Presentation 15 – Sam Donta

CSP#475 ANTIBIOTIC TREATMENT OF GULF WAR VETERANS' ILLNESSES

Background

- In 1990 and 1991, the U.S. deployed about 700,000 troops to the Persian Gulf to liberate Kuwait from Iraqi occupation.
- While there were few causalities, many individuals returned with unexplained symptoms and illnesses, which have been termed Gulf War Veterans' Illnesses (GWI).
- None of the putative etiologic agents or conditions causing GWI is supported by sufficient evidence.
- One explanation that has received widespread attention is systematic Mycoplasma fermentans infection.

Primary Study Objective

- To determine whether a 12 month course of doxycycline treatment in deployed Gulf War veterans presenting with symptoms of Gulf War Veterans' Illnesses and testing as mycoplasma positive improves patients' functional status (measured by the Physical Component Scale (PCS) of the SF-36V) compared to placebo.

Secondary Hypotheses

- To determine whether doxycycline treatment reduces symptoms of GWI including pain, fatigue and neurocognitive concerns.
- Determine whether doxycycline treatment converts mycoplasma positive patients to mycoplasma negative.
- Determine if the benefits of 12 months doxycycline treatment persist after termination of treatment.

Inclusion Criteria

- Patient deployed to Gulf (8/90 – 8/91)
- Patient has two or three of the following symptoms:
  - Fatigue
  - Musculoskeletal pain
  - Neurocognitive dysfunction
- Symptoms onset occurred during or after Gulf War
- Symptoms have occurred for at least six months and are occurring up to the present
- Patient is mycoplasma species positive (*Fermentans, Genitalium, Pneumoniae*)

Exclusion Criteria

- Medical illness capable of causing patient's symptoms
- Severe psychiatric illness
- Have received or expected to receive an organ or tissue transplant
- Requires chronic antibiotic treatment for other condition
- Life expectancy less than one year
- Known allergy to study drug

Exclusion Criteria - continued

- Patient requires phenytoin, carbamazepine, or barbiturates
- Female who refuses to use acceptable contraceptives
- Patient involved in another interventional trial
- Patient has score greater than 40 on the PCS of the SF-36V
- Patient unable to understand or give informed consent
- Patient known to have Hepatitis C

Study Overview

- This study is a 30 month, prospective, randomized, double-blind clinical trial. Patients who met all inclusion/exclusion criteria and are mycoplasma positive were randomized to one of two treatment groups:
  - Doxycycline for 12 months (200mg/day)
  - Placebo for 12 months

Primary Endpoint Measure

- Proportion of patients in each treatment group (doxycycline and placebo) with a >7 point increase in the Physical Component Scale of SF36V at 12 months, relative to baseline.

Secondary Endpoint Measures

- **Reduction in GWI Symptoms**
  - Pain: short form of McGill Pain Questionnaire
  - Fatigue: Multidimensional Fatigue Inventory
  - Neurocognitive: Cognitive Failures Questionnaire
- **Improvement in Emotional Functioning**
  - mental component scale (MCS) of SF36V
- **Mycoplasma status**
  - at 6, 12, and 18 months, relative to baseline.

Patient Intake

- **SF-36V**

Total:	Ineligible	**Eligible**
2149:	569	**1580**

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Registered :**1421** → Mycoplasma PCR results: 850(-) **550(+)**

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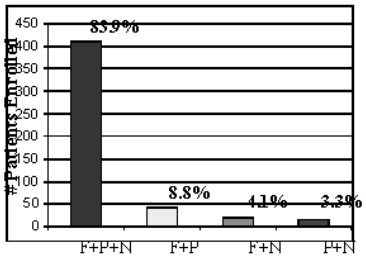
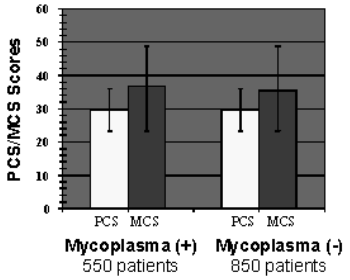
RANDOMIZED **491**

Qualifying Symptoms



F : Fatigue
P : Pain
N : Neurocognitive dysfunction

Mycoplasma Status and PCS/MCS



Compliance as Rated by Site Personnel by Treatment Group

Compliance Rating	Doxycycline		Placebo	
	#Visits	% Visits	#Visits	% Visits
Excellent	1565	57.4	1627	58.1
Good	426	15.6	458	16.4
Fair	176	6.5	174	6.2
Poor	161	5.9	197	7.0
Missing	397	14.6	342	12.2
Total	2725	100.0	2798	100.0

Number of Patients Reporting Adverse Events Considered Possibly or Definitely Related to Study Drug at Least Once During Treating Phase of Study

Costart Adverse Event	Doxycycline Group (n=245)		Placebo Group (n=246)		P-Value
	N	%	N	%	
Amnesia	21	8.6	16	6.5	0.40
Arthralgia	31	12.7	40	16.3	0.31
Asthenia	41	16.7	32	13.0	0.26
Diarrhea	40	16.3	33	13.4	0.38
Dizziness	14	5.7	9	3.7	0.30
Dyspepsia	26	10.6	20	8.1	0.36
GI Disorder	9	3.7	7	2.8	0.62
Headache	47	19.2	46	18.7	0.91
Infection	9	3.7	9	3.7	1.00
Insomnia	8	3.3	7	2.8	0.80
Myalgia	3	1.2	11	4.5	0.05
Nausea	91	37.1	25	10.2	<0.001
Pain-General	40	16.3	40	16.3	1.00
Pain-Abdomen	13	5.3	9	3.7	0.39
Pain-Back	8	3.3	13	5.3	0.37
Photosensitivity	36	14.7	15	6.1	0.002
Rash	37	15.1	27	11.0	0.18

Number of Patients Who Changed From Mycoplasma Species Positive at Baseline to Mycoplasma Species Negative at 6, 12 and 18 Months by Treatment Group

Rating Period	Doxycycline Group			Placebo Group			P
	N	#Neg	% Neg	N	#Neg	% Neg	
6 Months	206	114	55.3	213	124	56.8	0.56
12 Months	200	154	75.4	211	159	76.2	0.73
18 Months	170	154	90.6	178	154	86.5	0.25

CONCLUSIONS

- Study shows that Doxycycline is an ineffective treatment for GWVI.
- Study casts doubt on the relationship between a persistent mycoplasma infection and GWVI.
- Study documents that patients with GWVI are very ill.

Hospitalizations During Study

	Doxycycline		Placebo	
	N	%	N	%
# Patients Hospitalized At Least Once	24	9.8	33	13.4
# Patients Hospitalized For Medication Toxicity	0	0.0	0	0.0
# Patients Hospitalized For GWVI	1	0.4	5	2.0

Number of Patients Prescribed Another Antibiotic at Least once During Treatment Period

	N	%
Doxycycline	74	30.2
Placebo	101	41.1