TACT: Surprising, puzzling benefit from chelation therapy after MI

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Los Angeles, CA (updated) - A randomized, double-blind trial of chelation therapy has suggested that the alternative-medicine mainstay may modestly improve clinical outcomes in patients after an acute MI, leaving its own investigators and other knowledgeable observers scratching their heads.

Over a four-year follow-up, those who followed an arduous regimen involving up to 40 separate three-hour infusions of a standard chelation-therapy solution of multiple ingredients, compared with a placebo, showed an 18% drop in the trial's primary end point. Adverse effects were mostly minimal.

The difference in the end point—a composite of all-cause mortality, MI, stroke, coronary revascularization, and hospitalization for angina—barely reached the trial's prespecified threshold for statistical significance.

The Trial to Assess Chelation Therapy (TACT) was reported here at the American Heart Association (AHA) 2012 Scientific Sessions by **Dr Gervasio A Lamas** (Mount Sinai Medical Center, Miami Beach, FL). In a formal presentation for the media, Lamas said in TACT, chelation therapy "showed some evidence of a potentially important treatment signal in post-MI patients already on evidence-based therapy" and "appears to be safe" as given and monitored in the trial. But, he added, the treatment's "clinical application" can't be recommended based on the current "unexpected" results.


Dr Gervasio A Lamas

On the other hand, the trial "hints that there may be a biological effect and that the biological effect should be taken seriously and pursued with additional research."

The trial itself has been controversial in its long history. As reported by heartwire, ethics questions had been raised about the quality of disclosure to patients about possible treatment effects and criticisms leveled at a perceived waste of public money. Enrollment had been slow, and it was stopped and restarted a number of times.

Indeed, Lamas observed, slow enrollment led to some protocol changes. The data safety and monitoring board of the trial, with an original target of at least 2372 patients followed for one year, approved a smaller enrollment target and longer follow-up to preserve statistical power.

"Unusually polarized" opinion

The literature, Lamas noted, is variously supportive and dismissive of chelation therapy, which promotes elimination of heavy metals from the body and likely has other effects, as treatment for coronary disease. TACT was launched with backing of the **National Institutes of Health** after the evidence for and against reached enough equipoise.


Dr Paul Armstrong

Dr Paul Armstrong (University of Alberta, Edmonton), the scheduled discussant for Lamas's formal presentation of TACT, acknowledged the treatment's controversial nature in his comments to reporters: "I think there are occasions when equipoise is associated with divided opinion, but in this instance I think the opinion is unusually polarized."

At his center, he said, "we don't advocate this therapy." To a patient who asks him about it, "I say there's significant potential for hazard, and I'm unaware of any benefit, and I would advise against it. And my advice to that patient today would be the same as one year ago."


Dr Mark Hlatky

Dr Mark Hlatky (Stanford University School of Medicine, CA), also slated to formally speak on TACT, found the primary-end point difference "pretty surprising. Obviously the significance level was not high—it was somewhat borderline. But it was significant. . . . I certainly think we need to have some confirmation, but nevertheless the trial results are very provocative."

Speaking with heartwire, **Dr E Magnus Ohman** (Duke University, Durham, NC), who wasn't connected with the trial, agreed that the efficacy difference was only marginal but pointed to the trial's subgroup analysis, which suggested that diabetics seemed to show a significantly more pronounced benefit from chelation therapy than the population as a whole. "So there's a subgroup that appears to have a very strong signal."

Ohman observed that chelation therapy, at least in North Carolina, "is predominantly used in patients who have run out of options. They've had their revascularization—nothing seems to have worked for them, and they gravitate to these [chelation] clinics. That may not be exactly the population that was studied, but I think it opens the door [to asking] is there something in the alternative-medicine realm that we haven't explored before? Should we explore it in the future? Absolutely."

Complex formula

TACT tested "the most common" formulation of the solution used at US chelation clinics, according to Lamas, which contained disodium ethylenediaminetetraacetic acid (EDTA), ascorbic acid, magnesium chloride, potassium chloride, sodium bicarbonate, B vitamins, procainamide, a small amount of standard heparin, and water. The placebo consisted of saline with some glucose—the latter added, Lamas said, as part of a process that helped preserve double-blinding when preparing the solutions for administration.

About 65% of the 1708 randomized patients completed all 40 prescribed infusions; 76% completed at least 30, Lamas said; 79 patients discontinued the infusions due to reaching an end point or adverse effects.

The hazard ratio (HR) for the primary end point for chelation therapy vs placebo, by intention to treat, was 0.82 (95% CI 0.69-0.99; p=0.035). That narrowly met the trial's prespecified limit for statistical significance (p<0.036).

There were no significant differences in the individual components of the primary end point. The rate of hospitalization for angina was 1.5% for chelation patients and 2.1% for controls (p=0.359), but there was a trend toward a benefit for coronary revascularization, which occurred in 15.5% of chelation patients and 18.1% of controls (p=0.076).

In a prespecified subgroup analysis, chelation therapy provided a stronger benefit for the primary end point in the 31% of the total population who were diabetic compared with the entire population. In diabetics, the HR was 0.61 (95% CI 0.45-0.83; p=0.002); in nondiabetics, it was 0.96 (95% CI 0.77-1.20; p=0.725).

In fact, Armstrong observed, the benefit in diabetics accounted for "a large majority of the intergroup difference" in the trial population as a whole. Of the 39 primary end-point events that constituted the difference between chelation-therapy patients and control patients, 35 were in diabetics.

Complex results

The trial's outcomes are hard to interpret for a number of reasons, observed everyone presenting on and commenting to heartwire regarding TACT. One such reason, for example, is that the mechanism of the observed benefit isn't understood, **Dr Daniel B Mark** (Duke University Medical Center, Durham, NC), who was on the schedule to formally speak on TACT, told the media.


Dr Daniel B Mark

What is known, Mark said, is that clinicians were first drawn to chelation therapy for coronary disease because of an antiangina effect observed in the earliest studies. "It may be that in this study—because the proportion of patients with angina is low, because the type of baseline therapy has changed substantially from those early years, and because we tend not to tolerate in this country people having long-term chronic angina if there's an alternative strategy, namely invasive therapy—that maybe . . . the nature of problem has changed, that the opportunity to show effects in angina in this type of a population is much reduced and that other types of effects are going to be more important."

When interviewed, Hlatky proposed that perhaps the extra efforts made to preserve double-blinding "may have interfered with the actual results. The fact that you're giving extra glucose infusions to people with diabetes, might that have had something to do with the difference in the diabetes group? Was chelation helping them or did giving sugar infusions hurt them? I don't know, [but it's] an interesting question."

Also at the media briefing, sessions program chair **Dr Elliot Antman** (Brigham and Women's Hospital, Boston, MA) read a formal statement from the AHA regarding TACT. It read, in part, "As intriguing as the results are, they're unexpected and should not be interpreted as an indication to adopt chelation therapy into clinical practice. Much more information is needed about which elements of the complex infusion mixture might provide benefit; the marked discordance between the observed treatment effect in diabetics vs nondiabetics needs to be understood. . . . TACT raises more questions that must be answered before we are ready to act on the observations that were reported here today."

"Disconnect" in the TACT quality-of-life analysis

In a random sample of 911 patients in TACT, chelation therapy compared with placebo had almost no effect on standard measures of quality of life assessed at baseline and at six, 12, and 24 months.

The exception was slight improvement in self-reported anginal symptoms with chelation therapy at one year ($p=0.016$), but not at any other assessment, observed Mark at the TACT media briefing.

The quality-of-life tests included the Medical Outcomes Study Short Form-36 (SF-36), including its Mental Health Inventory-5 (MHI-5) component that assessed anxiety and depression. The MHI-5 along with the Duke Activity Status Index (DASI), a measure of cardiac functional status, were "co-principal end points" for the analysis, Mark said. Also included were the Seattle Angina Questionnaire (SAQ) Anginal Frequency and Quality of Life subscales.

According to the SAQ, about 80% of the patients had no anginal symptoms at baseline, "so the proportion of patients reporting any anginal symptoms at all was a small minority of the total population," Mark said. That may account for chelation therapy's lack of effect on self-reported symptoms: patients already scored well for angina-related quality of life, so "it was difficult to show any further improvement on the basis of any therapeutic intervention."

Ohman told heartwire that the patients he knows who have received chelation therapy for coronary disease do it expressly because of a perceived improvement in quality of life. "So we have a disconnect between why individual patients today choose it and what the science shows."

The trial's primary analysis of clinical response to chelation therapy "tells us maybe there's something to it," Ohman said. But there's no effect on quality of life, "there's no doubt about that."