A study to assess the effects of a broad-spectrum immune modulatory therapy on mortality and morbidity in patients with chronic heart failure: The ACCLAIM trial rationale and design

Guillermo Torre-Amione MD¹, Robert C Bourge MD², Wilson S Colucci MD³, Barry Greenberg MD⁴, Craig Pratt MD¹, Jean-Lucien Rouleau MD⁵, Francois Sestier MD⁶, Lemuel A Moyé MD PhD⁷, John A Geddes⁸, Agnes J Nemet MD⁸, James B Young MD⁹; for the ACCLAIM Investigators

G Torre-Amione, RC Bourge, WS Colucci, et al; for the ACCLAIM Investigators. A study to assess the effects of a broad-spectrum immune modulatory therapy on mortality and morbidity in patients with chronic heart failure: The ACCLAIM trial rationale and design. *Can J Cardiol* 2007;23(5):369-376.

BACKGROUND: Evidence has accumulated regarding the importance of inflammatory mediators in the development and progression of heart failure (HF). Although targeted anticytokine treatment strategies, specifically antitumour necrosis factor- α , have yielded disappointing results, this may simply reflect the redundancy of the cytokine cascade and the fact that antitumour necrosis factor- α therapies do not stimulate increased activity of the anti-inflammatory arm of the immune system.

Ex vivo exposure of autologous blood to controlled oxidative stress and subsequent intramuscular administration is a device-based procedure shown in experimental studies to have a broad-spectrum effect on a number of immune mediators. These studies have demonstrated that this approach downregulates inflammatory cytokines, whereas several anti-inflammatory cytokines are increased. In a feasibility study of 73 patients with moderate to severe HF, active therapy (versus placebo) had a significant benefit on both mortality and hospitalization, and was not associated with adverse hemodynamic or metabolic effects.

METHODS: The Advanced Chronic heart failure CLinical Assessment of Immune Modulation therapy (ACCLAIM) trial is a multicentre, randomized, double-blind, placebo-controlled clinical trial of New York Heart Association functional class II to IV chronic HF patients with left ventricular ejection fraction of 30% or less. Enrolling approximately 2400 subjects at 177 sites, the primary end point of the study was the cumulative incidence (time to first event) of the combined end point of total mortality or hospitalization for cardiovascular causes. The study was completed in late 2005, when 701 primary end point events had occurred and all patients had been treated for six months.

CONCLUSIONS: If the ACCLAIM trial confirms earlier results, this approach represents a novel nonpharmacological treatment for HF that targets a pathogenic mechanism contributing to progression of this syndrome not addressed by current therapies.

Key Words: Heart failure; Immune modulation; Ventricular dysfunction

Une étude pour évaluer les effets d'une thérapie à modulation immunitaire à large spectre sur la mortalité et la morbidité des patients atteints d'insuffisance cardiaque chronique : Le motif et la méthodologie de l'essai ACCLAIM

HISTORIQUE : Les données probantes se sont accumulées au sujet de l'importance des médiateurs inflammatoires dans l'apparition et l'évolution de l'insuffisance cardiaque (IC). Bien que les stratégies de traitement ciblé aux anticytokines, notamment le facteur de nécrose tumorale α , aient donné des résultats décevants, elles reflètent peut-être simplement la redondance de la cascade de cytokine et le fait que les traitements au facteur de nécrose tumorale α ne stimulent pas l'augmentation de l'activité anti-inflammatoire du système immunitaire.

L'exposition *ex vivo* du sang autologue au stress oxydatif contrôlé et l'administration intramusculaire subséquente sont des interventions dépendant d'outils qui, d'après les études expérimentales, ont un effet à large spectre sur plusieurs médiateurs immunitaires. D'après ces études, cette méthode régularise les cytokines inflammatoires de manière négative, tandis que plusieurs cytokines anti-inflammatoires augmentent. Dans le cadre d'une étude de faisabilité auprès de 73 patients atteints d'une IC moyenne à grave, un traitement actif (par rapport à un placebo) avait des effets bénéfiques considérables sur la mortalité et l'hospitalisation et ne s'associait pas à des effets hémodynamiques ou métaboliques néfastes.

MÉTHODOLOGIE : L'essai sur l'évaluation clinique de la thérapie à modulation immunitaire en cas d'insuffisance cardiaque chronique avancée (l'essai ACCLAIM) est un essai clinique multicentrique à double insu, aléatoire et contrôlé contre placebo, auprès de patients atteints d'une IC de classe fonctionnelle II à IV selon la *New York Heart Association* et dont la fraction d'éjection ventriculaire gauche était de 30 % ou moins. Menée auprès d'environ 2 400 sujets dans 177 établissements, l'étude avait comme paramètre primaire ultime d'obtenir l'incidence cumulative (délai jusqu'au premier événement) du paramètre combiné de mortalité totale ou d'hospitalisation pour des causes cardiovasculaires. L'étude a pris fin à la fin de 2005, après l'occurrence de 701 événements ultimes et le traitement de tous les patients pendant six mois.

CONCLUSIONS : Si l'essai ACCLAIM confirme les résultats précédents, cette méthode constituera un traitement non pharmacologique novateur de l'IC, qui ciblera un mécanisme pathogène contribuant à l'évolution de ce syndrome et qui n'est pas traité au moyen des thérapies courantes.

¹Methodist Hospital, Houston, Texas; ²University of Alabama at Birmingham, Birmingham, Alabama; ³Boston University School of Medicine, Boston, Massachusetts; ⁴University of California, San Diego Medical Center, San Diego, California, USA; ⁵Faculty of Medicine, Université de Montréal; ⁶Hôtel-Dieu du CHUM, Centre de Recherche, Montreal, Quebec; ⁷University of Texas, Houston, Texas, USA; ⁸Vasogen Inc, Mississauga, Ontario; ⁹The Cleveland Clinic Foundation, Cleveland, Ohio, USA

Correspondence: Dr James B Young, Division of Medicine, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Desk T-13, Cleveland, Ohio 44195, USA. Telephone 216-444-2270, fax 216-445-7853, e-mail youngj@ccf.org

Received and accepted for publication February 5, 2007

Current guidelines for the pharmacological management of chronic heart failure (HF) recommend drug combinations that include an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker, and a beta-adrenergic blocker (beta-blocker), with or without an aldosterone antagonist, digitalis and appropriate diuretics (1). Anticoagulants, brain natriuretic peptide and inotropic agents are also prescribed for selected patients. The efficacy and safety of combination therapy in patients with chronic HF have been well documented in large-scale clinical trials (1). However, despite the effectiveness of such therapy, chronic HF remains characterized by progressive morbidity and high mortality. Additionally, the multiple treatment protocols create challenges requiring specialized skills for management. As a result, there is an ongoing effort to develop new strategies for improving outcomes in patients with chronic congestive HF.

In the mounting evidence indicating that inflammatory cytokines play a central role in at least the progression of chronic HF, these inflammatory mediators present an attractive therapeutic target (2). The pathophysiological effects of tumour necrosis factor- α (TNF- α), in particular, have been examined in detail. Transgenic mice that overexpress cardiac-specific TNF- α die prematurely and exhibit pathological changes consistent with HF (3-5). Myocardial tissue and plasma levels of TNF- α are elevated in HF (6,7) and reportedly correlate with disease severity (8,9).

The association between TNF- α levels and chronic HF severity encouraged investigators to conduct clinical trials aimed at evaluating the effects of neutralizing TNF- α activity in patients with chronic HF. However, this highly specific anti-cytokine approach has produced disappointing results (10,11).

A number of explanations for the failure of these trials, despite convincing evidence of the increased role for TNF- α in chronic HF have been proposed. These include the possibility that the biological agents used to antagonize TNF- α activity were intrinsically toxic or may have stimulated, rather than neutralized, TNF- α activity (2). Also, TNF- α is not the only inflammatory mediator with elevated levels in chronic HF (6,9). Because only a single cytokine was targeted in these trials, it is possible that other inflammatory cytokines (eg, interleukin-1 and interleukin-6) were increased to levels sufficient to overcome any benefits derived from neutralizing TNF- α . Furthermore, targeted anti-TNF- α treatment is not associated with an upregulation of anti-inflammatory mediators, which would restore the balance between inflammatory and anti-inflammatory cytokines.

Additional immunomodulating strategies that still have control of cytokine activity as their basis have been evaluated. There are indications that by adopting a broad-spectrum approach to immune response modulation, a clinical benefit may be observed in patients with chronic HF. Such approaches seek to attenuate the inflammatory response and/or activate anti-inflammatory pathways. Support for this less specific strategy to modify the immune response has come from a series of small clinical trials that have documented some benefit from the use of steroids (12), intravenous immunoglobulin (13) and immunoadsorption therapy (14).

A novel broad-spectrum immune modulatory therapy represents a new strategy with therapeutic potential for patients with chronic HF. This therapy is a point-of-care outpatient procedure that uses medical device technology for the ex vivo exposure of a sample of autologous blood to controlled levels

of oxidative stress. The treated sample is readministered to the same patient by intramuscular injection. Current evidence suggests that the ex vivo exposure of a blood sample to oxidative stress initiates apoptosis of leukocytes, and that the apoptotic process is completed soon after intramuscular injection. The physiological response of the recipient's immune system to apoptotic cells results in a decrease in inflammatory cytokines and the upregulation of anti-inflammatory cytokines (15,16). The combined effect may be especially beneficial in patients with chronic HF, because the inflammation associated with this condition reflects an imbalance of the two opposing arms of the cytokine network (17).

Preclinical studies have documented responses consistent with such a mechanism in several models of inflammation – changes that may be beneficial in the treatment of patients with chronic HF. These effects include decreases in inflammation and production of inflammatory mediators (18-20), increased anti-inflammatory cytokine expression and decreased apoptosis (20). Although initial human trials in peripheral arterial disease have shown that this approach is safe and favourably influences vascular endothelial function (21) and claudication distance (22), a randomized trial of approximately 550 patients with stable claudication failed to replicate the results on walking distance (23). Such a modulation of tissue immune responses may favourably influence a number of the pathological processes associated with progression of HF, including myocardial apoptosis, left ventricular dysfunction and electrophysiological abnormalities.

Results from a preliminary, randomized, controlled phase II study (24) in 73 patients with advanced chronic HF have been encouraging. The enrolled patients had a relatively advanced degree of HF as depicted by New York Heart Association (NYHA) functional class (III or IV), a low (mean of 22%) left ventricular ejection fraction (LVEF) and limited exercise capacity (less than a 300 m, 6 min walk distance). Patients received active treatment or placebo for six months in a double-blind fashion. Active treatment was shown to significantly reduce the risk of both mortality and hospitalization, improve a clinical composite score and have favourable electrocardiographic effects; both QT interval and QT dispersion were decreased in the active group compared with the placebo group. There were no between-group differences in the 6 min walk distance or in the mean LVEF. However, there were trends favouring active therapy when considering NYHA class and the Minnesota Living with Heart Failure Questionnaire (MLHFQ) quality of life (QoL) score. A particularly desirable feature of this approach was the absence of detrimental hemodynamic, metabolic and other adverse effects, allowing the treatment to be safely combined with standard therapies for HF.

As a result of these encouraging results, a large, pivotal phase III trial in patients with chronic HF was initiated.

ADVANCED CHRONIC HEART FAILURE CLINICAL ASSESSMENT OF IMMUNE MODULATION THERAPY (ACCLAIM) – STUDY DESIGN

The Advanced Chronic heart failure CLinical Assessment of Immune Modulation therapy (ACCLAIM) trial was designed to evaluate the effects of a broad-spectrum approach to immune modulation on morbidity and mortality in a large cohort of patients with chronic HF.

The ACCLAIM trial is a prospective, double-blind, randomized, placebo-controlled, parallel-group, multicentre clinical trial that randomly assigned 2426 NYHA class II to IV chronic HF patients with LVEF of 30% or less who were already receiving optimal HF therapy. Optimal therapy included treatment with an ACE inhibitor or angiotensin II receptor blocker, with or without a beta-blocker, digitalis, diuretic or an aldosterone antagonist.

Eligible consenting patients were randomly allocated in a 1:1 manner to a course of active treatment or an equivalent volume of saline in addition to their pre-existing HF therapy for the duration of the study.

Patient population

Patients were recruited from 177 participating clinical centres located in Canada, Denmark, Germany, Israel, Norway, Poland and the United States. Patients included adults who had NYHA class II to IV chronic HF and LVEF of 30% or less, and who were hospitalized for the treatment of HF or received outpatient (eg, clinic or emergency department) intravenous administration of an inotropic agent (therapeutic dose for HF), human B-natriuretic peptide or a diuretic within the previous 12 months. If patients were classified as NYHA class III or IV and had an LVEF of less than 25%, the hospitalization or outpatient intravenous therapy in the prior 12 months was not required. A complete list of inclusion and exclusion criteria appears in Table 1. Study patients must have met all the inclusion criteria and none of the exclusion criteria.

Device description

Active therapy involved outpatient administration of autologous blood that had been treated *ex vivo* by exposure to strictly controlled levels of oxidative stress at an elevated temperature using a medical device. The VC7000A Autologous Blood Treatment System (Celacade system, Vasogen Inc, Canada) consists of a treatment unit (model VC7001A, Vasogen Inc, Canada) and a sterile, single-use, disposable cartridge (model VC7002, Vasogen Inc, Canada).

Treatment procedure

Venous blood (10 mL) was collected into 2 mL of sodium citrate USP as an anticoagulant. The citrated sample was immediately transferred to the VC7002 cartridge and was then inserted into the VC7001A device for *ex vivo* treatment. Treatment of the sample was performed over a period of approximately 20 min. Within the treatment unit, the sample was exposed to strictly controlled levels of oxidative stress (a gas mixture of 14.5 µg/mL ozone in medical O₂, delivered at a flow rate of 240 mL/min, and ultraviolet light at a wavelength of 253.7 nm) at an elevated temperature of 42.0°C. The treated autologous sample was then removed from the system and administered to the same patient by intragluteal injection after an injection of a local anesthetic.

Treatment schedule

After random assignment, two treatments were administered on consecutive days, followed by a third treatment on day 14. Subsequent treatments were administered at four-week intervals for at least 22 weeks or until study completion. The mean follow-up time was approximately 10 months from the start of treatment. The study design and visit schedule design are shown in Figure 1.

TABLE 1

The Advanced Chronic heart failure CLinical Assessment of Immune Modulation therapy (ACCLAIM) trial patient enrolment criteria

Inclusion criteria

- Age of 18 years or older
- Chronic systolic heart failure
- New York Heart Association class II to IV
- LVEF of 30% or less measured within the previous six months (by any technique), unless there was a cardiovascular event that could have modified the LVEF during that period (eg, CABG, myocardial infarction). If the patient was started on a beta-blocker or biventricular pacing (CRT), the LVEF measurement must have been taken at least three months after starting the therapy
- Hospitalization for heart failure or outpatient (eg, clinic, emergency department) intravenous administration of an inotropic agent (therapeutic dose for heart failure), human B-natriuretic peptide or an intravenous diuretic (minimum 40 mg of furosemide or equivalent) within the previous 12 months (stable for at least two weeks). Exceptions: patients in New York Heart Association class III or IV who had an LVEF of less than 25%
- On standard therapy for chronic heart failure, which must have included an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker (unless contraindicated or if patient was intolerant) with or without other appropriate agents. If on a beta-blocker, patients must have been on the beta-blocker for at least three months
- No changes in cardiac medication (indicated for heart failure) during the two weeks before treatment
- Written, informed consent

Exclusion criteria

- Inability to comply with the conditions of the protocol
- Presence of a transplanted tissue or organ, or left ventricular assist device support (or the expectation of the same within the next 12 months)
- Planned AICD or CRT within the next 12 months
- Acute myocardial infarction, CABG, percutaneous transluminal coronary angioplasty, AICD or CRT within the previous three months
- Need for chronic intermittent inotropic therapy
- Malignancy: evidence of disease within the previous five years. Exceptions: basal cell carcinoma, provided it was neither infiltrating nor sclerosing, or carcinoma *in situ* of the cervix
- Active myocarditis or early postpartum cardiomyopathy (within the first six months after delivery)
- Systemic corticosteroids, cytostatics and immunosuppressive drug therapy (cyclophosphamide, methotrexate, cyclosporine, azathioprine, etc), DNA-depleting or cytotoxic drugs taken within four weeks before study treatment
- Pregnancy, or patient of childbearing potential not using adequate contraceptive methods
- Porphyria
- Allergy to sodium citrate or any -caine type of local anesthetic
- Previous treatment using the Celacade system (Vasogen Inc, Canada)
- Patient scheduled for hospice care
- Clinically relevant abnormal findings in the clinical history, or on physical examination, electrocardiogram or laboratory tests at the screening assessment that would have interfered with the objectives of the study, or findings that would have, in the investigator's opinion, precluded the safe completion of the study. Abnormal findings may include known HIV infection or other immunodeficiency, chronic active viral infection (such as hepatitis B or C), acute systemic infections (defined as patients undergoing treatment with antibiotics), gastrointestinal tract bleeding, or any severe or acute concomitant illness or injury
- Any other medical, social or geographical factor that would have made it unlikely that the patient would have complied with study procedures. Such factors include alcohol abuse, lack of permanent residence, severe depression, disorientation, distant location or a history of noncompliance

AICD Automatic implantable cardioverter defibrillator; CABG Coronary artery bypass grafting; CRT Cardiac resynchronization therapy; LVEF Left ventricular ejection fraction

Figure 1) Overall design of the Advanced Chronic heart failure CLinical Assessment of Immune Modulation therapy (ACCLAIM) trial

END POINTS

A summary of end points is shown in Table 2.

Primary end point

The primary end point of the ACCLAIM trial was defined as the cumulative incidence from randomization of the combined end point of all-cause mortality or hospitalization for cardiovascular indication.

Secondary end points

In addition to the individual components of the primary end point, secondary end points consisted of hospitalization for worsening HF, all-cause hospitalization, cardiovascular mortality, a clinical composite score at six and 12 months, days alive and out of hospital, change in NYHA functional class, change in C-reactive protein concentration, health-related patient QoL, electrocardiographic parameters (corrected QT interval) and health care resource use. Blood samples were collected and frozen for subsequent analysis of select inflammatory and/or prognostic markers.

Definition of specific secondary end points

Clinical composite score: The clinical composite score (25) classifies each randomly assigned patient as worse, improved or unchanged, depending on the clinical response during treatment and the clinical status. A patient is classified as:

- worse – if during the first six and 12 months of double-blind treatment, he/she experienced a major clinical event (died for any reason or was hospitalized due to, or associated with, worsening HF), permanently discontinued study treatment due to worsening HF, worsening by one or more NYHA functional class, or moderate or marked worsening in the global assessment of clinical status, as assessed by the patient (see below);
- improved – if the patient was not classified as ‘worse’ as defined above and, at the six- and 12-month visits, the patient either improved by one or more NYHA functional class, or the global assessment of clinical

TABLE 2

The Advanced Chronic heart failure CLinical Assessment of Immune Modulation therapy (ACCLAIM) trial end points

Primary end point

- All-cause mortality or cardiovascular hospitalization

Secondary end points

- All-cause mortality or hospitalization for all causes
- All-cause mortality or hospitalization due to worsening heart failure
- Individual components of the composite end points
- Cardiovascular deaths
- Clinical composite score
- Total days alive and out of hospital
- Combined incidence of selected cardiovascular outcomes
 - sudden cardiac death
 - nonfatal myocardial infarction
 - nonfatal ischemic stroke
 - unstable angina
 - coronary revascularization
- Change in corrected QT interval
- Change in New York Heart Association classification
- Change in health-related quality of life
- Cardiovascular-related health care use
- Change in C-reactive protein concentration

status, as assessed by the patient, moderately or markedly improved (see below); or

- unchanged – if the patient was classified as neither ‘improved’ nor ‘worse’.

Patient global assessment

Patients assessed their clinical status by answering the question, “how would you rate your heart failure condition since starting the study treatment?” using the following 7-point scale:

1. Markedly improved
2. Moderately improved
3. Slightly improved
4. Unchanged
5. Slightly worse
6. Moderately worse
7. Markedly worse

Hospitalization due to worsening HF

Patients were considered to have been hospitalized due to, or associated with, worsening HF (including pulmonary edema, cardiogenic shock) if:

- the reason for admission was worsening HF that required the administration or augmentation of intravenous HF therapy; or
- the patient had worsening HF at the time of admission.

Under both circumstances, the following conditions had to be met:

- duration of hospitalization of at least 24 h;

- clear symptoms or signs of worsening HF (fluid retention or peripheral hypoperfusion); and
- documentation or medical records that indicated that aggravated HF was the reason for hospitalization. If competing reasons judged to be of equal importance were available, the HF diagnosis took preference.

NYHA classification

Patient NYHA functional class was assessed at each visit. Changes from baseline were analyzed at months 3, 6, 9 and 12, and at the end of the study, and were expressed as the percentage of patients whose HF worsened or improved by at least one functional class.

Health-related QoL

Health-related QoL was assessed using the MLHFQ (26,27). The instrument was administered at visit 2 (before random assignment and treatment) and every three months thereafter until the end of the study. The MLHFQ is a 21-item, self-administered measure of patients' perceptions of the effects of HF on their lives. Eight items address physical limitations, while five address emotional impacts of the disease; physical and emotional subscores, respectively, may be calculated using these items. The remaining eight items in the MLHFQ address the effects of HF on the patient's ability to earn a living, the presence of edema, impact on sexual activity and appetite, cost of medical care, medication side effects and hospitalization. Response options to all items are presented as a 6-point ordinal scale, ranging from a 'no' limitation (assigned a value of 0) to 'very much' (assigned a value of 5). The maximum score for the MLHFQ is 105, and lower MLHFQ scores indicate improved QoL.

Cardiovascular-related health care use

At each study visit after screening, information was obtained on cardiovascular-related inpatient and outpatient care received since the patient's last study visit. Attention was focused on all cardiovascular-related hospital admissions, selected cardiovascular-related outpatient diagnostic studies (eg, angiography or cardiac catheterization, nuclear imaging and echocardiography) and selected cardiovascular-related outpatient visits (eg, for administration of inotropic agents).

Substudies

Two substudies were approved by the steering committee:

- In up to 400 patients, echocardiography Doppler imaging was obtained at baseline and six months, with assessment for changes in both ventricular structure and function (systolic and diastolic).
- In up to 60 patients, flow-mediated endothelial function, using brachial artery ultrasound, was assessed 10 weeks and six months after random assignment and compared with baseline values.

Monitoring and safety assessments

The ACCLAIM trial was conducted and monitored according to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice and applicable regulatory

guidelines. Adverse events (including hospitalization), NYHA class, vital signs, weight and concomitant drug use were recorded at each visit. In addition, health economic assessments (the cost of each cardiovascular-related hospitalization or procedure) were estimated using secondary data and were compared with baseline at the end of the follow-up. Patients were evaluated by laboratory tests, patient global assessments and the MLHFQ at baseline, and every third month thereafter until the end of the study. A physical examination and an electrocardiogram were performed at screening and at six-month intervals thereafter.

STATISTICAL CONSIDERATIONS

Assuming a cumulative incidence of death from all causes or hospitalization for cardiovascular causes of 38% over a 15-month period in the control group, a two-sided $\alpha=0.049$ (to adjust for two interim analyses) and 90% power, 2016 patients were required to demonstrate an 18% reduction of events in the active group.

The ACCLAIM trial is an outcome event-driven trial. Patients were treated until 701 primary end point events had occurred, and all patients had been followed-up for at least six months. In the analyses, the effect of the therapy on the primary end point was evaluated using Cox proportional hazards modelling. The effects of treatment on selected secondary end points are reported, in addition to measures of effect sizes, standard errors and confidence intervals.

Secondary analyses

Health-related QoL: The MLHFQ was administered before random assignment at baseline (ie, visit 2) and every three months thereafter until the end of the study. In the analyses, attention was focused mainly on the MLHFQ total score, although physical and emotional subscores were also examined. The change in scores between the baseline and each follow-up assessment was calculated for each scale score and treatment group, and is reported along with its corresponding standard error. A repeated measures analysis of variance model was used to examine the overall effect of treatment on QoL (ie, all follow-up assessments versus baseline); a separate model was used for each MLHFQ scale (ie, physical, emotional and total).

Cardiovascular-related care: The number of cardiovascular-related encounters (hospital admissions and inpatient days, selected diagnostic tests and procedures, and selected outpatient visits) between baseline and the end of follow-up was compared between patients randomly assigned to active treatment and placebo. The cost of cardiovascular-related care was compared between the two treatment groups by assigning an estimated cost to each cardiovascular-related admission, test and visit. These costs were estimated using secondary data based on information collected on study case report forms. The estimated costs of all cardiovascular-related admissions, tests and visits were summed to yield a total cost of cardiovascular-related care. The mean total estimated cost of cardiovascular-related care was then compared between active treatment and placebo patients. Estimates of use and costs are presented, along with their corresponding 95% CI.

Subgroup analyses

The consistency of the treatment effect on the cumulative incidence rate of the combined end point of total mortality or hospitalization for cardiovascular cause was assessed by

TABLE 3
Primary end point subgroups for analysis

- Age
- Sex
- Race
- New York Heart Association classification
- Systolic blood pressure
- Heart rate
- Left ventricular ejection fraction
- C-reactive protein concentration
- Hypertension
- Prior myocardial infarction
- Diabetes
- Use of the following:
 - automatic implantable cardioverter defibrillator
 - cardiac resynchronization therapy
 - digoxins
 - statins
 - beta-blockers
 - warfarin
 - cyclooxygenase 2 inhibitors
 - aldosterone inhibitors
 - antiplatelets

subgroup analyses. The prospectively identified evaluations are for the subgroups listed in Table 3.

Effect sizes and confidence intervals were evaluated for each of these subgroup strata. Uniformity of therapy effect was evaluated using a Cox proportional hazards analysis, with a term each for treatment, subgroup and treatment by interaction in the model.

STUDY ORGANIZATION AND ADMINISTRATION

Vasogen Inc (Canada) is the sponsor of the ACCLAIM trial. Day-to-day responsibility for the execution of the study in North America rested with an operations group of representatives from the sponsor. Local contract research organizations undertook these responsibilities in Europe and Israel. A central laboratory (Quest Diagnostics, USA) conducted the safety and research blood testing. A steering committee (see Appendix) provided scientific, clinical and methodological guidance, and was responsible for protocol amendments, publications and presentations, as well as overseeing site and patient recruitment. A data and safety monitoring board monitored the study, receiving and reviewing reports of adverse events. A central event committee (CEC), whose members were blinded to treatment group, adjudicated all deaths and hospitalizations according to definitions pre-specified in the event classification manual of the ACCLAIM trial. The decisions made by the CEC were considered final, and were used for the primary and secondary analyses. An independent data management group was responsible for data entry and management, and prepared safety reports and adjudication files for the data and safety monitoring board and CEC review, respectively. McDougall Scientific Ltd (Canada) was responsible for the statistical analyses.

Preliminary recruitment experience

The first group of patients were randomly assigned into the trial on June 30, 2003. Table 4 shows the baseline demographic and other data from these 2300 patients. These data confirm that

TABLE 4
Preliminary patient baseline characteristics: first 2300 randomly assigned Advanced Chronic heart failure CLinical Assessment of Immune Modulation therapy (ACCLAIM) trial patients

Characteristic	
Age, years (mean $\pm$ SD)	64.3 $\pm$ 12.0
Men, %	80
Women, %	20
Race, %	
White	92
Black (African-American)	5
Other	3
New York Heart Association classification, %	
II	29
III	67
IV	4
Left ventricular ejection fraction, % (mean $\pm$ SD)	22.7 $\pm$ 5.2
Etiology, %	
Ischemic	68
Nonischemic	32
Heart rate, beats/min (mean $\pm$ SD)	72.2 $\pm$ 17.1
Systolic blood pressure, mmHg (mean $\pm$ SD)	119.5 $\pm$ 19.1
Diastolic blood pressure, mmHg (mean $\pm$ SD)	71.6 $\pm$ 11.4
Weight, kg (mean $\pm$ SD)	84.8 $\pm$ 22.4
Height, cm (mean $\pm$ SD)	171.2 $\pm$ 12.4

patients similar to those in the phase II study were recruited into the ACCLAIM trial. It is important to note that the mean LVEF is almost identical to that observed in the earlier study.

DISCUSSION

The hypothesis being tested in the ACCLAIM trial is that a broad-spectrum immunomodulatory approach favourably modifies the progression of HF by ameliorating the well-characterized inflammatory state in this syndrome. The effects of this treatment approach are in contrast to the highly specific anticytokine strategy of recent trials (10,11), which studied the effects of neutralizing the activity of a single inflammatory cytokine, TNF- α . Two clinical trials (10,11) that pursued this strategy failed to produce a benefit in patients with HF. Despite the disappointing results, the quality of evidence for aberrant cytokine activity in HF remains substantial, encouraging the development of alternative therapeutic strategies that seek to modulate and control such inflammatory pathways.

The ACCLAIM trial has enrolled a large cohort of patients with diverse demographic profiles. Multiple efficacy and safety end points have been incorporated into the ACCLAIM trial; the primary end point of all-cause mortality or cardiovascular hospitalization is a composite of well-defined and easily measurable outcomes that are standard for evaluating pharmacological and other types of intervention in chronic HF. The study was designed to ensure that the patients, as well as the clinicians conducting the study measurements and evaluations, were blinded to the study treatment.

While further work is necessary to definitively establish the mechanism of action of this therapy, the promising results of the phase II trial are consistent with the hypothesis that immune inflammatory activation contributes directly to the progression of HF. Moreover, preliminary studies also indicate that this

approach is safe and potentially efficacious to use in conjunction with existing conventional therapies for HF. Indeed, the lack of detrimental hemodynamic effects and the absence of the potential for pharmacological interactions mean that this form of immune modulation may be added to existing strategies of ACE inhibitors, beta-blockers and diuretics, without the tolerability problems that may occur when traditional vasoactive neurohormonal antagonists are used in combination. Because patients enrolled in the ACCLAIM trial continued with the chronic HF medication they were taking before random assignment, the study provides the opportunity to evaluate this novel therapeutic approach in the context of ongoing pharmacological and implantable device therapy for chronic HF.

CONCLUSION

The ACCLAIM trial is a prospective, double-blind, placebo-controlled, randomized, parallel-group, multicentre trial, with the objective of determining the efficacy and safety of therapy using the Celacade system when added to standard therapy in patients with advanced chronic HF. If the ACCLAIM trial confirms the results of the phase II study, it represents a novel nonpharmacological approach to the treatment of HF – one that targets a pathological mechanism contributing to the progression of this syndrome not addressed by current therapies.

APPENDIX

Individuals contributing to the design and conduct of the Advanced Chronic heart failure CLinical Assessment of Immune Modulation therapy (ACCLAIM) trial

Steering committee

James Young (Chair), The Cleveland Clinic, Cleveland, Ohio, USA
 Stefan Anker, Charité, Campus Virchow-Klinikum, Berlin, Germany
 Robert C Bourge, University of Alabama at Birmingham, Birmingham, Alabama, USA
 Wilson Colucci, Boston University School of Medicine, Boston, Massachusetts, USA
 Barry Greenberg, University of California, San Diego Medical Center, San Diego, California, USA
 Per Hildebrandt, Frederiksberg Hospital, Frederiksberg, Denmark
 Andre Keren, Bikur Cholim Hospital, Jerusalem, Israel
 Michael Motro, The Chaim Sheba Medical Center, Tel Hashomer, Israel
 Jan Erik Otterstad, Hospital of Vestfold, Toensberg, Norway
 Craig Pratt, Methodist Hospital, Houston, Texas, USA
 Piotr Ponikowski, Military Hospital, Wroclaw, Poland
 Jean Lucien Rouleau, Faculty of Medicine, Université de Montréal, Montreal, Quebec
 Francois Sestier, Hôtel-Dieu du CHUM, Centre de Recherche, Montreal, Quebec
 Guillermo Torre-Amione, Methodist Hospital, Houston, Texas, USA
 Bernhard Winkelmann, Kardiologische Gemeinschaftspraxis, Frankfurt, Germany

Central end point committee

Robert C Bourge (Chair), University of Alabama at Birmingham, Birmingham, Alabama, USA
 Victoria Bernstein, Vancouver Hospital & Health Sciences Centre, Vancouver, British Columbia
 Garrie J Haas, Davis Heart and Lung Research Institute, Columbus, Ohio, USA
 T Barry Levine, Allegheny General Hospital, Pittsburgh, Pennsylvania, USA

Data and safety monitoring board

John Cairns (Chair), University of British Columbia, Vancouver, British Columbia

Barry Massie, San Francisco Veterans Affairs Medical Center,
 San Francisco, California, USA

William Wilkinson, Duke University Medical Centre & Health System,
 Durham, North Carolina, USA

Statistician

Lemuel A Moyé, University of Texas School of Public Health, Houston, Texas, USA

NOTE: Since this manuscript was submitted, preliminary results from the ACCLAIM trial were presented at the World Congress of Cardiology 2006, and revealed no significant impact of therapy on the primary end point.

REFERENCES

- Hunt SA; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2005;46:e1-82. (Erratum in 2006;47:1503-1505).
- Mann DL. Inflammatory mediators and the failing heart: Past, present, and the foreseeable future. *Circ Res* 2002;91:988-98.
- Bryant D, Becker L, Richardson J, et al. Cardiac failure in transgenic mice with myocardial expression of tumor necrosis factor-alpha. *Circulation* 1998;97:1375-81.
- Franco F, Thomas GD, Giroir B, et al. Magnetic resonance imaging and invasive evaluation of development of heart failure in transgenic mice with myocardial expression of tumor necrosis factor-alpha. *Circulation* 1999;99:448-54.
- Kubota T, McTiernan CF, Frye CS, et al. Dilated cardiomyopathy in transgenic mice with cardiac-specific overexpression of tumor necrosis factor-alpha. *Circ Res* 1997;81:627-35.
- Matsumori A, Yamada T, Suzuki H, Matoba Y, Sasayama S. Increased circulating cytokines in patients with myocarditis and cardiomyopathy. *Br Heart J* 1994;72:561-6.
- Torre-Amione G, MacLellan W, Kapadia D, et al. Tumor necrosis factor-alpha is persistently expressed in cardiac allografts in the absence of histological or clinical evidence of rejection. *Transplant Proc* 1998;30:875-7.
- Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med* 1990;323:236-41.
- Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: A report from the Studies of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol* 1996;27:1201-6.
- Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT; Anti-TNF Therapy Against Congestive Heart Failure Investigators. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: Results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation* 2003;107:3133-40.
- Mann DL, McMurray JJV, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: Results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation* 2004;109:1594-602.
- Parrillo JE, Cunnion RE, Epstein SE, et al. A prospective, randomized, controlled trial of prednisone for dilated cardiomyopathy. *N Engl J Med* 1989;321:1061-8.
- Gullestad L, Aass H, Fjeld JG, et al. Immunomodulating therapy with intravenous immunoglobulin in patients with chronic heart failure. *Circulation* 2001;103:220-5.
- Staudt A, Schaper F, Stangl V, et al. Immunohistological changes in dilated cardiomyopathy induced by immunoadsorption therapy and subsequent immunoglobulin substitution. *Circulation* 2001;103:2681-6.

15. Fadok VA, Bratton DL, Konowal A, Freed PW, Westcott JY, Henson PM. Macrophages that have ingested apoptotic cells in vitro inhibit proinflammatory cytokine production through autocrine/paracrine mechanisms involving TGF-beta, PGE₂, and PAF. *J Clin Invest* 1998;101:890-8.
 16. Voll RE, Herrmann M, Roth EA, Stach C, Kalden JR, Girkontaite I. Immunosuppressive effects of apoptotic cells. *Nature* 1997;390:350-1.
 17. Aukrust P, Ueland T, Lien E, et al. Cytokine network in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1999;83:376-82.
 18. Babaei S, Stewart DJ, Picard P, Monge JC. Effects of VasoCare therapy on the initiation and progression of atherosclerosis. *Atherosclerosis* 2002;162:45-53.
 19. Shivji GM, Suzuki H, Mandel AS, Bolton AE, Sauder DN. The effect of VAS972 on allergic contact hypersensitivity. *J Cutan Med Surg* 2000;4:132-7.
 20. Nolan Y, Minogue A, Vereker E, Bolton AE, Campbell VA, Lynch MA. Attenuation of LPS-induced changes in synaptic activity in rat hippocampus by Vasogen's Immune Modulation Therapy. *Neuroimmunomodulation* 2002;10:40-6.
 21. Edvinsson LIH, Edvinsson ML, Angus Deveber G. Vasogen's immune modulation therapy (IMT) improves postischemic foot skin blood flow and transcutaneous pO₂ recovery rates in patients with advanced peripheral arterial occlusive disease. *Int Angiol* 2003;22:141-7.
 22. McGrath C, Robb R, Lucas AJ, et al. A randomised, double blind, placebo-controlled study to determine the efficacy of immune modulation therapy in the treatment of patients suffering from peripheral arterial occlusive disease with intermittent claudication. *Eur J Vasc Endovasc Surg* 2002;23:381-7.
 23. Olin JW. A multicenter, randomized, double-blind, placebo-controlled study of immune modulation therapy in patients with symptomatic peripheral arterial disease: The SIMPADICO trial. American College of Cardiology 55th Annual Scientific Sessions. Atlanta, March 11 to 14, 2006.
 24. Torre-Amione G, Sestier F, Radovancevic B, Young J. Effects of a novel immune modulation therapy in patients with advanced chronic heart failure: Results of a randomized, controlled, phase II trial. *J Am Coll Cardiol* 2004;44:1181-6.
 25. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail* 2001;7:176-82.
 26. Rector TS, Kubo SH, Cohn JN. Patients' self-assessment of their congestive heart failure. Part 2: Content, reliability, and validity of a new measure, the Minnesota Living with Heart Failure Questionnaire. *Heart Fail* 1987;198-209.
 27. Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. *Am J Cardiol* 1993;71:1106-7.
-