Trial to Assess Chelation Therapy

TACT 2012 Update

Specific Aims

- To determine whether chelation or high-dose supplements in patients with CHD will reduce the incidence of clinical cardiovascular events;

- To determine whether chelation and high-dose supplements have acceptable safety profiles.

Study Overview

- Infusion Visits (ACAM protocol EDTA chelation vs. placebo)
  - Initial - Weekly X 30 wks
  - Maintenance - Every 2 – 8 weeks X 10

- Patient Follow-up:
  - 3 phone calls/year (average 2.5 years f/u)
  - 1 annual clinic visit
  - Clinic visit at end of study

Status of TACT as of March 27, 2012

- Number of subjects enrolled 1708
- Number of infusions completed >55, 000
- Number of patients who have completed all 40 infusions 1117
- Length of follow-up (months) 55.3

Design of the Trial to Assess Chelation Therapy (TACT)

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Abstract

- The Trial to Assess Chelation Therapy (TACT) is an NIH-sponsored, randomized, double blind, placebo-controlled, 2x2 factorial clinical trial testing the benefits and risks of 40 infusions of a multi-component Na2EDTA-chelation solution compared with placebo, and of an oral, high-dose multivitamin and mineral supplement.
- The trial is designed to have >85% power to detect a 25% relative reduction in the primary endpoint for each treatment factor.
- TACT has randomized and followed 1708 patients for an average of approximately 4 years. The primary endpoint is a composite of all cause mortality, myocardial infarction, stroke, coronary revascularization, and hospitalization for angina. A 900 patient substudy will examine quality of life outcomes.
- Enrollment began in September 2003 and was completed in October 2010.

Introduction

- National surveys consistently show that over 1/3 of adult patients in the U.S. use alternative therapies, for which reliable evidence of net benefits is lacking. Chelation therapy with disodium ethylenediaminetetraacetic acid (Na_2EDTA), a drug currently without indication in the US, is one such therapy.
- **T**he ongoing use of a therapy with the potential for benefit as well as harm led to the release of a Request for Applications by the National Center for Complementary and Alternative Medicine (NCCAM), co-funded by NCCAM and the National Heart, Lung, and Blood Institute (NHLBI) of the US National Institutes of Health.

Methods

- TACT is a randomized, double blind, placebo-controlled, 2x2 factorial trial testing the benefits and risks of 40 infusions of a standard multi-component disodium EDTA-chelation solution compared with placebo, and of an oral, high-dose multivitamin and mineral supplement compared with placebo.

- The trial uses the components, route, and methods of administration of disodium EDTA chelation recommended by the American College for Advancement in Medicine (ACAM)

Trial Administration

- The Clinical Coordinating Center (CCC) is located at Mount Sinai Medical Center, Miami Beach FL.
- The Duke Clinical Research Institute (Durham, NC) serves as the Data Coordinating Center (DCC), and the Economics and Quality of Life Coordinating Center.
- The TACT central pharmacy (Accu-Care Services Pharmacy, Miami FL 9/10/2003 TO 6/18/2010, and Universal Arts Pharmacy from 6/28/2010 to the present) has mixed and delivered, to date, over 50,000 bags of blinded chelation solution and the corresponding oral vitamin supplements to clinical sites.

Data Collection

- TACT data collection takes place through an Internet-based, electronic data capture system (TrialMaster™, OmniComm Systems, Davie FL).
- This permits real-time, patient-specific prescription of the EDTA dose of the active chelation solution, based on an individual patient's estimated glomerular filtration rate (eGFR).
- An unblinded physician not otherwise involved with the study at the CCC gives patient-specific prescription approval.

Patient Safety Oversight and Adverse Event

- The NIH, FDA, and local or central IRBs oversee TACT.
- A Data and Safety Monitoring Board (DSMB) reviews unblinded outcome and safety data approximately every 6 months, and recommends whether to continue the trial.
- The members of the DSMB include experts in clinical trial design and interpretation, bioethics, cardiology, pharmacology, chelation therapy, and biostatistics.

Patient Safety Oversight and Adverse Event

- All eligible consenting patients are randomized to receive 40 infusions of either chelation solution (Table I) or placebo, consisting of 500 mL of normal saline and 1.2% dextrose. The first 30 infusions occur weekly. The final 10 infusions may occur between 2 weeks and up to 8 weeks apart.

- Each patient is also randomized to receive either an oral high-dose vitamin and mineral supplement, or identical-appearing placebo pills (Table II). (next slide)

Table I. Chelation Solution

Additive
Up to 3 grams of disodium EDTA
2 grams of magnesium chloride
100 mg of procaine HCL
2500 units of heparin
7 grams of ascorbate
2 mEq KCl
840 mg sodium bicarbonate
250mg pantothenic acid
100mg of thiamine
100mg of pyridoxine
QS with sterile water to 500ml

Table II. High Dose Oral Contents

High Dose Regimen (Taken Twice Daily)	Total Amount for 6 Pills	% RDA
Vitamin A	25,000 IU	500%
Vitamin C	1,200 mg	2000%
Vitamin D_3	100 IU	25%
Vitamin E	400 IU	1333%
Vitamin K_1	60 mcg	75%
Thiamin	100 mg	6667%
Niacin	200 mg	1000%
Vitamin B_6	50 mg	2500%
Folate	800 mcg	200%
Vitamin B_{12}	100 mcg	1667%
Biotin	300 mcg	100%
Pantothenic acid	400 mg	4000%
Calcium	500 mg	50%
Iodine	150 mcg	100%
Magnesium	500 mg	125%
Zinc	20 mg	133%
Selenium	200 mcg	286%
Copper	2 mg	100%
Manganese	20 mg	400%
Chromium	200 mcg	167%

OTHER COMPONENTS	
Choline	150 mg
Inositol	50 mg
PABA	50 mg
Boron	2 mg
Vanadium	39 mcg
Citrus Bioflavonoids	100 mg
Croscarmellose sodium	-
Microcrystalline cellulose	-
Magnesium stearate	-
Hydroxypropyl cellulose	-
Silicon dioxide	-

Blinding

- The chelation solution is blinded using a previously piloted method.
- The shipped and refrigerated infusion pack contains an ascorbic acid syringe (or ascorbic acid placebo), one syringe with EDTA (or EDTA placebo), and a bag for intravenous infusion with all the other components already mixed (or a bag containing only normal saline if the patient is assigned to the placebo arm).

Safety Monitoring

- The most important potential adverse events are hypocalcemia and renal toxicity.
- Nephrotoxicity has been encountered with far higher doses than TACT uses as well as more frequent administration , and in patients with underlying renal disease.
- Patients with a baseline creatinine >2.0 are excluded from the trial. Renal function is assessed at baseline, and 9 additional times during the infusion regimen.

Study Endpoints

- The primary endpoint is a composite of all cause mortality, myocardial infarction, stroke, coronary revascularization, and hospitalization for angina.

- A key secondary endpoint is the composite of cardiovascular death, non-fatal MI, or non-fatal stroke.

- There are 4 other pre-specified secondary endpoints: 1] quality of life; 2] cost-effectiveness of therapy, 3] high sensitivity C-reactive protein, and 4] estimated GFR.

Clinical CVD Event Rates and Statistical Power

- TACT originally planned to enroll 2372 patients over 3 years. Difficulties in enrolling the requisite numbers of patients ultimately led to a reduction in the total sample size to 1700 patients, with a counterbalancing extension in median follow-up to 4 years.

- The event rates in each control arm of TACT were estimated based on published data on similar post-MI patient populations participating in clinical trials, namely 20% or higher after 2.5 years of follow-up.

- The level of non-compliance with EDTA (or placebo) infusion therapy and oral vitamin (or placebo) expected in TACT was estimated as 7.2% of patients per year, or 22% over 3 years. We also assumed a loss to follow-up rate of up to 3% of patients in the trial. This statistical plan provides 85% power for detecting a 25% relative reduction in the primary endpoint for each treatment.

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Statistical Analysis

- All major treatment comparisons will be performed according to the principle of intention-to-treat. Statistical comparisons will be performed using two-sided significance tests.
- The primary statistical assessments will compare EDTA chelation with placebo infusions, and oral high-dose vitamins with oral placebo.
- The log-rank test will be used for the adjusted comparisons of each treatment factor.
- Cumulative event rates will be calculated according to the Kaplan-Meier method.
- Hazard ratios with associated confidence intervals and will be derived from the Cox proportional hazards model. The Cox model will also be used to assess whether there is an interaction of EDTA chelation therapy with high dose vitamins.
- Interim treatment comparisons are monitored with the use of 2-sided, symmetric

Subgroup Analyses

A limited number of pre-specified subgroup analyses of the primary outcome and selected secondary outcomes will test the efficacy of chelation therapy and/or high dose vitamins. Treatment comparisons will be performed within subgroups defined by:

- Age >70 years versus younger patients;
- Gender;
- Race;
- MI location;
- Time from index MI to trial enrollment;
- Diabetes and metabolic syndrome;
- Patients in whom statin therapy is not being used;
- Patients at risk to have had exposure to lead during their lifetime;
- Patients who have received 80% of assigned therapy, whether infusions or oral high-dose vitamin therapies;
- Patients who have received at least one infusion as assigned.

Discussion

- Besides challenges typical of large multisite trials, TACT was faced with several additional hurdles. Substantial recruitment difficulties led NIH to organize a review of trial progress carried out by a panel of experts in cardiovascular research independent of NIH, of the trial DSMB, and of trial investigators.
- Despite estimates that trial completion would be delayed several years, this independent committee concluded TACT should continue with a reduced sample size.

Discussion Cont.

- Concerns about the informed consent process, and about trial conduct at several clinical sites also prompted investigations by OHRP and FDA respectively. Following their reviews, each Federal agency recommended the trial could continue after corrective steps were taken.
- All sites met NIH, FDA, and Office for Human Research Protections requirements for participation in federally-funded studies, including ethics review by a local or central IRB with a Federal-Wide Assurance.

Conclusions

TACT has been designed to test whether EDTA chelation therapy and high-dose oral vitamin and mineral therapy offer clinical, quality of life, and economic benefits for patients with a prior MI.

At this time TACT has finished enrollment, has delivered the final infusions and vitamins, and is expected to present final results in 2012.