® (Bifidobacterium infantis 35624). We therefore requested the Department of Defense to give us permission to use a different commonly used probiotic, VSL#3. We received the new contract in September 2011.

The distributors and manufactures of VSL#3 have helped several investigators obtain an IND and have agreed to support our protocol. The Confidential Disclosure Agreement between VSL Pharmaceuticals Inc and the Department of Veterans Affairs has been agreed and the formal agreement should be completed soon. Once the contract has been signed, we will apply to the FDA for IND.

Key Research Accomplishments

We presented our preliminary findings, the basis for our current proposal at the Digestive Disease Week in Chicago at the American Gastroenterology Association meeting in May 2010. **Changes in Fecal Microbiota of Gulf War Veterans with Irritable Bowel Syndrome.**

I was invited to write an editorial in the journal of Digestive Disease Sciences. The editorial is in print. **Deployment Associated Functional Gastrointestinal Disorders: Do we know the etiology?**

Reportable Outcomes

Nil

Conclusion

Our current problem is obtaining an IND for the probiotic.

Permission to use VSL#3 has resulted in progress and we are hopeful to have the IND and approval from the IRB soon.

References

Nil

Appendices

Abstract (Presented at the Digestive Disease Week

Changes in Fecal Microbiota of Gulf War Veterans with Irritable Bowel Syndrome
Ashok K. Tuteja, Yvette M. Piceno, Sarah M. Craig, Nicholas J. Talley, Gary L. Andersen.

Background: Gastroenteritis is associated with sevenfold increased risk of irritable bowel syndrome (IBS) (Am J Gastroenterol. 2006, 101(8):1894). Deployment is associated with the development of IBS in Gulf War (GW) Veterans post gastroenteritis (Gastroenterology 2008, 124(4):A391), and gastroenteritis is key factor in changing gut microflora (Br J Nutr 2002;88:S67-72). The aim of this pilot study was to determine if altered gut microflora is associated with IBS in GW Veterans. We compared the fecal microflora of GW Veterans with and without IBS.
Methods: Fresh stool specimens were collected from GW Veterans as a part of the larger study on IBS in GW Veterans. More than 450 subjects have been enrolled in the epidemiology and 150 in the treatment part of this study. To determine the role of gut microflora in relationship to deployment and IBS, the genomic DNA was isolated from stool by the bead beating method. The 16S rRNA gene was amplified, labeled, hybridized overnight to a custom microarray (PyloChip), and the image was captured using Affymetrix scanner and software. The PhyloChip is capable of detailed measurements of microbial community composition in a high-throughput and reproducible manner. Definition of IBS and its sub-type was based on Rome III criteria.
Results: Data are available from 7 GW Veterans (4 normal, 2 IBS, and 1 with inflammatory bowel disease/Crohn's Disease). All subjects were men; mean age 54 years, range 46- 62 years. GW Veterans with diarrhea-predominant IBS had fewer detectable bacterial groups (average of 270 subfamilies) than mixed IBS (average of 360 subfamilies) and healthy Veterans (average of 322). The following bacterial families were less abundant in IBS veterans compared to controls: Lactobacillus, Clostridium, Fecalibacterium, and Ruminococcus ($P \leq 0.01$, uncorrected for multiple tests). A heatplot of the hybridization fluorescence intensities of bacterial groups (OTU) in the families above is shown in Figure 1.
Conclusion: With the use of state of the art DNA microarray method, both qualitative and quantitative alterations in the GI microflora of GW Veterans with IBS were found. A larger study to confirm these finding is in progress.