

Benefits and Harms of Doxycycline Treatment for Gulf War Veterans' Illnesses

A Randomized, Double-Blind, Placebo-Controlled Trial

Sam T. Donta, MD; Charles C. Engel Jr., MD, MPH; Joseph F. Collins, ScD; Joel B. Baseman, PhD; Lisa L. Dever, MD; Thomas Taylor, MD; Kathy D. Boardman, RPh; Lewis E. Kazis, ScD; Suzanne E. Martin; Rebecca A. Horney, BS; Annette L. Wiseman; Douglas S. Kernodle, MD; Raymond P. Smith, MD; Aldona L. Baltch, MD; Christine Handanos, MD; Brian Catto, MD; Luis Montalvo, MD; Michael Everson, PhD; Warren Blackburn, MD; Manisha Thakore, MD; Sheldon T. Brown, MD; Larry Lutwick, MD; Dorothy Norwood, MD; Jack Bernstein, MD; Catherine Bacheller, MD; Bruce Ribner, MD; L.W. Preston Church, MD; Kenneth H. Wilson, MD; Prabhakar Guduru, MD; Robert Cooper, MD; Joseph Lentino, MD; Richard J. Hamill, MD; Arnold B. Gorin, MD; Victor Gordan, MD; David Wagner, MD; Cliff Robinson, MD; Pierre DeJace, MD; Ronald Greenfield, MD; Lisa Beck, MD; Marvin Bittner, MD; H. Ralph Schumacher, MD; Fredric Silverblatt, MD; James Schmitt, MD; Edward Wong, MD; Margaret A.K. Ryan, MD, MPH; Javier Figueroa, MD; Christopher Nice, MD; and John R. Feussner, MD, MPH, for the VA Cooperative #475 Group

Background: It has been hypothesized that certain *Mycoplasma* species may cause Gulf War veterans' illnesses (GWVIs), chronic diseases characterized by pain, fatigue, and cognitive symptoms, and that affected patients may benefit from doxycycline treatment.

Objective: To determine whether a 12-month course of doxycycline improves functional status in Gulf War veterans with GWVIs.

Design: A randomized, double-blind, placebo-controlled clinical trial with 12 months of treatment and 6 additional months of follow-up.

Setting: 26 U.S. Department of Veterans Affairs and 2 U.S. Department of Defense medical centers.

Participants: 491 deployed Gulf War veterans with GWVIs and detectable *Mycoplasma* DNA in the blood.

Intervention: Doxycycline, 200 mg, or matching placebo daily for 12 months.

Measurements: The primary outcome was the proportion of participants who improved more than 7 units on the Physical

Component Summary score of the Veterans Short Form-36 General Health Survey 12 months after randomization. Secondary outcomes were measures of pain, fatigue, and cognitive function and change in positivity for *Mycoplasma* species at 6, 12, and 18 months after randomization.

Results: No statistically significant differences were found between the doxycycline and placebo groups for the primary outcome measure (43 of 238 participants [18.1%] vs. 42 of 243 participants [17.3%]; difference, 0.8 percentage point [95% CI, -6.5 to 8.0 percentage points]; $P > 0.2$) or for secondary outcome measures at 1 year. In addition, possible differences in outcomes at 3 and 6 months were not apparent at 9 or 18 months. Participants in the doxycycline group had a higher incidence of nausea and photosensitivity.

Limitations: Adherence to treatment after 6 months was poor.

Conclusion: Long-term treatment with doxycycline did not improve outcomes of GWVIs at 1 year.

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For author affiliations, see end of text.

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An estimated 15% to 20% of the 700 000 troops who were deployed to the Persian Gulf in 1990 through 1991 have reported debilitating symptoms that as yet have no definitive explanation (1-6). The most common are fatigue, musculoskeletal pain, and neurocognitive problems. This complex of symptoms is clinically indistinguishable from that of the chronic fatigue syndrome and fibromyalgia, and the resulting disorders have been called Gulf War veterans' illnesses (GWVIs).

Several explanations for GWVIs have been proposed, including exposure to bacterial pathogens or neurotoxic chemicals, allergic reactions, metabolic disorders, rheumatologic conditions, and psychological factors (7-11). However, the cause or causes of GWVIs have yet to be identified. It has been hypothesized that GWVIs are caused by an underlying systemic infection with *Mycoplasma* species, the most common being the bacterial pathogen *M. fermentans*, and that long-term treatment with doxycycline might be efficacious (7, 12-14). Preliminary observations were not strong, and controlled clinical trials to support this

treatment approach were lacking. However, because of the need to provide relief to veterans with GWVIs, the U.S. Departments of Veterans Affairs and Defense conducted a randomized, placebo-controlled clinical trial to determine whether doxycycline treatment would improve physical function.

METHODS

The background, methods, and rationale for the study design have been described in detail elsewhere (15) and are only briefly described here.

Study Design and Participants

We performed an 18-month, randomized, double-blind, placebo-controlled clinical trial. The primary objective was to determine whether a 12-month course of treatment with doxycycline improved functional status in deployed veterans with GWVIs whose blood tested positive for *Mycoplasma* DNA. Secondary objectives were to determine whether doxycycline treatment reduced the

Context

Some experts hypothesize that *Mycoplasma* species cause Gulf War veterans' illnesses (GWVIs).

Contribution

In this double-blind trial, 491 deployed Gulf War veterans with GWVIs and detectable *Mycoplasma* DNA in their blood were randomly assigned to receive either doxycycline, 200 mg, or matching placebo daily for 1 year. There were no long-term differences between the 2 groups in physical or mental function or in pain or fatigue symptoms. Patients given doxycycline had nausea and photosensitivity more often than did patients given placebo.

Implications

Long-term doxycycline treatment probably doesn't benefit veterans with GWVIs and may harm them.

—The Editors

symptoms of GWVIs and whether results of DNA tests for *Mycoplasma* species converted from positive to negative after treatment.

The study was conducted at 26 Department of Veterans Affairs and 2 Department of Defense medical centers between April 1999 and November 2001. Participants were recruited through mailings, advertisements, and physician referrals. Veterans were eligible for study enrollment if they had been deployed from active duty, the National Guard, or the military Reserve to the Southwest Asia theater of operations between August 1990 and August 1991 and developed at least 2 of 3 primary symptoms of GWVIs after deployment (fatigue, musculoskeletal pain involving 2 or more regions of the body, and cognitive problems). Symptoms had to have lasted more than 6 months and had to be present at the time of screening. Additional requirements were a score less than 40 on the Physical Component Summary of the Veterans Short Form-36 (SF-36) Health Survey, which was completed at screening, and a positive result on a polymerase chain reaction DNA test for *M. fermentans*, *M. genitalium*, or *M. pneumoniae* DNA in whole blood (sensitivity level, 1 to 10 *Mycoplasma* genomes).

The study coordinator initially reviewed veterans for study eligibility, but physician-investigators at each site made the final determination regarding inclusion. Veterans were excluded for the following reasons: attribution of symptoms to another medical condition (morbid obesity; autoimmune diseases; uncontrolled cardiopulmonary and endocrine disorders; malignant conditions, except skin cancer, within 2 years; or known current liver disease); doxycycline allergy; previous treatment with doxycycline for more than 6 months since the onset of symptoms; continuous treatment with a tetracycline, macrolide, or quinolone antibiotic for more than 1 month during the

past year; history of severe psychiatric illness (history of psychosis or hospitalization for mental illness in the past 2 years); active substance abuse requiring hospitalization or active treatment within 2 years of enrollment; organ transplantation; life expectancy of less than 1 year; required treatment with phenytoin, carbamazepine, or barbiturates; unwillingness to be randomly assigned to doxycycline or placebo; or, if female, unwillingness to use barrier-method contraceptives. Veterans who had received a diagnosis of the chronic fatigue syndrome or fibromyalgia were not excluded because these disorders are similar in character and definition to GWVIs. All participants provided written informed consent.

Treatment Protocol

The Department of Veterans Affairs Cooperative Studies Evaluation Committee, a central human rights committee, and each participating site's institutional review board approved the study protocol. An independent data and safety monitoring board reviewed the study semi-annually. Participants assigned to the doxycycline group received doxycycline, 200 mg/d, and those assigned to the placebo group received identically matched lactose capsules. Because doxycycline can cause photosensitivity to sunlight, all participants were provided with sunscreen (sun protection factor, 30) and were advised to limit sun exposure. Participants were followed for an additional 6 months after withdrawal of study drugs to determine potential relapse rates.

Because of the expense of *Mycoplasma* testing and an expected 3- to 4-week delay in receiving the test results, participants had to meet all other eligibility criteria before blood was drawn. To ensure that outcome measure testing was performed as close as possible to the start of treatment with the study drug, baseline testing, including repeated administration of the Veterans SF-36 Health Survey, was completed at randomization just before the study drug was dispensed to participants.

Major assessments were completed at baseline and at 3, 6, 9, 12, and 18 months. Major assessments consisted of the Veterans SF-36 Health Survey (16–18), the McGill Pain Questionnaire (19), the Multidimensional Fatigue Inventory (20), and the Cognitive Failures Questionnaire (21). Monthly follow-up visits were conducted to dispense medication; to monitor adherence to treatment regimen by pill counts and discussions with participants; and to collect information on hospitalizations, clinic visits, other medications used, and adverse events. Participants who were not taking their medications routinely were encouraged to do so. Laboratory evaluations (blood chemistry tests and testing of doxycycline level) were performed on participant blood samples at the 6- and 12-month follow-up visits. Polymerase chain reaction detection of *M. fermentans*, *M. genitalium*, and *M. pneumoniae* DNA was determined in blood samples obtained at baseline and at 6, 12, and 18 months.

Table 1. Secondary Outcome Measures

Secondary Outcome Measure	Range of Values	Indicator of Better Function	Rating Period Collected
McGill Pain Questionnaire		Low score	Baseline and 3, 6, 9, 12, and 18 mo
Sensory	0–33		
Affective	0–12		
Pain now	0–10		
Typical pain	0–13		
Multidimensional Fatigue Inventory	4–20 for each component	Low score	Baseline and 3, 6, 9, 12, and 18 mo
General fatigue			
Physical fatigue			
Reduced activity			
Reduced motivation			
Mental fatigue			
Cognitive Failures Questionnaire	0–100	Low score	Baseline and 3, 6, 9, 12, and 18 mo
Veterans Short Form-36 Health Survey	Standardized with mean of 50 for each component	High score	Screening; baseline; and 3, 6, 9, 12, and 18 mo
Standardized Physical Component Summary score			
Standardized Mental Component Summary score			
Positive results on tests for <i>Mycoplasma</i> species	Negative–positive (≥ 1 to 10 genomes) for each species	Negative results	Baseline and 6, 12, and 18 mo
<i>M. fermentans</i>			
<i>M. pneumoniae</i>			
<i>M. genitalium</i>			

Outcome Assessments

The primary outcome measure was the Physical Component Summary score of the Veterans SF-36 Health Survey at follow-up compared with baseline. The Veterans SF-36 Health Survey is modified from the Medical Outcomes Study SF-36 Health Survey and is adapted for use in veterans with improved reliability and precision (16–18, 22–24). The Physical Component Summary is a weighted standardized summary measure, normalized to a mean score of 50 on the basis of a general U.S. population (18). Higher scores denote better functional status. The Physical Component Summary was selected as the primary outcome measure because there is no validated disease-specific assessment of functional status for GWVIs and because the Veterans SF-36 Health Survey spans a spectrum of functional status that is conceptually and clinically relevant to GWVIs. The primary end point was the dichotomous measure of the proportion of participants with more than a 7-unit increase in the Physical Component Summary score at 12 months. Treatment was considered to have failed in participants who did not have more than a 7-unit increase from their baseline Physical Component Summary score, those who did not complete the study, and those who had missing 12-month Physical Component Summary scores. The change of 7 units or greater was selected because it is outside the 95% CI for an individual participant score (standard error of the measurement), as estimated from the standard deviation and score reliability (25). Differences of this magnitude have also been shown to be clinically relevant (26–29).

The secondary outcomes were reduction in symptoms, improvement in physical and mental health function as continuous measures of change, and conversion to *Mycoplasma* negativity (that is, negative results for *Mycoplasma* DNA by polymerase chain reaction testing of whole blood). A reduction in symptoms was determined by using

3 self-report questionnaires: the McGill Pain Questionnaire, the Multidimensional Fatigue Inventory, and the Cognitive Failures Questionnaire. Changes in physical and mental health function were measured by using continuous measures of change in the Physical Component Summary and Mental Component Summary scores of the Veterans SF-36 Health Survey. Table 1 summarizes the measures from each of these questionnaires.

Laboratory Methods

Polymerase chain reaction testing was performed at the University of Texas Health Science Center in San Antonio, Texas. Whole blood samples were drawn from participants at baseline and at 6, 12, and 18 months by using a sterile technique. Samples were immediately frozen, shipped on dry ice to San Antonio, and kept frozen at -80°C until testing. The tests were performed by using a slightly modified version of previously developed polymerase chain reaction assays (30–32). Positive and negative DNA controls were included for each group of test samples, and *Mycoplasma* DNA could be detected at levels of 10 genomes by using a combination of polymerase chain reaction and hybridization–autoradiography techniques.

Doxycycline levels were determined to help assess adherence to doxycycline therapy. Coded blood samples from 6 and 12 months were transferred from the central laboratory to the doxycycline testing laboratory. Doxycycline was extracted from 1 mL of whole blood by using Varian Bond Elut C18 cartridges (Varian, Inc., Palo Alto, California) and was quantified by using high-performance liquid chromatography with ultraviolet detection (33). The lower limit of detection of doxycycline was 50 ng/mL.

Adverse Events

The principal investigators at each site used an open-ended questionnaire to evaluate adverse events at every follow-up visit. They determined date of onset, severity,

required action, outcome, and date of resolution, as well as whether the event was attributable to the study medication. Adverse events were defined as serious if they were fatal or life-threatening, resulted in hospitalization, or led to persistent disability. Serious adverse events were reported to the study chairman and pharmacy coordinating center within 24 hours. The data and safety monitoring board reviewed a summary of adverse events by treatment group at 6-month intervals.

Randomization and Blinding

Randomization was performed separately for each site by using varying block sizes. The site coordinator randomly assigned participants by calling into a central, automated telephone randomization system at the coordinating center. After the system verified that the participant met the study entry criteria and had provided informed consent, a treatment kit number that randomly assigned the participant to doxycycline or placebo was given to the coordinator. This kit number corresponded to a drug treatment kit located in the facility's pharmacy. In an emergency, the blind could be broken by calling the central pharmacy or the coordinating center or, if they were not available, by opening a sealed envelope at the local pharmacy. No attempt was made to assess the adequacy of blinding.

Adherence

We assessed adherence with the study medication by using monthly pill counts and discussions with participants. Doxycycline levels in blood were obtained at 6 and 12 months but were not determined until after completion of the study.

Statistical Analysis

The projected study sample size of 450 participants was based on the ability to detect a difference of 15 percentage points (15% vs. 30%) between the placebo group and the doxycycline group for the primary outcome measure (>7-unit increase in the Physical Component Summary score from baseline to 12 months). The α value was 0.05 and the power was 0.95, with an expected 10% loss to follow-up.

Intention-to-treat analyses were performed by using 2-sided statistical testing. The primary outcome variable, as well as other dichotomous variables, was analyzed by using the Fisher exact test. Continuous variables were analyzed by using analysis of covariance, where the baseline score of the particular variable being analyzed was used as the covariate. Secondary outcome measures and adverse events were reported as differences between groups (doxycycline – placebo) with 95% CIs.

All participants who had a baseline Physical Component Summary score or who had no baseline score but terminated the study early were included in the primary outcome analysis (10 participants who completed 12 months of treatment were excluded from the primary analysis because they had missing baseline scores). Treatment

was considered to have failed in participants with missing 12-month Physical Component Summary scores. Thus, all available data (except those for the 10 participants with missing baseline scores) were used in the primary analysis. Only participants who had data for the secondary outcome measures at the appropriate times are included in those analyses.

A secondary analysis of treatment failure and success (>7-unit increase in Physical Component Summary score from baseline) at 3-month time intervals was performed by using generalized estimating equations (PROC GENMOD, SAS software, version 8, SAS Institute, Inc., Cary, North Carolina). The generalized estimating equation method accommodates correlations among the repeated observations and allows inclusion of available data from persons with missing observations. In our model, both treatment group and time were modeled as class variables, which allows assessment of both main effects for treatment group assignment (the overall difference between treatment groups across all time points) and interactions of treatment group by time (the difference in slopes). We used an unstructured covariance structure, which allows the observations for each pair of times to have their own unique correlation. The model was adjusted for the baseline value of the Physical Component Summary score. Only observed data were used in this analysis (that is, missing values were treated as missing and not as treatment failures). Longitudinal analyses of the secondary outcome measures, which were all continuous, were performed with a random-effects repeated-measures analysis (PROC Mixed, SAS statistical software, version 8), using the same class and covariance structure as for the generalized estimating equations. Baseline scores for each measure were used as covariates.

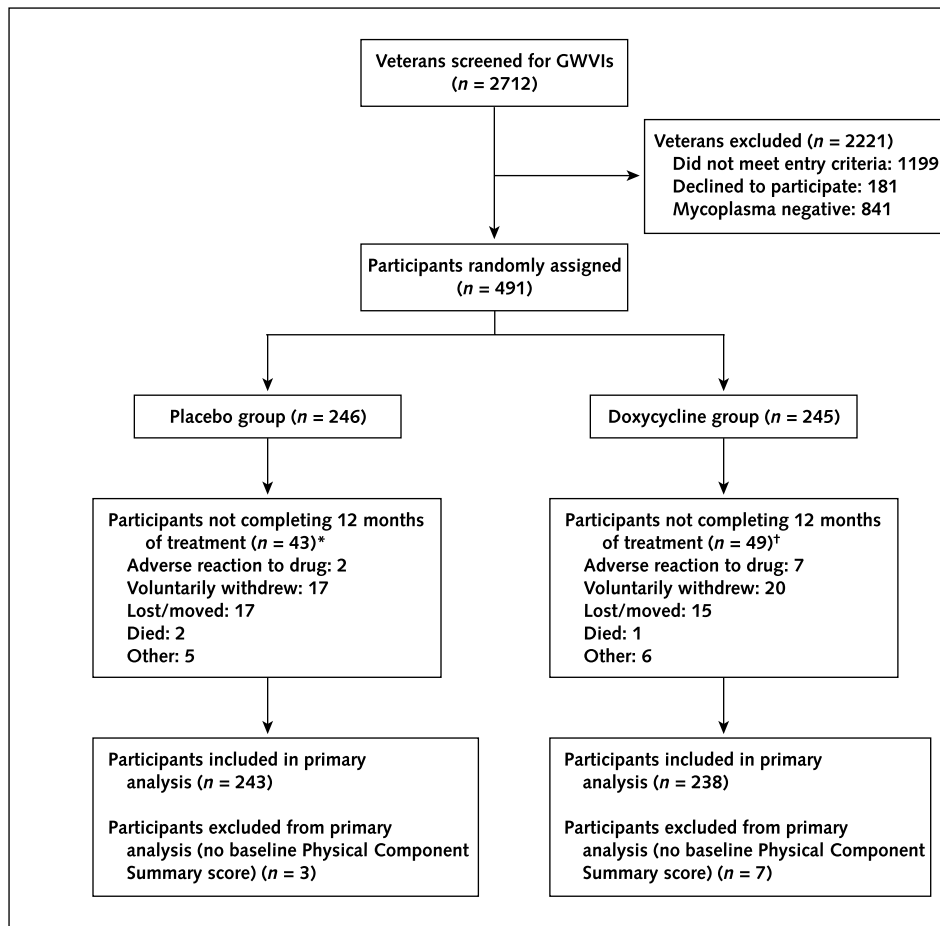
Role of the Funding Sources

The Cooperative Studies Program of the U.S. Department of Veterans Affairs Office of Research and Development and the U.S. Department of Defense funded the study. The Veterans Affairs Cooperative Studies Evaluation Committee scientifically reviewed and approved the study protocol. John R. Feussner, MD, MPH, the chief research and development officer of the Department of Veterans Affairs and an author on this paper, initiated the planning process and served on the planning and executive committees but did not participate in the review process by either the Veterans Affairs Cooperative Studies Evaluation Committee or the data and safety monitoring board. Both sponsors approved the manuscript for submission for publication, but neither sponsor was involved in the collection, analysis, or interpretation of the data.

RESULTS

Figure 1 shows the flow of participants through the study. Of the 2712 veterans who were screened, 2134 met the clinical inclusion criteria. Of these, 1565 had a score of less than 40 on the Veterans SF-36 Health Survey. Thirty-

Figure 1. Progress of participants through the trial.



*Of these participants, 15 returned for the 12-month visit and had 12-month data for the Physical Component Summary score, while the remaining 28 were considered to have had treatment failure for the primary outcome measure. †Of these participants, 14 returned for the 12-month visit and had 12-month data for the Physical Component Summary score; treatment was considered to have failed in the remaining 35. GWVIs = Gulf War veterans' illnesses.

nine percent of the participant blood samples tested (541 of 1387) were positive for 1 or more *Mycoplasma* species. Four hundred ninety-one participants were randomly assigned: 245 to the doxycycline group and 246 to the placebo group. Fifty participants infected with *Mycoplasma* species were not randomly assigned, and 12 participants did not complete the Veterans SF-36 Health Survey at baseline. Four hundred eleven participants (83.7%), 199 in the doxycycline group and 212 in the placebo group, completed the Veterans SF-36 Health Survey both at baseline and at 12 months.

Baseline Characteristics

Participants randomly assigned to the 2 groups were comparable at baseline (Table 2). Sex, age, and ethnicity were similar, as were Physical Component Summary score, Mental Component Summary score, and other outcome measures. The mean Physical Component Summary scores of 30.6 in the doxycycline group and 30.5 in the placebo group indicated that the participants had serious physical problems.

All participants randomly assigned to a study group had positive results on polymerase chain reaction for 1 or more species of *Mycoplasma*. Three hundred twenty-four participants (66%) had *M. fermentans* infection, 197 (40.1%) had *M. genitalium* infection, and 53 (10.8%) had *M. pneumoniae* infection, singly or in combination. The 2 treatment groups did not differ in the distribution of *Mycoplasma* species.

We compared baseline characteristics (Table 2) in participants who had a Physical Component Summary score at 12 months and those who did not. Participants who completed the 12-month evaluations were more likely to be older, white, and married and to have lower (worse) Physical Component Summary scores (30.2 vs. 32.7; $P = 0.007$) and higher (better) Mental Component Summary scores at baseline (36.8 vs. 31.1; $P = 0.016$).

Outcomes

Primary Outcome Measure

No statistically significant difference in the primary outcome measure, that is, improvement in physical health

Table 2. Baseline Characteristics of Participants*

Characteristic	Doxycycline Group (n = 245)	Placebo Group (n = 246)
Age, y	41.1 ± 9.2	40.3 ± 8.6
Women, n (%)	38 (15.5)	33 (13.4)
Ethnicity, n (%)		
White	151 (61.6)	161 (65.4)
Black	65 (26.5)	47 (19.1)
Hispanic	19 (7.8)	30 (12.2)
Married, n (%)	170 (69.4)	165 (67.1)
Full-time employment, n (%)	180 (73.5)	171 (69.5)
Qualifying symptoms, n (%)		
Fatigue and pain only	21 (8.6)	22 (8.9)
Fatigue and neurocognitive symptoms only	12 (4.9)	8 (3.3)
Pain and neurocognitive symptoms only	7 (2.9)	9 (3.7)
All 3	205 (83.7)	207 (84.1)
Veterans Short Form-36 Health Survey scores†		
Physical Component Summary	30.6 ± 7.3	30.5 ± 7.4
Mental Component Summary	36.7 ± 11.6	35.8 ± 12.0
McGill Pain Questionnaire scores‡		
Sensory	15.6 ± 7.5	15.8 ± 7.2
Affective	5.4 ± 3.0	5.5 ± 3.2
Pain now	5.6 ± 2.2	5.5 ± 2.2
Typical pain	6.1 ± 2.0	6.2 ± 1.9
Multidimensional Fatigue Inventory scores‡		
General fatigue	16.8 ± 3.0	16.8 ± 3.0
Physical fatigue	15.5 ± 3.2	15.7 ± 3.2
Reduced activity	14.0 ± 3.7	14.2 ± 3.9
Reduced motivation	12.6 ± 3.3	12.9 ± 3.6
Mental fatigue	15.0 ± 4.0	15.5 ± 3.9
Cognitive Failures Questionnaire‡	61.0 ± 18.0	62.1 ± 17.7

* Values presented with a plus/minus sign are means ± SD.

† Twelve participants (8 in the doxycycline group and 4 in the placebo group) did not have scores on the Veterans Short Form-36 Health Survey at baseline.

‡ One participant in the doxycycline group did not have postrandomization, pre-study medication; a baseline form; or both for this measure.

function, was seen between the 2 groups after 12 months. Overall, 18.1% of participants (43 of 238) in the doxycycline group and 17.3% (42 of 243) in the placebo group had increases of more than 7 units in Physical Component Summary scores at 12 months (difference, 0.8 percentage point [95% CI, -6.5 to 8.0 percentage points]; $P > 0.2$) (Figure 2). A statistically significantly greater proportion of participants in the doxycycline group compared with the placebo group showed improvement at 3 months (51 of 237 [21.5%] vs. 24 of 242 [9.9%]; difference, 11.6 percentage points [CI, 4.7 to 18.5 percentage points]; $P = 0.001$), but not at 6, 9, 12, or 18 months (Figure 2). Sensitivity analyses using varying increases in Physical Component Summary scores from 5 to 7 yielded the same results as were found with the increase of more than 7 units.

When only participants infected with the most common *Mycoplasma* species, *M. fermentans*, were considered, results were similar to those in the primary analyses. That is, no difference was seen between the doxycycline and placebo groups at 12 months (34 of 164 participants [20.7%] vs. 29 of 154 participants [18.8%]; difference, 1.9

percentage points [CI, -7.5 to 11.3 percentage points]; $P > 0.2$), and a statistically significant difference in favor of doxycycline was seen at 3 months (33 of 163 participants [20.2%] vs. 12 of 153 participants [7.8%]; difference, 12.4 percentage points [CI, 4.3 to 20.5 percentage points]; $P = 0.002$).

The secondary analysis using a generalized estimating equation to compare treatment failure and success over time indicated a statistically significant visit-by-treatment interaction ($P = 0.042$). Consideration of the contrasts at each time point in this analysis showed significant differences at 3 months ($P < 0.001$) and 6 months ($P = 0.035$) but not at 9 months ($P > 0.2$) and 12 months ($P > 0.2$).

Secondary Outcomes

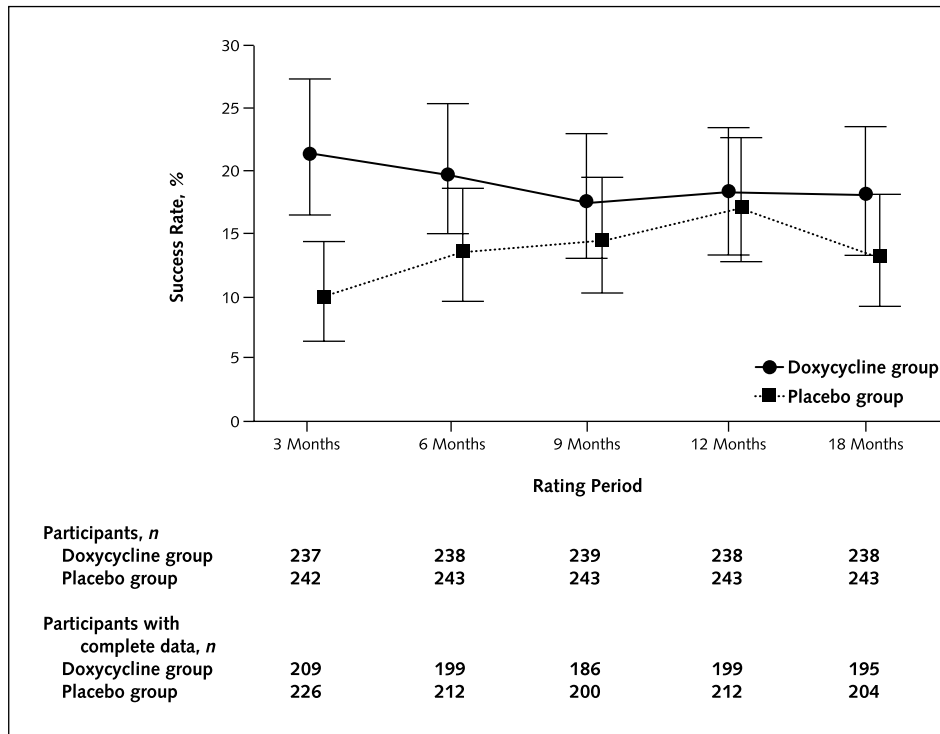
No statistically significant differences were seen between the treatment groups in any of the measures of pain, fatigue, cognitive symptoms, and mental health function (that is, Mental Component Summary score) at 12 months (Table 3). As with the primary outcome, mean Physical Component Summary scores (±SD) showed a significant difference in favor of doxycycline compared with placebo at 3 months (32.4 ± 8.4 vs. 30.7 ± 7.9 at 3 months and 30.3 ± 7.3 vs. 30.2 ± 7.3 at baseline; difference, 1.7 [CI, 0.6 to 2.8]; $P = 0.004$); a difference was also seen at 6 months (32.4 ± 8.2 vs. 31.0 ± 8.5 at 6 months and 30.4 ± 7.3 vs. 30.2 ± 7.4 at baseline; difference, 1.2 [CI, 0.0 to 2.4]; $P = 0.049$), but not at the other time points. A random-effects repeated-measures model showed statistically significant differences between groups for the Physical Component Summary score at 3 months ($P = 0.003$) and 6 months ($P = 0.045$) but not at 9 months ($P = 0.09$) or 12 months ($P = 0.12$). The random-effects repeated-measures models for the other secondary outcomes showed no statistically significant differences.

The percentage of participants whose blood remained positive for *Mycoplasma* species by polymerase chain reaction testing decreased throughout the treatment period in both treatment groups. One hundred fourteen of 206 participants in the doxycycline group (55.3%) and 124 of 213 participants in the placebo group (58.2%) had negative results on tests for any *Mycoplasma* species at 6 months. One hundred fifty-four of 200 participants in the doxycycline group (77%) and 159 of 211 participants in the placebo group (75.4%) had negative results at 12 months, and 171 of 190 participants in the doxycycline group (90%) and 174 of 201 participants in the placebo group (86.6%) had negative results at 18 months.

Adverse Events

Thirteen serious adverse event forms were submitted for 12 participants in the doxycycline group, and 19 forms were submitted for 17 participants in the placebo group. Most of these serious adverse events (24 of 32) were considered to be unrelated to the study drug, 4 were rated as having an “unknown” relationship, and the remaining 4

Figure 2. Study participants who improved more than 7 units on the Veterans Short Form-36 Health Survey Physical Component Summary score at each rating period compared with baseline.



Error bars represent 95% CIs.

(1 in the doxycycline group and 3 in the placebo group) were considered possibly related. Most adverse events (23 of 32) were reported because they resulted in hospitalization. Three adverse events led to death (1 in the doxycycline group and 2 in the placebo group); all 3 were con-

sidered to be unrelated to the study drug. Table 4 lists the most common adverse reactions that the site investigators rated as possibly or probably related to the study drug. Adverse events were similar in both treatment groups except for an expected higher incidence of nausea and pho-

Table 3. Comparison of Secondary Outcome Measures in the Doxycycline and Placebo Groups at 12 Months*

Secondary Outcome Measure	Doxycycline Group			Placebo Group			Difference at 12 Months (95% CI)†	P Value
	Participants, n	Score at Baseline	Score at 12 Months	Participants, n	Score at Baseline	Score at 12 Months		
McGill Pain Questionnaire								
Sensory	207	15.6 ± 7.5	15.2 ± 8.2	214	15.9 ± 7.2	16.0 ± 8.4	-0.6 (-1.8 to 0.6)	>0.2
Affective	206	5.3 ± 3.0	4.8 ± 3.4	214	5.6 ± 3.2	5.0 ± 3.2	0.0 (-0.5 to 0.5)	>0.2
Pain now	207	5.6 ± 2.2	5.4 ± 2.5	213	5.6 ± 2.2	5.7 ± 2.4	-0.3 (-0.7 to 0.1)	0.18
Typical pain	206	6.1 ± 1.9	5.8 ± 2.2	213	6.2 ± 1.9	5.9 ± 2.2	0.0 (-0.4 to 0.3)	>0.2
Multidimensional Fatigue Inventory								
General fatigue	206	16.9 ± 2.8	16.4 ± 3.4	214	16.7 ± 3.1	16.5 ± 3.4	-0.1 (-0.7 to 0.5)	>0.2
Physical fatigue	206	15.6 ± 3.2	15.1 ± 3.5	214	15.7 ± 3.2	15.3 ± 3.5	-0.1 (-0.6 to 0.5)	>0.2
Reduced activity	207	13.9 ± 3.7	14.3 ± 4.0	214	14.1 ± 3.9	14.3 ± 4.0	0.0 (-0.6 to 0.7)	>0.2
Reduced motivation	206	12.4 ± 3.3	12.4 ± 3.7	214	12.8 ± 3.6	12.8 ± 3.8	-0.2 (-0.8 to 0.4)	>0.2
Mental fatigue	206	15.0 ± 4.0	14.9 ± 4.3	213	15.4 ± 4.0	15.2 ± 4.0	0.0 (-0.6 to 0.6)	>0.2
Cognitive Failures Questionnaire								
Total	207	60.8 ± 18.2	59.3 ± 20.3	214	62.2 ± 17.8	61.6 ± 19.0	-1.2 (-3.7 to 1.4)	>0.2
Veterans Short Form-36 Health Survey								
Physical Component Summary	199	30.2 ± 7.2	32.0 ± 8.4	212	30.1 ± 7.3	30.9 ± 8.5	1.0 (-0.3 to 2.4)	0.12
Mental Component Summary	199	37.4 ± 11.7	37.6 ± 13.6	212	36.2 ± 12.2	36.7 ± 12.5	0.0 (-1.8 to 1.8)	>0.2

* Values presented with a plus/minus sign are means ± SD.
 † Least-square mean (doxycycline group - placebo group).

Table 4. Adverse Events Considered Possibly or Definitely Related to the Study Drug*

Adverse Event	Doxycycline Group (n = 245), n (%)	Placebo Group (n = 246), n (%)	Difference (95% CI), percentage point†	P Value
Amnesia	22 (9.0)	16 (6.5)	2.5 (−2.7 to 7.6)	>0.2
Arthralgia	31 (12.7)	40 (16.3)	−3.6 (−10.2 to 3.0)	>0.2
Asthenia	41 (16.7)	32 (13.0)	3.7 (−3.0 to 10.4)	>0.2
Diarrhea	40 (16.3)	33 (13.4)	2.9 (−3.8 to 9.6)	>0.2
Dizziness	15 (6.1)	9 (3.7)	2.5 (−1.8 to 6.7)	>0.2
Dyspepsia	26 (10.6)	20 (8.1)	2.5 (−3.1 to 8.0)	>0.2
GI disorder	9 (3.7)	7 (2.8)	0.8 (−2.7 to 4.4)	>0.2
Headache	47 (19.2)	46 (18.7)	0.5 (−6.9 to 7.8)	>0.2
Infection	9 (3.7)	9 (3.7)	0.0 (−3.7 to 3.7)	>0.2
Insomnia	8 (3.3)	7 (2.8)	0.4 (−3.0 to 3.9)	>0.2
Myalgia	3 (1.2)	11 (4.5)	−3.3 (−6.6 to 0.1)	0.05
Nausea	91 (37.1)	25 (10.2)	27.0 (19.4 to 34.5)	<0.001
Pain—general	39 (15.9)	40 (16.3)	−0.3 (−7.3 to 6.6)	>0.2
Pain—abdomen	13 (5.3)	9 (3.7)	1.7 (−2.4 to 5.7)	>0.2
Pain—back	8 (3.3)	12 (4.9)	−1.6 (−5.5 to 2.3)	>0.2
Photosensitivity	36 (14.7)	15 (6.1)	8.6 (2.8 to 14.4)	0.002
Rash	37 (15.1)	27 (11.0)	4.1 (−2.2 to 10.5)	0.18
Withdrawal due to adverse events	7 (2.9)	2 (0.8)	2.0 (−0.7 to 4.8)	0.11

* This table includes adverse events that occurred at least once during the treatment phase of the study (only events that occurred in $\geq 3\%$ of participants are reported). GI = gastrointestinal.

† The values in this column do not precisely equal doxycycline – placebo because they are based on ≥ 1 decimal place while the actual percentages for each treatment group have been rounded to 1 decimal place.

tosensitivity in the doxycycline group and a higher incidence of reported myalgia among participants receiving placebo.

Adherence

Participants appeared equally adherent regardless of treatment type in terms of clinic visits, pill counts, and timely completion of outcome questionnaires. Site personnel rated adherence as good or excellent in 77.5% of the doxycycline group (176 of 227 participants) and 74.5% of the placebo group (172 of 231 participants) at 6 months and in 65.6% of the doxycycline group (145 of 221 participants) and 66.6% of the placebo group (156 of 234 participants) at 12 months. In the doxycycline group, among those who had blood samples available, doxycycline levels were undetectable in 20.3% (42 of 207) at 6 months and 38.9% (75 of 193) at 12 months. Doxycycline levels were undetectable in 99.1% of participants taking placebo at 6 months (211 of 213) and in 98% (199 of 203) at 12 months.

Use of Health Care Resources

During the 12-month treatment period, compared with the doxycycline group, participants in the placebo group had more unscheduled clinic visits (201 of 243 [82.7%] vs. 216 of 244 [88.5%]; difference, −5.8 percentage points [CI, −12.4 to 0.9 percentage points]) and hospitalizations (24 of 243 [9.9%] vs. 33 of 244 [13.5%]; difference, −3.6 percentage points [CI, −9.8 to 2.5 percentage points]) and used more nonstudy antibiotics (74 of 243 [30.5%] vs. 101 of 244 [41.4%]; difference, −10.9 percentage points [CI, −19.8 to −2.1 percentage points]). No participants were hospitalized for study medication toxicity, although 12 participants (8 in the doxycycline

group and 4 in the placebo group) were seen at unscheduled clinic visits because of suspicion of such toxicity.

DISCUSSION

Veterans with GWVIs have relatively poor physical function as measured by the Physical Component Summary score. The mean baseline scores of 30.6 in the doxycycline group and 30.5 in the placebo group are about 2.5 SDs below the U.S. population norm and about 0.6 SD below the score for veterans who receive Veterans Affairs care (22). To put this score into further context, reports have shown that the mean baseline Physical Component Summary score is 42 for persons with type 2 diabetes mellitus, 36 for persons with chronic obstructive pulmonary disease, and 35 for persons with chronic heart failure (24, 25). Studies of individuals with the chronic fatigue syndrome have reported mean baseline Physical Component Summary scores of 25 to 29 for those with and without current psychiatric comorbid conditions (34, 35).

Our study was designed to examine whether doxycycline treatment would significantly improve symptoms in veterans with GWVIs whose blood tested positive for certain *Mycoplasma* species. It had been postulated that *Mycoplasma* species, the most common being *M. fermentans*, may be important in the pathogenesis of GWVIs. This hypothesis was based on preliminary observations of *Mycoplasma* species in the blood of 40% to 50% of selected participants with GWVIs, according to positive results on polymerase chain reaction DNA tests (13).

In our study, doxycycline treatment did not lead to the hypothesized outcome. At 12 months, 18.1% of participants in the doxycycline group and 17.3% of participants

in the placebo group improved more than 7 points on the Physical Component Summary scale. More participants receiving doxycycline improved at 3 months (21.5% vs. 9.9%), but no statistically significant differences were seen at later time periods of 9, 12, and 18 months. Analyses using the mean Physical Component Summary scores showed that some improvement may have extended up to the 6-month rating period. However, even most participants who improved still had considerable symptoms and Physical Component Summary scores that reflected continued physical dysfunction. In addition, no differences were seen in any of the secondary outcome measures.

Veterans receiving doxycycline were significantly less likely to use nonstudy antibiotics. They also had fewer unscheduled clinic visits and hospitalizations, although the difference was not statistically significant. Therefore, veterans received some benefit from long-term use of doxycycline that may or may not have been related to their GWVIs.

Doxycycline may have had limited effectiveness in treating GWVIs because there was no underlying infection, or the GWVIs may have been sequelae of previous infection. Nonadherence to the doxycycline regimen over a 12-month period may have affected our results. A significantly greater proportion of participants in the doxycycline group was improving at 3 months, and it cannot be determined whether greater adherence to doxycycline treatment over the remaining 9 months would have resulted in greater improvement or a progressive increase in the proportion of participants improving by the end of the 12-month trial. Conversely, a subpopulation of participants may have responded to doxycycline at 3 months because of some underlying or intercurrent infection susceptible to that antibiotic or because of a possible anti-inflammatory effect of the drug (36). It is also possible that another antibiotic regimen might have been more effective (37).

Polymerase chain reaction testing of DNA in whole blood showed that, in accordance with preliminary observations (2, 3), 39% of participants with GWVIs who met the study's entry criteria had *M. fermentans*, *M. genitalium*, or *M. pneumoniae* infection. Most participants were infected with *M. fermentans* or *M. genitalium*. Rates of *Mycoplasma* positivity decreased dramatically over the 18-month observation period, but the decrease was similar in both groups. Because not much is known about the typical or predictable infectious course associated with chronic *Mycoplasma* infections, it is difficult to predict whether such a decrease should be expected (38). In addition, other factors can influence the sensitivity and specificity of polymerase chain reaction assays, such as source and quality of individual clinical samples, handling and storage conditions, and polymerase chain reaction-related reagents. (39). It is also possible that the low levels of *Mycoplasma* DNA present in the blood of participants at baseline reflected an underlying reservoir of *Mycoplasma* infection elsewhere in the body. It is, however, difficult to reconcile

the findings of equal rates of decreasing *Mycoplasma* positivity over time in both doxycycline-treated and placebo groups with any relationship between *Mycoplasma* infection and illness. These results do not necessarily exclude a possible immunomodulatory role of previous *Mycoplasma* infection.

In our study, doxycycline was no better than placebo in improving physical function and symptoms in participants with GWVIs. However, nonadherence to doxycycline treatment may have affected the results. No relationship between persistent *Mycoplasma* infection and GWVIs could be established. It is possible that participants in the doxycycline group received less medical care because the study drug was helping to treat an unrecognized infection. Further studies are needed to determine whether infectious or noninfectious causes are responsible for GWVIs.

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Requests for Single Reprints: Joseph F. Collins, ScD, Veterans Affairs Maryland Healthcare System, Cooperative Studies Program Coordinating Center (151 E), PO Box 1010, Perry Point, MD 21902.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Donta: Boston Veterans Affairs Medical Center, 151 South Huntington Avenue, Boston, MA 02130.
Dr. Engel: Department of Psychiatry, Uniformed Services University, 4301 Jones Bridge Road, Bethesda, MD 20815.
Dr. Collins, Ms. Horney, and Ms. Wiseman: Veterans Affairs Maryland Health Care System, Cooperative Studies Program Coordinating Center (151E), PO Box 1010, Perry Point, MD 21902.
Dr. Baseman: Department of Microbiology, University of Texas Health Sciences Center, 7703 Floyd Curl Drive, San Antonio, TX 78284.
Dr. Dever: Veterans Affairs New Jersey Health Care System, 385 Tremont Avenue, East Orange, NJ 07018.
Dr. Taylor: White River Junction Veterans Affairs Hospital, 215 North Main Street, White River Junction, VT 05008.
Ms. Boardman: Cooperative Studies Program, 2401 Centre Avenue SE, Albuquerque, NM 87106.
Dr. Kazis: Boston University School of Public Health, 715 Albany Street, T3-W, Boston, MA 02118.
Ms. Martin: Cell Signaling Technology, Inc., 166 B Cummings Center, Beverly, MA 01915.
Dr. Kernodle: Nashville Veterans Affairs Medical Center, 1310 24th Avenue South, Nashville, TN 37212-2637.
Drs. Smith and Baltch: Stratton Veterans Affairs Medical Center, 113 Holland Avenue, Albany, NY 12208.
Dr. Handanos: Veterans Affairs Medical Center, 1501 San Pedro SE, Albuquerque, NM 87108.
Drs. Catto and Montalvo: Veterans Affairs Medical Center Augusta, 1 Freedom Way (235), Augusta, GA 30904.
Dr. Everson: Capstone Clinical, 1222 14th Avenue South, Suite 208, Birmingham, AL 35205.
Dr. Blackburn: Birmingham Veterans Affairs Medical Center, 700 19th Street, Birmingham, AL 35233.
Dr. Thakore: VA Medical Center (151), 150 Huntington Avenue, Boston, MA 02130.
Dr. Brown: Bronx Veterans Affairs Medical Center, 130 West Kingsbridge Road, Bronx, NY 10468.
Drs. Lutwick and Norwood: Veterans Affairs New York Harbor Health Care System, 800 Poly Place, Brooklyn, NY 11209.
Dr. Bernstein: Veterans Affairs Medical Center, 4100 West Third Avenue, Dayton, OH 45429.
Dr. Bacheller: Wright State University/Veterans Affairs, 4000 West Third Street, Dayton, OH 45429.
Dr. Ribner: Emory University, 1364 Clifton Road NE, Atlanta, GA 30322.
Dr. Church: Veterans Affairs Medical Center, 109 Bee Street, Charleston, SC 29403.
Dr. Wilson: Veterans Affairs Medical Center, 508 Fulton Street, Durham, NC 27705.
Drs. Guduru and Cooper: Veterans Affairs Medical Center, 2101 North Elm Street, Fargo, ND 58102.
Dr. Lentino: Hines Veterans Affairs Hospital, Fifth Avenue at Roosevelt Road, Hines, IL 60141.
Dr. Hamill: Veterans Affairs Medical Center (111G), 2002 Holcombe Boulevard, Houston, TX 77030.
Dr. Gorin: Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030.
Dr. Gordan: Veterans Affairs Medical Center, 718 Smyth Road, Manchester, NH 03104.
Dr. Wagner: Zablocki Veterans Affairs Medical Center, 5000 West National Avenue, Milwaukee, WI 53295.
Dr. Robertson: Central Alabama Veterans Health Care System, 215 Perry Hill Road, Montgomery, AL 36109.

Dr. DeJace: Veterans Affairs Medical Center, 1601 Perdido Street, New Orleans, LA 70112.
Drs. Greenfield and Beck: Oklahoma City Veterans Affairs Medical Center, 921 NE 13th Street, Oklahoma City, OK 73104.
Dr. Bittner: Veterans Affairs Medical Center, 4101 Woolworth Avenue (111D), Omaha, NE 68105.
Dr. Schumacher: Veterans Affairs Medical Center (151K), University and Woodland Avenues, Philadelphia, PA 19104.
Dr. Silverblatt: Providence Veterans Affairs Medical Center, 830 Chalkstone Avenue, Providence, RI 02908.
Drs. Schmitt and Wong: McGuire Veterans Affairs Medical Center, 1201 Broad Rock Boulevard, Richmond, VA 23249.
Dr. Ryan: Branch Medical Clinic, Naval Training Center, 2659 Stockton Road, Room A203, San Diego, CA 92106.
Dr. Figueroa: Veterans Affairs Medical Center, 10 Casia Street, San Juan, Puerto Rico 00921.
Dr. Nice: Veterans Affairs Hospital, North Main Street, White River Junction, VT 05001.
Dr. Feussner: Medical University of South Carolina, 96 Jonathan Lucas Street, Charleston, SC 29425.

Author Contributions: Conception and design: S.T. Donta, C.C. Engel Jr., J.F. Collins, J.B. Baseman, L.E. Kazis, R.A. Horney, A.L. Wiseman, V. Gordan, P. DeJace, M. Bittner, H.R. Schumacher, J.R. Feussner. Analysis and interpretation of the data: S.T. Donta, C.C. Engel Jr., J.F. Collins, J.B. Baseman, L.L. Dever, T. Taylor, L.E. Kazis, S.E. Martin, R.A. Horney, A.L. Wiseman, K.H. Wilson, D. Wagner, P. DeJace, M. Bittner, F. Silverblatt, M.A.K. Ryan, J.R. Feussner. Drafting of the article: S.T. Donta, C.C. Engel Jr., J.F. Collins, J.B. Baseman, T. Taylor, S.E. Martin, R.P. Smith, A.B. Gorin, P. DeJace, M. Bittner, J.R. Feussner. Critical revision of the article for important intellectual content: S.T. Donta, C.C. Engel Jr., J.F. Collins, J.B. Baseman, L.L. Dever, T. Taylor, K.D. Boardman, L.E. Kazis, S.E. Martin, D.S. Kernodle, S.T. Brown, D. Wagner, M. Bittner, H.R. Schumacher, F. Silverblatt, M.A.K. Ryan, J.R. Feussner. Final approval of the article: S.T. Donta, C.C. Engel Jr., J.F. Collins, L.L. Dever, T. Taylor, K.D. Boardman, R.P. Smith, A.L. Baltch, C. Handanos, L. Montalvo, W. Blackburn, S.T. Brown, L. Lutwick, J. Bernstein, C. Bacheller, K.H. Wilson, R. Cooper, R.J. Hamill, V. Gordan, D. Wagner, P. DeJace, R. Greenfield, M. Bittner, H.R. Schumacher, F. Silverblatt, J. Schmitt, E. Wong, M.A.K. Ryan, C. Nice, J.R. Feussner. Provision of study materials or patients: S.T. Donta, C.C. Engel Jr., L.L. Dever, T. Taylor, K.D. Boardman, D.S. Kernodle, R.P. Smith, A.L. Baltch, C. Handanos, B. Catto, L. Montalvo, M. Everson, W. Blackburn, M. Thakore, B. Ribner, L.W.P. Church, K.H. Wilson, P. Guduru, R.J. Hamill, A.B. Gorin, V. Gordan, D. Wagner, C. Robinson, P. DeJace, R. Greenfield, L. Beck, M. Bittner, H.R. Schumacher, F. Silverblatt, J. Schmitt, E. Wong, M.A.K. Ryan, J. Figueroa, C. Nice. Statistical expertise: J.F. Collins. Obtaining of funding: J.F. Collins, A.L. Wiseman. Administrative, technical, or logistic support: J.F. Collins, S.E. Martin, R.A. Horney, A.L. Wiseman, D. Norwood, A.B. Gorin, D. Wagner, L. Beck, C. Nice, J.R. Feussner. Collection and assembly of data: J.F. Collins, J.B. Baseman, T. Taylor, R.A. Horney, A.L. Wiseman, D.S. Kernodle, A.L. Baltch, C. Handanos, B. Catto, L. Montalvo, M. Everson, W. Blackburn, M. Thakore, S.T. Brown, L. Lutwick, D. Norwood, J. Bernstein, C. Bacheller, B. Ribner, P. Guduru, R. Cooper, J. Lentino, A.B. Gorin, D. Wagner, R. Greenfield, L. Beck, H.R. Schumacher, J. Schmitt, E. Wong, M.A.K. Ryan, C. Nice.